International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Nanotechnology-Based Modulation of Autoimmune Microenvironments in Sjögren's Syndrome: A Review of Mechanistic Perspectives

Yiming Liu[1], Weixun Zheng[2], Shan Cong[3], Feng Xu[3], Yixian Zhang[3], Dongxue Wang[1]

[1]Department of Pharmacy, The Second Hospital of Jilin University, Changchun, 130000, People's Republic of China; [2]Department of Neurosurgery, The Second Hospital of Jilin University, Changchun, 130000, People's Republic of China; [3]Department of Nephrology, The Second Hospital of Jilin University, Changchun, 130000, People's Republic of China

Correspondence: Dongxue Wang, Email wdx@jlu.edu.cn

Abstract: Sjögren's syndrome (SS) refers to a chronic, systemic autoimmune disease that features infiltration of the exocrine glands by lymphocytes, dysfunction of the salivary and lacrimal glands, generation of autoantibodies, and deregulation of the immune system. Treatment of SS currently focuses on alleviating symptoms and immunosuppression without much success in repairing the damage and restoring immune tolerance. Growing research supports the view that the autoimmune microenvironment, comprising epithelial cells, immune cell populations, cytokines, oxidative mechanisms, and ectopic lymphoid tissue, is the key driver of disease initiation and development. Reprogramming the autoimmune microenvironment thus represents a new potential treatment approach. Immunomodulation is particularly well-suited to nanotechnology owing to its unique characteristics in drug targeting and delivery. In this review, the pathophysiological features of SS, as well as all the important therapeutic targets within the microenvironment of the autoimmune response, have been described in great depth. Moreover, recent progress made in nanotechnology platforms, including polymeric nanoparticles, lipid delivery systems, inorganic nanoparticles, biomimetic nanoparticles, and hydrogel nanotherapy, has been extensively discussed regarding their relevance towards achieving successful immune modulation and regenerating the salivary glands. Future directions regarding current research status, translational progress, precision nanomedicine, AI-based nanomaterials, and multi-functional smart nanomedicines have been included here.

Keywords: Sjögren's syndrome, autoimmune microenvironments, nanotechnology, salivary gland, regeneration

Introduction

The Sjogren's syndrome (SS), now being more commonly referred to as Sjögren's Disease (SjD), can be defined as an autoimmune disease wherein there exists an autoimmune attack on the exocrine glands, particularly the salivary and lacrimal glands, causing problems like dry mouth syndrome (xerostomia) and dry eyes syndrome (keratoconjunctivitis sicca).[1] This disease is now considered as a prototype for autoimmune epithelitis wherein there is significant involvement of the epithelial cells in triggering the immune system response.[2] Apart from the glandular presentation, SS has systemic involvement of other organs such as lungs, kidneys, nervous system, and vascular structures, highlighting its systemic autoimmune nature.[3] SS develops via complex mechanisms, involving interactions between innate and adaptive immune systems, which include the activation of the type I interferon (IFN) signaling pathway, B cell hyperactivity, and the production of autoantibodies. Inflammation leads to slow destruction of glands and tissues.[4] Notably, the formation of lymphocytic infiltrates consisting of large numbers of $CD4^+$ T-cells and B cells in the salivary glands represents the importance of the local immune microenvironment in the pathogenesis of the disease.[2]

The condition predominantly affects women, particularly those in their middle age, owing to various hormonal and genetic factors.[5] It may be considered one of the most common forms of systemic autoimmune diseases, but the prevalence rate will be affected by geographical factors and classification.[6,7] The symptoms of Sjogren's syndrome are not limited to the sicca syndrome but involve such conditions as fatigue, arthralgia, neuropathies, as well as involvement

https://doi.org/10.2147/IJN.S625156
Received: 16 May 2026
Accepted: 4 July 2026
Published: 24 July 2026

of the organs of the body.[8] It is also noteworthy that SS patients have a higher incidence of lymphoproliferative disorders, especially B-cell non-Hodgkin's lymphomas, which result in morbidity and mortality.[9] Moreover, the disease is associated with high economic cost as a result of long-term management of the disease, late diagnosis, and the absence of any cure for the disease. It has been revealed by various studies that the symptoms of the disease are variable.[10]

SS may be co-occurrent with other systemic or organ-specific autoimmune diseases such as systemic lupus erythematosus (SLE) or neuromyelitis optica spectrum disorder /neuromyelitis optica (NMOSD/NMO). The clinical relevance of these overlapping syndromes is possibly due to the similar immunologic mechanisms such as the activation of type 1 interferon, B cell hyperactivity, production of autoantibodies, imbalance of the cytokines and inflammatory damage in target tissues. In this context the nanotechnology driven approaches that allow for the targeted modulation of immune responses, controlled delivery of anti inflammatory agents, redox modulation or the antigen specific immune tolerance might be helpful for the treatment of not only for SS but also for other overlapping syndromes.[11,12] However, this is a theoretical event and further research is required to see if manipulation of common auto-immune pathways via nanomedicine platforms can be safe and effective in patients with overlapping SS, SLE, and NMOSD/NMO.

In spite of all the recent developments in understanding the pathophysiology of SS, treatment has remained focused on symptomatic measures, which are largely ineffective. Conventional therapy is focused on alleviating the symptoms of dryness and lowering systemic inflammation with the help of immunosuppressive drugs and biological agents. However, conventional treatment techniques might fail to bring about disease reduction.[13] Biological treatments, particularly for B-cells, including anti-CD20 and B-cell activating factor (BAFF) inhibitors, have shown erratic results among patients of Sjogren's syndrome because of the varied immune system processes that lead to this disorder.[14,15] Moreover, systemic immunosuppressant drugs have been known to possess severe side effects, alongside a lack of effectiveness, since they are not able to selectively affect the inflamed glands.[13,15] These limitations suggest the necessity of developing more focused therapies targeting specific pathways involved in modulating the immune response locally, rather than suppressing the immune system at large.[3]

It is thought that the role of the autoimmune microenvironment constitutes a key characteristic of the onset and progression of SS. The term autoimmune microenvironment refers to a sophisticated environment made up of various cells and substances in tissues where chronic inflammation occurs.[2] The local microenvironment plays a role in maintaining continuous activation, survival, and differentiation of immune cells, which in turn results in maintaining signaling pathways of inflammation leading to disease development and tissue damage.[16]

It has been shown recently that epigenetic modulation through DNA methylation, histone modifications, and noncoding RNAs contributes significantly to the immune response in SS microenvironments, leading to dysregulated gene expression and inflammation in the salivary glands.[17,18] The epigenetic mechanisms act as a dynamic interface between environmental signals and immune dysfunction, sustaining abnormal immune response.[18,19] Thus, approaches that concentrate on modifying the autoimmune environment rather than targeting particular immune mechanisms have been considered as possible therapeutic interventions to maintain the balance of the immune system.[2]

Breakthrough for immunotherapy treatment due to the development of nanotechnology, which provides the opportunity to have control over the immune system response.[20] Delivery of therapeutics to sites of inflammation or to particular immune cells may be accomplished by the use of engineered nanoparticles. This will improve effectiveness of the treatments while lowering their toxicity.[21] Nano systems have demonstrated remarkable potential as an approach to induce tolerance against specific antigens, manipulate cytokine profiles, and modulate immune cell functions in autoimmune diseases, which is a revolution in the field of immunology.[22] As for SS, recent studies show that nanotechnology could possibly help solve many problems connected with conventional treatment by means of altering the disease microenvironment. For example, there has been some study on the role played by extracellular vesicles and nanotechnology in regulating the body's immune system and promoting wound healing.[23] This implies the enormous capacity of nanotechnology in developing precision immunomodulation treatments for autoimmune disorders.

The purpose of this paper is to provide an overall evaluation of nanotechnology-based strategies that allow for the reprogramming of immune microenvironments in SS. While conventional techniques focus on suppressing the effects of systemic immunity, this study highlights the role of localized immune microenvironments in the progression of the disease and its resistance to treatment. The research examines how the advances in immunology, nanomedicine, and systems biology

can be combined to develop innovative ways to manipulate immunity, restore immune tolerance, and regenerate glands. One of the biggest drawbacks within the current body of evidence is that the nanotechnology-based strategies have not been directly tested in patients with Sjögren's disease or directly tested in disease-specific Sjögren's animal models. Thus, their importance to Sjögren's disease is mainly speculative and mechanistic. The potential of nanomedicine platforms to safely and effectively target these pathways in the pathogenesis of Sjögren's is not certain and these pathways are likely to be targeted in Sjögren's disease. Going forward, validation into appropriate Sjögren's disease models, pharmacokinetic, biodistribution, toxicity, immunogenicity and efficacy studies should be performed prior to clinical translation.

Methodology

This is a narrative review, which was created using a literature search in PubMed, Scopus, Web of Science and Google Scholar. Searches were conducted with the combinations of keywords: "Sjögren's syndrome", "Sjögren disease", "autoimmune microenvironment", "nanotechnology", "nanomedicine", "nanoparticles", "drug delivery", "immunomodulation", "B-cell activation", "interferon signaling", "BAFF", "cytokines", "oxidative stress", "epithelial dysfunction", "ectopic lymphoid structures" and "precision medicine". Peer-reviewed articles were searched primarily from 2015 to 2026 (and prior pioneering articles) with a focus on recent studies, as well as foundational literature relevant to the pathogenesis of SS. As direct clinical study of nanotechnology based therapy in patients with SS is limited or lacking, the studies discussed in this review were chosen based on mechanism of relevance rather than disease-specific clinical validation. We focused our investigations on nanoplatforms targeting immune and tissue-injury pathways that are thought to play a role in SS pathogenesis and that include interferon-associated inflammation, B-cell activation, cytokine signaling, oxidative stress, epithelial function, antigen presentation, lymphoid organization and regenerative repair. These studies thus need to be understood as being preclinical or conceptual in nature, and support future investigation in SS, not as proof of therapeutic efficacy in SS. Articles were excluded if they did not include a mechanism or a translational perspective relevant to the scope of this review, if they were not related to autoimmune pathogenesis, or if they were not relevant to the modulation of immune/tissue microenvironment by nanotechnology.

Pathophysiology of Sjögren's Syndrome

Genetic and Environmental Triggers

The etiopathogenesis of SS is a result of the complex interaction between genetic and environmental influences. Through genome-wide association studies, loci within the HLA class II region and non-HLA gene clusters like IRF5 and STAT4, which play an important role in regulating the interferon pathway and immune function, were found to be associated with SS.[19] The environmental triggers, especially viral infections, have been proposed to trigger disease onset through the activation of innate immunity pathways and production of type I interferon, which serves as a key driver for autoimmunity.[24] These components, when put together, create an environment that is conducive to dysregulated immunity and chronic inflammation.

Role of Epithelial Cells in Disease Initiation

The assurance of SS is that the epithelial cell activation is part of the immune response pathway. This supports the idea of autoimmunepithelitis. The salivary gland epithelial cells are non-professional APCs presenting MHC molecules and providing co-stimulatory signals to activate the T cells.[2] Moreover, these cells secrete chemokines and cytokines that attract immune cells and maintain the inflammatory response. Apoptosis of epithelial cells results in the secretion of intracellular autoantigens, which further activate the immune response and promote loss of tolerance.[25] This interplay between the epithelium and immune system creates a cycle of inflammation that feeds on itself, which is vital in the pathogenesis of the disease.

Autoantibody Production (Anti-Ro/SSA, Anti-La/SSB)

The development of autoantibodies is another major characteristic of SS because of the abnormal regulation of B cells. The development of these antibodies occurs in response to the performance of the autoantigen after the exposure of cellular antigens due to epithelial cell apoptosis.[26] Immune complexes formed in this manner can lead to the activation of the complement system and inflammation. It should be noted that the formation of autoantibodies may occur even before any signs appear, which emphasizes their diagnostic significance.[6]

Lymphocytic Infiltration and Germinal Center Formation

Lymphocyte infiltration of the exocrine glands is one of the most common features of SS pathogenesis. The infiltrating lymphocytes include $CD4^+$ T cells and B cells that form germinal center-like lymphoid aggregates. Such lymphoid aggregates provide conditions for antigen presentation, B cell differentiation, and somatic hypermutation and thus support autoantibody production.[4] Such persistence of well-organized immunological tissues reveals disease severity and a tendency towards lymphoma formation. Chronic lymphocyte infiltration causes glandular degeneration and subsequent loss of function. Other chronic auto-immune conditions such as inflamed synovial tissue in rheumatoid arthritis and CNS associated auto-immune inflammation in multiple sclerosis/CNS auto-immunity have also been reported to display similar tissue associated lymphoid aggregates or tertiary lymphoid structures. Thus, lymphoid aggregate formation in SS must be understood in the context of the chronic tissue-specific autoimmunity in which persistent antigenic stimulation and local immune organization might be expected to be important in the amplification of disease activity and the maintenance of autoreactive B and T-cell responses.[27,28]

Cytokine Networks

Cytokine imbalance plays an important role in the etiology of SS, and type I interferons have been identified as being crucial to the disease. They help in antigen presentation, activate B-cells, and increase inflammation.[26] Contemporarily, BAFF is an important regulator of B-cell survival and differentiation; thus, autoantibodies are produced in response to it. Cytokines that exhibit pro-inflammatory activity, such as IL-6 and TNF-α, also lead to immune stimulation and destruction. Moreover, cytokines such as IL-21 connect innate and adaptive immunity through T follicular helper cell and B-cell activation processes.[29] Interactions between these cytokines generate an inflammatory network that sustains the development of diseases.

B-Cell Hyperactivity and T-Cell Dysregulation

One of the key characteristics of SS is the hyperactivation of B-cells that proliferate, differentiate to plasma cells, and produce excessive amounts of immunoglobulins due to factors such as cytokines like BAFF and T follicular helper cells.[24,30,31] Moreover, the dysfunction of T-cells is caused by the imbalance between effectors and regulatory cells. Th1 and Th17 contribute to inflammatory responses, whereas regulatory T-cells lose their suppressor activity, resulting in immune tolerance disruption. A feedback loop formed between B and T cells in the autoimmune environment ensures the persistence of inflammation and cell damage.[4,32–37]

Autoimmune Microenvironment in Sjögren's Syndrome

Definition of Autoimmune Microenvironment

SS autoimmune microenvironment describes a very specific and dynamic milieu in affected exocrine glands, specifically salivary glands, where immune cells, epithelial structures, stromal components, and soluble factors collaborate in order to perpetuate the ongoing process of chronic inflammation. This microenvironment is described by constant state of immune system activation, dysfunctional cytokines signaling, and remodeling, all leading to malfunctioning of the affected glands. In contrast to systemic immune responses, the microenvironment is defined as a perpetual source of inflammation that controls the process of immune cell recruitment, differentiation, and proliferation. Recent studies have identified increased activity of specific pathways involved in antigen presentation, lymphocyte activation, and interferon response in SS salivary gland tissues. The overall immune microenvironment organization of salivary gland is shown in Figure 1.[38]

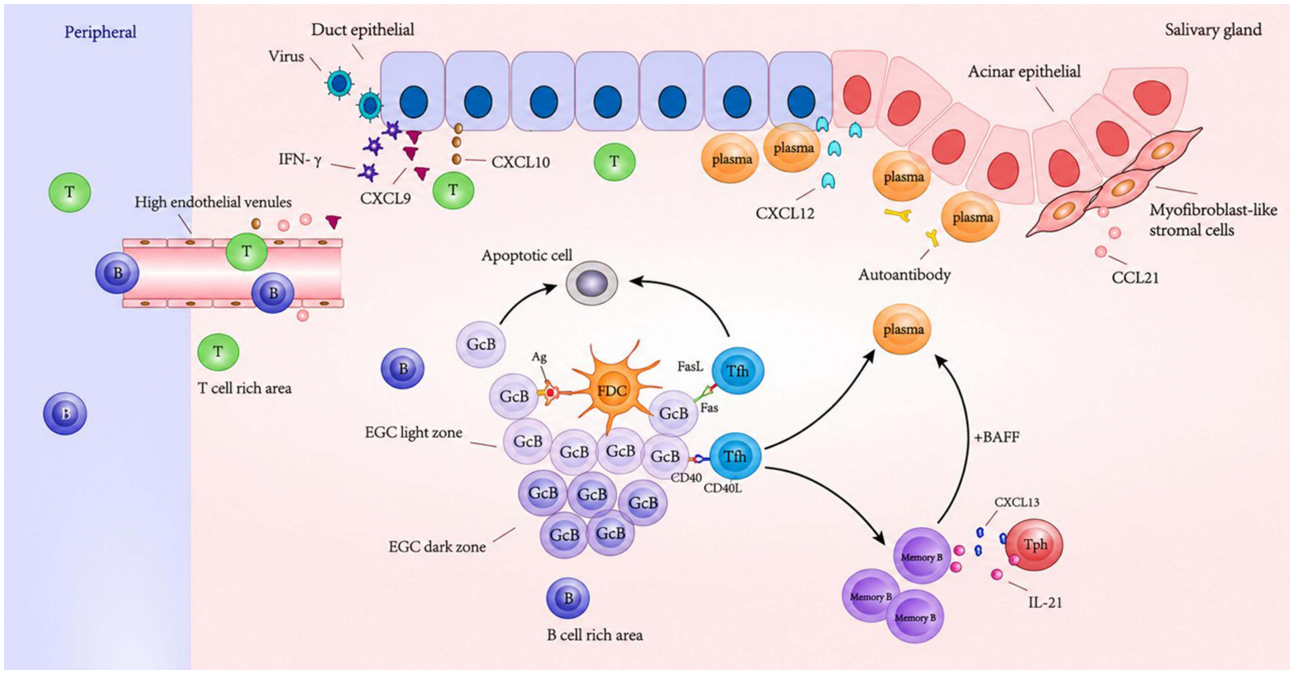

Figure 1 Ectopic lymphoid structures (ELSs) formed within the salivary glands of a patient with Sjögren's syndrome. The central component consists of ectopic germinal centers (EGCs), which are organized into dark and light zones. In the light zone, germinal center B (GcB) cells are selected by follicular dendritic cells (FDCs). Non-selected GcB cells undergo apoptosis, whereas positively selected cells differentiate into memory B cells or plasma cells under the influence of follicular helper T (Tfh) cells, or are eliminated via Tfh-mediated regulation. In parallel, T peripheral helper (Tph) cells produce IL-21 and CXCL13, promoting B cell activation; memory B cells further differentiate into plasma cells under the combined influence of BAFF and related survival factors. Plasma cells accumulate around ductal and acinar epithelial cells expressing CXCL12, contributing to local autoantibody production. Distinct B cell–rich and T cell–rich zones are present surrounding the EGCs. High endothelial venules (HEVs) develop in the T cell–dominant areas at the periphery of lymphoid aggregates, a process driven in part by CCL21 secreted from myofibroblast-like stromal cells. Inflammatory stimulation, including viral triggers, induces IFN-γ expression, which promotes CXCL9 and CXCL10 release, facilitating further recruitment of circulating T and B lymphocytes into the gland via HEVs and sustaining chronic information.[38]

Immune Cell Composition

SS autoimmunity microenvironment is made up of a combination of innate and adaptive immunity cells that synergize in the process of disease pathogenesis. The immune cells' interactions play a crucial role in setting the level of inflammation through their interplay.

T Helper Subsets (Th1, Th17, Tfh)

$CD4^+$ T helper (Th) cells play an important role in coordinating the response to autoimmune disease in SS. Th1 cells generate interferon-γ, which leads to macrophage activation and inflammation, while Th17 cells secrete IL-17, leading to chronic inflammation and epithelial damage. T follicular helper cells (Tfh) are especially important for their role in activating B cells and producing antibodies. These cell types are abundant within the salivary gland infiltrate, helping to organize immune structures.[39] The difference between these T cell populations establishes an inflammatory milieu that contributes to the chronic nature of the disease.

Regulatory T Cells (Tregs)

The regulatory T cells (Tregs) play a vital role in ensuring immune tolerance; however, the functioning of the Tregs is compromised in SS. While Tregs can be found in the sites of inflammation, their ability to suppress the activity of other immune cells may be hampered by alterations in signaling mechanisms and exposure to inflammatory cytokines. This compromise results in an inability to regulate autoimmunity, leading to chronic inflammation. The involvement of Tregs in disrupting immune tolerance is evident in the context of SS.[40]

B Cells and Plasma Cells

B cells play an important role in SS pathogenesis and are a prominent feature of the autoimmune milieu. B cells become activated and expand their clone into plasma cells, producing autoantibodies responsible for disease pathology. Glandular

milieu promotes the survival and maturation of B cells due to the effect of cytokines like BAFF. This abnormal activity of B cells is accompanied by immune complex formation, inflammation, and the development of lymphoma. It has been shown in numerous studies that autoreactive B lymphocytes are crucial in the development of SS.[3,30,41,42]

Dendritic Cells and Macrophages

The role of innate immune cells like dendritic cells (DCs) and macrophages is very important for contributing to the SS microenvironment. The plasmacytoid DCs generate large quantities of type I interferons that enhance immune response and facilitate adaptive immunity.[43–46] On the other hand, the macrophages are involved in damaging the tissue by generating pro-inflammatory cytokines and reactive oxygen species. Innate immune cells are thus involved in linking the environment with adaptive immunity.[38]

Stromal and Epithelial Cell Interactions

Both epithelial and stromal cells are involved in contributing to the autoimmune microenvironment in SS. The salivary gland epithelial cells serve as non-professional antigen-presenting cells, while releasing cytokines like CXCL13 and CCL21 that facilitate the recruitment and accumulation of the lymphocytes. In addition, the role played by the stromal cells is to provide a framework that helps in retention and organization of the immune cells. The interaction of the epithelial and the immune cells generates a feedback mechanism, which ensures the development of inflammation and remodeling of the tissues.[2]

Hypoxia, Oxidative Stress, and Metabolic Reprogramming

The autoimmune microenvironment of SS consists of hypoxia and oxidative stress that play an important role in modulating immune responses. The hypoxic environment created by the inflamed glands triggers the activity of hypoxia inducible pathways resulting in inflammation and increased immune cell viability.[47,48] On the other hand, the increase in reactive oxygen species (ROS) levels causes epithelial destruction and promotes immune responses. Research in recent times has also shown that metabolic changes, such as glycolysis, are responsible for the activation of immune cells and the expression of their effector functions.[38]

Ectopic Lymphoid Structures (ELS)

Ectopic lymphoid structures (ELS) are characteristic features of the SS microenvironment that mimic the secondary lymphoid organs in their anatomy and physiology. ELS possess organized B cell follicles, T cell areas, and FDC networks, which make it possible to present antigens locally and undergo affinity maturation.[49,50] The development of ELS is mediated by chemokines and cytokines that control lymphocyte trafficking and localization. ELS are linked with greater disease severity and the propensity for lymphoma due to their ability to induce B-cell activation and antibody production.[39]

Immune Checkpoint Dysregulation

Immune checkpoints are vital players in regulating the immune system. These checkpoints play a key role in balancing immune activation while promoting immune tolerance. Disruption in the immune checkpoints, including Pd-1 and CTLA-4, results in an inability to inhibit immune activation and causes overactivation of autoreactive T-cells in SS. The development of immunotherapy through the inhibition of immune checkpoints can be considered a promising new approach in treating SS.[10]

Therapeutic Targets Within the Autoimmune Microenvironment

In SS, the autoimmune microenvironment is a sophisticated, ever-changing milieu comprising various immune cells, epithelial compartments, and soluble factors that maintain ongoing inflammation. Treatment targeting the autoimmune microenvironment can be considered a novel therapy, as this approach provides opportunities to modulate local immune dysfunction without suppressing the entire immune system. Studies have highlighted the need for therapies to interrupt

abnormal signaling networks, re-establish immune homeostasis, and correct metabolic defects in the target glandular niche.[38]

Cytokine Modulation

Cytokine-mediated signaling is vital for generating an SS microenvironment, especially BAFF and type I IFN signaling. BAFF is essential for inducing B cell survival, maturation, and autoantibody formation, causing continuous B cell activation. Increased BAFF expression in salivary glands maintains autoreactive B cell clones, leading to disease advancement.[38] The interferon pathway, particularly the type I interferons, is the primary upstream mediator that activates the immune system in SS. IFN signaling facilitates antigen presentation, induces B-cell activation, and amplifies cytokine feedback loops. Significantly, transcriptomics studies have revealed IFN gene expression as an important biomarker of disease severity and treatment efficacy.[51] Consequently, IFN pathway modulation via receptor blocking or signaling inhibition is becoming an attractive strategy with increasing proof of its efficacy as a critical target for treating SS.[52]

Immune Cell Reprogramming

Immune cell reprogramming is a paradigm change that moves from traditional immunosuppressive approaches to more precise immunomodulatory techniques. In SS, immune response is generated due to aberrant interactions between T cells, B cells, and innate immune cells. Immune cell reprogramming entails altering their functional behavior and phenotype to correct any immune imbalance.[2,53] For instance, manipulating Th subsets, specifically T follicular helper (Tfh) cells, decreases B-cell activity and autoantibody generation. Furthermore, modifying macrophages' phenotype from pro-inflammatory (M1) to anti-inflammatory (M2) reduces inflammation and enhances the process of inflammation resolution. Additionally, dendritic cells are vital targets since altering their antigen presentation capability inhibits T-cell proliferation and cytokine secretion.[36,38] Nanoparticle-based targeted delivery of the drug is one such strategy that allows selective targeting of particular types of immune cells, reducing toxicity to the whole body. Such a treatment paradigm matches the idea of microenvironment remodeling by changing the functional state of immune cells in tumor tissue.[54–56]

Inhibition of Ectopic Germinal Centers

The presence of ectopic germinal centers (GCs) or lymphoid organs is crucial for creating a proper SS microenvironment and represents the local place of antigen presentation and B cell maturation to autoantibody-producing plasma cells. Ectopic lymphoid organs support persistent immune response and represent a significant marker of severe SS and lymphoma occurrence.[57,58] The approach to targeting the ectopic GC involves the inhibition of the mechanisms involved in ectopic GC formation and maturation. Lymphotoxin, chemokine CXCL13, and follicular dendritic cells are critical for ectopic GC maintenance, and interfering with these mechanisms may result in impairment of lymphoid organogenesis and immune response in the region.[38] In addition, manipulating Tfh cells, which regulate the functions of the GCs, can inhibit B cell activation and the development of autoantibodies. It is also possible to decrease the presence of auto-reactive immune responses by breaking down these complex immune niches.[45,59,60]

Restoration of Immune Tolerance

One of the critical problems associated with SS involves the disruption of immune tolerance, resulting in the stimulation of autoreactive lymphocytes. Thus, the restoration of immune tolerance has become an essential treatment strategy. Interventions designed to increase the potency of Tregs or induce antigen-specific tolerance have been extensively investigated.[61,62] Tregs are crucial for immune tolerance regulation; however, their immunosuppressive effect may be compromised in SS. By enhancing Treg functions, patients suffering from SS can achieve better suppression of autoimmunity and decrease inflammatory processes. Moreover, tolerogenic dendritic cells may be modified to deliver antigens in a non-inflammatory setting, thus inducing immune tolerance.[63] Novel therapies include antigen-specific tolerance induction utilizing modern delivery systems, such as nanoparticles. These techniques facilitate selective exposure of self-antigens to the immune system, minimizing immunosuppression without compromising the immune

response. Significantly, this method addresses the root cause of the immune malfunction rather than just managing the disease manifestations.[22,64,65]

Targeting Oxidative Stress and Hypoxia

Oxidative stress and hypoxia are two major characteristics of the SS environment and contribute immensely to disease progression. Increased oxidative stress results from high amounts of ROS that lead to cellular damage, release of autoantigens, and inflammation. Hypoxia, on the other hand, increases inflammation through hypoxia-inducible factors (HIFs) that regulate gene expression for survival and cytokines in immune cells.[38] The treatment options based on such metabolic alterations consist of antioxidants, ROS scavengers, and blockers of hypoxia-induced signaling pathways. Such strategies seek to interrupt the feedback mechanism of oxidative stress and activation of the immune system.[4,66,67] It is worth highlighting that due to recent developments in nanotechnology, stimuli-responsive systems have been created that release drugs in oxidative or hypoxic conditions. This allows achieving an efficient effect while avoiding adverse consequences.[68–71]

Nanotechnology in Autoimmune Disease Management

Nanotechnology provided an innovative approach towards autoimmune diseases based on technologies for manipulating immunity, optimizing pharmacokinetics, and achieving targeted delivery of therapeutic interventions. For example, in the case of an autoimmune disease like SS, where there is constant activation of the immune system along with an increase in immune cell populations in the salivary and lacrimal glands, the regulation of medicines to suppress the immune system showed limited efficiency in achieving remission in the disease condition. The introduction of nanotechnology has provided an innovative solution for addressing such problems by programming the immune response and reinstating immune tolerance.[72]

Overview of Nanomedicine Platforms

The different nanomedicine platforms that have been utilized in autoimmunity treatment therapies are lipid-based nanocarriers, polymeric nanoparticles, dendrimers, metallic nanoparticles, and biomimetic vesicles. Among lipid-based nanocarriers are LNPs like liposomes and solid lipid nanoparticles, which are utilized because of their high biocompatibility, as well as the capacity to encapsulate both hydrophilic and hydrophobic drugs.[73] The PLGA nanoparticle, on the other hand, allows sustained release, while dendrimers provide multivalency for ligand conjugation.[74,75] According to recent studies, lipid-based nano-carriers play a pivotal role in optimizing pharmacokinetic properties and delivering therapies in autoimmune disorders. Lipid-based nanoparticles such as liposomes, nano-structured lipid carriers, and lipid micelles have been found to optimize therapeutic performance in preclinical autoimmune models.[76] Moreover, biomimetic nanocarriers that mimic natural cell membranes are becoming more popular due to their potential to improve immune compatibility and increase circulating times, thus providing high suitability for treating chronic autoimmune disorders.[77]

Advantages of Nanotechnology in Immunomodulation

One of the main benefits of using nanotechnology in autoimmune disease treatment is the potential for exact immunomodulation without the need for complete immunosuppression. Traditional treatments like steroids and disease-modifying antirheumatic drugs (DMARDs) inhibit the general immune response and leave patients vulnerable to infections. However, nanoparticles make it possible to selectively target specific harmful immune cell populations, such as autoreactive B cells, activated T cells, and inflammatory macrophages.[78] Nanoparticles can be designed to deliver therapeutic agents such as cytokine inhibitors, small interfering RNA (siRNA), and antigen-specific peptides specifically to immune cells. With this approach, it is possible to regulate the pathways involved in immune response such as nuclear factor-kappa B (NF-κB), Janus kinase-signal transducer and activator of transcription (JAK/STAT), and inflammasomes. Moreover, nanomaterial-based therapy can induce a shift in macrophage phenotype from inflammatory M1 to anti-inflammatory M2 types.[72]

Targeted Drug Delivery Mechanisms

Specific drug targeting can be done by passive and active methods. Passive drug targeting is carried out based on inflammation-related increased permeability and retention of the nanoparticles in inflamed tissues.[79] In contrast, active drug targeting uses the coating of nanoparticles with certain biomolecules such as antibodies, peptides, and ligands to facilitate receptor binding.[80] Autoimmune disorders like SS result in the activation of endothelial cells to produce adhesion molecules like ICAM-1 and VCAM-1. Also, in autoimmunity, the use of nanoparticles coated with antibodies specific to CD20 (B cells) and CD4 (T helper cells) allow selective destruction of abnormal lymphocytes. It has been shown that specific targeting of monocytes/macrophages with nanoparticles is important for controlling inflammatory environments and immune activation.[81] Exosome-mediated mechanisms, diagnostics, and treatment in pSS is shown in Figure 2.[82]

Controlled Release and Stimuli-Responsive Systems

Controlled release technologies constitute an important innovation in autoimmune treatments using nanotechnology. They can deliver their cargo based on certain pathological stimuli, such as low pH, high levels of ROS, enzymes, or cytokines.[83,84] The inflamed milieu of autoimmune disease is characterized by oxidative stress and changes in enzymes, making it possible to use these conditions as stimuli for targeted drug delivery. Nanoparticles that respond to ROS have been synthesized for delivering anti-inflammatory drugs to the inflamed salivary gland without affecting other tissues. Additionally, MMP-responsive nanocarriers degrade due to the increased levels of matrix metalloproteinases (MMPs). The application of biomaterials engineering techniques in addition to these techniques makes drug delivery even more precise. The stimuli responsive nanomaterials give control over the amount of drugs released into the system, maintaining high drug levels in the disease site while decreasing the toxicity of the drugs.[85]

Safety and Biocompatibility Considerations

Despite their therapeutic potential, nanomedicine platforms need to be critically evaluated concerning safety, toxicity, and biocompatibility. The toxicity of nanoparticles can be associated with their physicochemical characteristics such as particle size, charge, surface modification, and their degradation products. In this regard, cationic nanoparticles might cause membrane damage and oxidative stress in case of improper design.[86,87] Degradable polymers like PLGA, lipids, and natural nanoparticles obtained from extracellular vesicles are regarded as safe because they metabolize easily and have less immunogenic effects. Moreover, modifications such as PEGylation improve biocompatibility by minimizing the process of opsonization and increasing circulation time. On the other hand, prolonged accumulation and elimination pathways need to be examined in preclinical animal models.[88] Recently published articles have underscored the significance of standardizing toxicity assessment methodologies such as biodistribution, immune response profiling, and target organ accumulation.[89] Furthermore, the issue of regulatory importance still remains critical to the translational aspect of medicine, especially in making sure that the therapeutic effect is reproducible and scalable.

Nanotechnology-Based Strategies for Reprogramming Autoimmune Microenvironments

The reprogramming of the autoimmune microenvironment of SS necessitates an integrated approach to immune regulation that focuses on the modulation of cytokines, activation of autoreactive lymphocytes, oxidative stress imbalance, hypoxic reprogramming, and disruption of epithelial-immune interactions. The microenvironment of SS in the salivary and lacrimal glands involves chronic lymphoid infiltration, activation of type I interferon signaling, and germinal centers.[2,4,90] Nanotechnology presents a sophisticated therapy approach that is able to influence these pathologic mechanisms via targeted delivery techniques, reprogramming immune cells, and responsive release mechanisms of drugs. Current research highlights the ability of nanomaterials to serve not only as vectors but also as activators of the immune system, facilitating a transition from immunosuppressive to immune normalization.

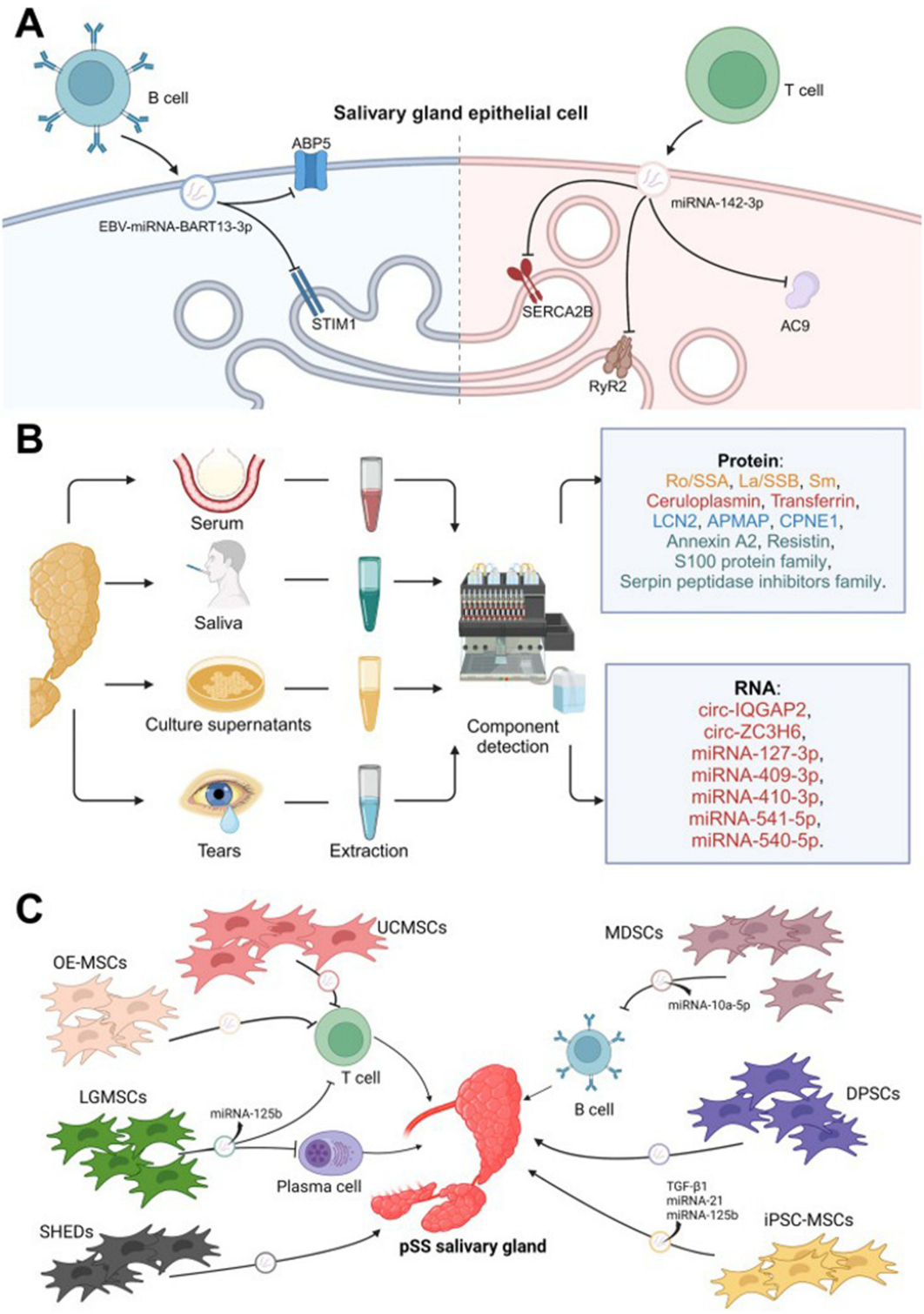

Figure 2 (**A**) Exosomes from EBV-infected B cells and activated T cells impair salivary gland epithelial function by delivering miRNAs that disrupt calcium and cAMP signaling, reducing AQP5 expression and saliva secretion. (**B**) Salivary, serum, and tear exosomes contain diagnostic biomarkers (eg, Ro/SSA, La/SSB, circRNAs) for non-invasive detection and disease monitoring in pSS. (**C**) MSC-derived exosomes modulate immune balance (Treg/Th17), promote tissue repair, and restore salivary gland function, offering a potential therapeutic strategy.[82]

Abbreviations: pSS, primary Sjögren's syndrome; EBV, Epstein–Barr virus; AQP5, aquaporin 5; STIM1, stromal interaction molecule 1; SERCA2B, sarco/endoplasmic reticulum Ca^{2+} ATPase 2B; RyR2, ryanodine receptor 2; Ro/SSA, Sjögren's syndrome-related antigen A; La/SSB, Sjögren's syndrome-related antigen B; miRNA, microRNA; MSCs, mesenchymal stem cells; iPSC-MSCs, induced pluripotent stem cell-derived MSCs; UCMSCs, umbilical cord MSCs; DPSCs, dental pulp stem cells; OE-MSCs, olfactory ecto-MSCs; SHEDs, stem cells from human exfoliated deciduous teeth; MDSCs, myeloid-derived suppressor cells; MSCs-exos, MSC-derived exosomes).

Nanoparticle-Mediated Cytokine Regulation

Cytokine imbalance plays a vital role in microenvironment dysregulation within the context of autoimmunity, especially an increase in TNF-α, IL-6, BAFF, and Type 1 Interferons, leading to B cell hyperactivity and chronic inflammation.[91] Regulation of cytokines using nanoparticles makes it possible to inhibit inflammatory signaling pathways, such as NF-κB and JAK/STAT, without inducing generalized immunosuppression. Several studies on lipid and polymer-based nanoparticles have been conducted in the past for siRNA and mRNA delivery to knock down transcription of pro-inflammatory cytokines.[92,93] Recently, there have been developments in nanoparticle gene delivery technology emphasizing their capabilities in regulating cytokine response in immune cells along with improved pharmacokinetics and intracellular delivery.[91] These delivery systems minimize overproduction of cytokines by directly administering nucleic acids to macrophages and dendritic cells, hence balancing the immune system in the inflamed tissue.

Nanocarriers for Immune Cell Targeting

The use of nanocarrier technology allows for highly targeted delivery to specific immune cells associated with autoimmune disease such as T cells, B cells, macrophages, and dendritic cells.

T-Cell Modulation

T-cell dysregulation, especially an increase in Th1 and Th17 cell subtypes, is known to be one of the prominent immunopathological features of Sjogren's syndrome. The up-regulation of T helper cells that secrete IL-17 and follicular helper T cells has been observed in patients, being highly correlated with disease progression and the development of autoantibodies.[36] Additional studies have shown that abnormal activation of $CD4^+$ T cells in SS leads to stimulation of B cells and systemic immune dysfunction, making T cells an important treatment focus.[94] Nanoparticles engineered to deliver immunomodulators to specific subsets of T cells using antibodies or ligands that specifically target $CD4^+$ and $CD8^+$ T cells have been made possible through nanoparticle engineering. This enables selective delivery of immunosuppressive drugs such as calcineurin inhibitors, mTOR inhibitors like rapamycin, and JAK inhibitors directly into activated lymphocytes with minimal toxicity.[95] The ability of biomaterial systems to work with advanced technology has shown that surface-engineered nanoparticles can be made to specifically bind with the circulating T cells to control the immune response in a tissue-specific manner.[54] From a functional standpoint, these nanocarriers inhibit the effector T cell activation pathways such as TCR-based signaling and cytokine production, while at the same time promoting the proliferation of Treg cells.[22] Cationic nanoparticles have displayed great potential for eliciting immune tolerance by altering the mechanisms of antigen presentation and T cell activation processes.[96]

B-Cell Depletion Strategies

The role played by B cells in the development of SS involves the generation of autoantibodies, the presentation of antigens, and the development of ectopic germinal centers. Some B-cell targeting approaches based on nanoparticles involve the use of CD20-functionalized particles and BAFF inhibitors.[95,97–99] By regulating monocyte and macrophage activation in nanomedicine treatment, indirect effects on B cells can be achieved via reduction of inflammatory cytokines produced in autoimmune niches, thus interfering with pathogenic feedback loops.[81]

Nanoparticles for Antigen-Specific Immune Tolerance

Induction of antigen-specific tolerance is a revolutionary concept in the treatment of autoimmunity. Nanoparticles may be constructed to deliver both the disease-linked autoantigen along with immunosuppressive cytokines such as IL-10 and rapamycin, facilitating tolerogenic DC development and regulatory T cells.[64,100,101] The proposed approach is able to suppress autoimmunity in patients while maintaining the overall functionality of the immune system. Cationic and polymeric nanoparticles have been found capable of reprogramming the immune response towards tolerance by increasing antigen presentation through inflammation-free mechanisms.[96]

ROS-Responsive and Redox-Modulating Nanoplatforms

Oxidative stress is an important cause of cell injury in SS, characterized by the excessive production of ROS, which damages the epithelium and enhances inflammatory responses. ROS-sensitive nanoparticles are engineered to deliver drugs only when the environment is oxidative.[102,103] The nanocarriers utilize ROS-sensitive linkages, such as thioketal bonds, that allow for specific drug delivery. Furthermore, ROS-sensing nanoparticles can effectively remove ROS molecules from cells, restoring redox homeostasis and preventing downstream NF-κB signaling.[104–106] They have been demonstrated to enhance therapeutic efficacy in inflammatory disorders by concurrently lowering oxidative stress and inflammation.[107,108]

Hypoxia-Modulating Nanomaterials

Autoimmune tissues affected by chronic inflammation often exhibit a state of hypoxia due to the presence of hypoxia inducible factor-1α (HIF-1α). Hypoxia contributes to autoimmune disorders by causing fibrosis, production of pro-inflammatory cytokines, development of new blood vessels, and alteration of cellular metabolism.[47,109,110] Nanoparticles that can be used to deliver or generate oxygen can reverse hypoxic status and inflammatory environments. Nanoparticles based on perfluorocarbons contain oxygen in significant amounts and have been widely studied as oxygen delivery agents aimed at overcoming hypoxia and blocking hypoxic signaling. Concurrently, nanoparticles loaded with catalase convert hydrogen peroxide into oxygen and suppress HIF-1α.[111–113] Also, catalytic nanozymes that display both catalase-like and superoxide dismutase-like properties are capable of regulating ROS production, maintaining optimal oxygen balance, and preventing immune-related inflammation. Oxygen-regulating nanoparticles are thus capable of restoring metabolic balance inside the tissue and constitute potential therapies for the treatment of autoimmune disorders such as SS, rheumatoid arthritis, and systemic lupus erythematosus.[110,114,115]

Exosome-Mimicking Nanovesicles

The exosomes mimicking nanovesicles can be regarded as the biomimetic advance of nanomedicine, which is intended to mimic the structure and functions of EVs found naturally. The nanocarriers facilitate efficient communication between cells and modulate immunity via delivery of proteins, lipids, messenger RNA, and miRNA to recipient cells.[116,117] Exosome-like nanoparticles engineered to carry anti-inflammatory miRNAs or cytokines can promote the polarization of macrophages toward anti-inflammatory phenotypes, reducing inflammation in tissues within autoimmune microenvironments.[118,119] They benefit from the advantage of better biocompatibility, prolonged circulation time, and reduced immunogenicity as compared to other artificial nanocarriers, which makes them ideal candidates for treating chronic autoimmune diseases requiring lifelong treatment.[116,120] Furthermore, vesicles derived from exosomes are involved in cell-to-cell interaction within immune cells, as well as controlling inflammatory signal transduction pathways by means of exosomal ncRNAs and miRNA interactions.[121,122] It should be noted that there is currently a great deal of research being done on the role of engineered exosomes in regulating the immune system and providing therapeutic options in autoimmune diseases.[123] Exosome-mimicking nanovesicles have emerged as promising biomimetic delivery systems due to their intrinsic biocompatibility, immune regulatory capacity, and ability to transport bioactive molecules in SS (Figure 3).[124]

Emerging Mechanisms in Sjögren's Syndrome Pathogenesis and Nanotechnology-Based Therapeutic Opportunities

In addition to classical immune mechanisms like interferon activation, BAFF-mediated B-cell stimulation, T-cell dysregulation and ectopic lymphoid organisation, several new mechanisms are now emerging and are discussed with regard to SS pathogenesis. These involve ferroptosis, immunometabolic remodeling, mitochondrial dysfunction, cellular senescence, endoplasmic reticulum (ER) stress, defective autophagy and cell-type-specific disease programs uncovered by single-cell transcriptomic analysis. All these processes might contribute to understanding why glandular epithelial cells are not just passive targets of inflammatory processes, but can be active participants in local activation.[125,126]

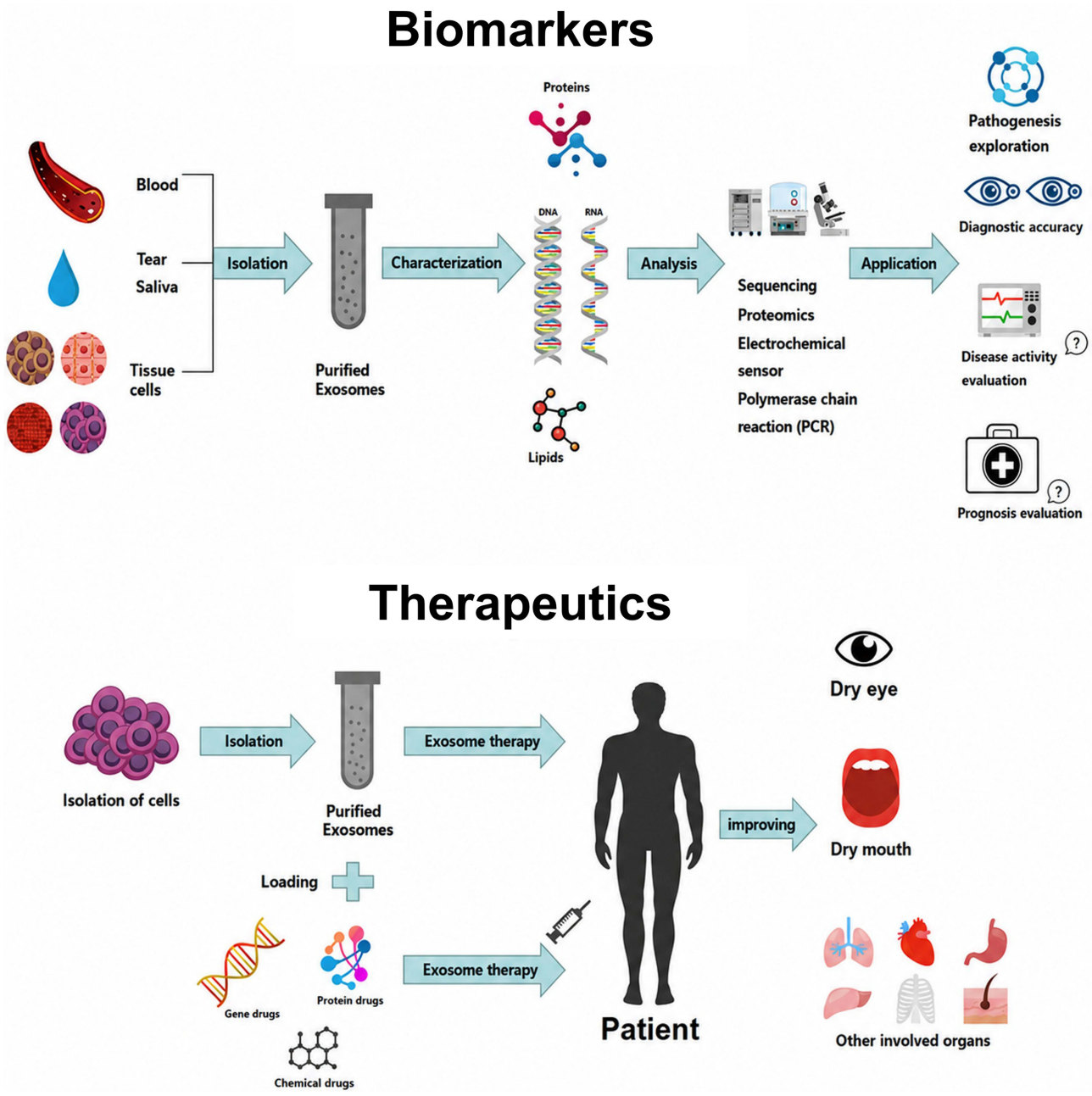

Figure 3 Exosomes as biomarkers and therapeutic tools in Sjögren's syndrome.[124]

Iron-dependent lipid peroxidation-associated cell death called ferroptosis may be a driver of epithelial injury and oxidative tissue damage. Immunometabolic dysregulation may lead to changes in function of epithelial cells, macrophages, B cells and T cells, including changes in energy utilization, cytokine production and survival pathways. This mitochondrial dysfunction can increase ROS production, innate immune activation and epithelial stress signaling. Defective autophagy, ER stress and senescence-associated secretory factors could play a role in sustaining inflammation and impairing protein handling, antigen processing, epithelial homeostasis, and immune tolerance, which would be a consequence of cellular senescence.[127,128]

All of these mechanisms provide new targets for nanotechnology-based intervention. Such strategies may involve antioxidant or anti-ferroptotic nanoparticles for decreasing lipid peroxidation, mitochondria-targeted nanocarriers for decreasing mitochondrial stress, metabolic modulators using controlled release systems, nanoplatforms to regulate

https://doi.org/10.2147/IJN.S625156

autophagy or ER-stress pathways, and local delivery systems to decrease senescence-associated inflammatory signaling. Single-cell transcriptomic profiling could also provide additional precision in nanomedicine by identifying epithelial, immune, stromal and endothelial cells most associated with disease activity and therapeutic resistance. These strategies however are still preliminary and their validity for SS needs to be confirmed in patient-derived organoids, in disease-specific animal models and in well designed translational studies.[129,130]

Representative Nanoplatforms Studied in Sjögren's Syndrome

The use of nanotechnology-based therapeutic systems for treating various autoimmune diseases, including SS, is now regarded as an effective strategy owing to its potential advantages in targeted and controlled drug delivery, modulation of immunity, tissue specificity, and reduced systemic toxicity. Traditional drugs like corticosteroids, hydroxychloroquine, and immunosuppressive drugs used for treating SS suffer from low efficiency and a host of side effects following prolonged treatment. The pathological environment of SS involves several biological components such as infiltration of lymphocytes into salivary and lacrimal glands, oxidative stress, programmed cell death of epithelial cells, and secretion of pro-inflammatory cytokines. Hence, the current research efforts concentrate on creating nanomaterials that are able to deliver immunosuppressive drugs locally, retain themselves in the eye and salivary gland region, and bring about restoration of normal immune function. Furthermore, nano-materials can perform additional functions, including anti-oxidants, mimicking of immune reactions, and sustained release of therapeutic agents, which are useful in chronic autoimmune diseases.[131,132]

Polymeric Nanoparticles for Immunosuppressive Drug Delivery

Polymer nanoparticles represent one of the most extensively studied nanocarrier systems for the treatment of autoimmune diseases due to their good biocompatibility, degradation properties, and efficient drug loading capacity. The focus of utilizing polymeric nanoparticles in SS has been on delivery of corticosteroids, cyclosporine A, tacrolimus, methotrexate, and anti-inflammatory biologics into the affected ocular and salivary glands. Degradable polymers including PLGA, PEG, chitosan, and polycaprolactone are often used due to their pharmacodynamic advantages and safe characteristics. These nanoparticles enhance the effectiveness of treatment by increasing the blood circulation time, improving cellular internalization, and providing extended drug release in affected inflammatory glandular tissues. Additionally, surface functionalization with ligands or antibodies helps in achieving selective targeting of activated immune cells, resulting in reduced side effects on systemic immunity.[132,133] Polymeric nanomicelles have exhibited potential for treating ocular symptoms related to SS-induced dry eye syndrome. The hydrophobic nature of the polymeric system facilitates the incorporation of hydrophobic drugs like cyclosporine A while enhancing the permeation of the cornea and precorneal retention of the drug. Polymeric micelles have been reported to provide greater tear film stability and inhibition of inflammatory cytokines released from ocular tissue relative to regular ophthalmic solutions. pH-responsive, oxidation-responsive, and enzyme-responsive polymeric nanoparticles have been synthesized for releasing active molecules in response to changes in pH, oxidative environment, or enzymes in an autoimmune microenvironment. These stimuli-responsive polymers could eventually facilitate targeted immunotherapeutic strategies for SS.[134–136]

Lipid-Based Nanocarriers (Liposomes, Solid Lipid Nanoparticles)

Nanocarriers such as liposomes and solid lipid nanoparticles (SLNs) also constitute an important class of nanoplatforms used in SS treatment. Liposomes can be defined as phospholipid-based vesicles that can contain both hydrophilic and hydrophobic substances, rendering them very flexible for delivery of immunosuppressive drugs. Due to the similarity between the structure of liposomes and biological membranes, liposome biocompatibility is extremely high. The ability to fuse with epithelial and immune cells further enhances their functionality. Liposomes filled with corticosteroids, tacrolimus, or cyclosporine A have shown an ability to penetrate corneas more easily in ocular SS and increase the duration of treatment. Moreover, liposomal artificial tears were used in SS-associated dry eye disease.[131,137] Solid lipid nanoparticles (SLN) formulations also present additional benefits, such as enhanced physical stability, stabilization of the active components against any degradation, and prolonged drug-release behavior. The use of SLN carriers has gained more interest as potential candidates in the design of both local and systemic immunomodulatory treatment due to their

safety profile and ability to increase mucus penetration. For instance, the use of SLN carriers for SS-related ocular disease presents better bioavailability, as well as fewer administration requirements when compared to conventional eye drops. Additionally, lipid-based nanocarriers can be used as potential candidates to deliver nucleic acids such as siRNA or microRNA molecules for the inhibition of inflammatory cytokines and the autoreactive signaling pathways. Hybrids such as cerasome and bicelles that mimic liposomes but have silica nanoparticle properties have been tested.[135,137,138]

Inorganic Nanoparticles (Gold, Silica, Cerium Oxide)

Inorganic nanoparticles have been extensively studied in autoimmune nanomedicine because of their distinctive physicochemical properties, imaging, and inherent bioactive features. Gold nanoparticles (AuNPs) exhibit exceptional anti-inflammatory and antioxidative features, and they can be modified with peptides, antibodies, and nucleic acids to modulate the immune system. According to various experimental studies on autoimmune disorders, AuNPs have been found to attenuate the macrophages' inflammatory process, decrease pro-inflammatory cytokine release, and inhibit NF-κB pathways. Furthermore, surface plasmon resonance attributes give AuNPs the ability to be used theranostically as both imaging and therapeutic agents. In SS, AuNPs are currently being explored as carriers of anti-inflammatory drugs.[132,137]

Mesoporous silica nanoparticles (MSN) are another important inorganic carrier system due to their enormous surface area, adjustable pore sizes, and impressive drug-loading ability for biological and chemical entities. MSN allows for controlled and stimulus-dependent drug release, which enables the surface modification for targeted delivery. The use of MSN in inflammatory and autoimmune diseases has shown an effective delivery of immunomodulators with low systemic toxicity. Moreover, hybrid MSNs have been found to be highly structurally stable with enhanced circulation properties, which can be ideal for chronic autoimmune diseases like SS.[136–138] Nanoceria (cerium oxide nanoparticles) has become increasingly popular due to its regenerative antioxidant properties and ROS scavenging abilities. Oxidative stress has been identified as one of the main contributors to epithelial cell injury and chronic inflammation in SS. The nanoceria particles have the capability of changing their oxidation states from Ce^{3+} to Ce^{4+}, similar to natural antioxidants like superoxide dismutase and catalase. In studies involving ocular inflammatory diseases, it was found that the cerium oxide nanoparticles could offer protection against oxidative damage and also inhibit inflammation without any notable toxicity.[139–141]

Biomimetic Nanoparticles

Biomimetic nanoparticles have emerged as an exciting field of nanomedicine, which is based on mimicking biological properties that resemble those of native cells or extracellular vesicles. These biomimetic nanoparticles encompass cell membrane-functionalized nanoparticles, exosome-mimicking nanovesicles, and extracellular vesicles for drug delivery purposes. Biomimetic nanoparticles exhibit superior immune avoidance, long circulation periods, and improved targetability as compared to synthetic nanoparticles. They can be helpful in treating autoimmune diseases by inducing immune tolerance through altering antigen presentation and attenuating immune activation.[131,142,143] Nanoparticles coated with cell membranes obtained from leukocytes, macrophages, or stem cells could be designed to preferentially target inflammatory tissue sites via specific interactions with adhesion molecules and inflammatory chemokines. These approaches might allow the direct delivery of anti-inflammatory compounds to the affected salivary glands without prompt elimination by the reticuloendothelial system. The use of exosome-mimicking nanoparticles represents an attractive approach owing to the natural role of extracellular vesicles in cell-to-cell immune communication. Exosomes isolated from mesenchymal stem cells were found to exhibit immunomodulatory and reparative properties in autoimmune models by modulating Th17 differentiation and promoting regulatory T-cell function. Therefore, biomimetic nanoparticles represent an extremely promising approach for establishing homeostatic conditions and reprogramming autoimmune environments in SS.[131,132]

Hydrogel-Based Nano-Systems for Localized Therapy

Nano-systems based on hydrogels have become very promising tools for targeted and prolonged drug delivery in SS due to their ability to hold water, extend drug presence, and deliver drugs in a controlled fashion in ocular and salivary

Table 1 Representative Nanoplatforms Studied in Sjögren's Syndrome for Modulation of Autoimmune Microenvironments

Nanoplatform/Study Focus	Application/Disease Model	Target Cell or Tissue	Key Findings	References
Polymeric exosome-guided butyrate nanocarriers	Primary SS	Tfh/Tfr cells	Restored immune balance	[144]
Polymeric immunosuppressive nanocarriers	Experimental SS	Salivary gland tissue	Enhanced local immunomodulation	[145]
Liposomal JAK inhibitor delivery	Dry-eye associated SS	Ocular epithelial cells	Improved topical retention	[146]
Nanoliposomes for tear osmolarity sensing	Dry eye/Sjögren-associated ocular disease	Tear film microenvironment	Sensitive osmolarity detection	[147]
Exosomal ferroptosis-associated nanoparticles	Primary SS	Salivary gland epithelial cells	Linked ferroptosis to SS pathology	[148]
Silica-associated nanostructures for delivery systems	Autoimmune-targeted delivery	Immune microenvironment	Controlled release capability	[149]
OE-MSC-derived exosomes	Experimental SS	Myeloid-derived suppressor cells	Restored suppressive immune function	[150]
Biomimetic exosome therapeutics	Sjögren immune modulation	Salivary gland immune cells	Low immunogenicity therapeutic platform	[124]

tissues. Hydrogels are three-dimensional polymer frameworks that can absorb considerable amounts of water without losing their shape. The combination of nanoparticles with hydrogels produces multifunctional hybrid nano-scaffolds with enhanced mechanical strength, mucoadhesiveness, and treatment efficacy. This type of nano-system is especially valuable in treating SS-related xerostomia and keratoconjunctivitis sicca.[135,136] Nanohydrogels responsive to changes in the pH levels, temperature, and inflammatory factors have also been designed in order to enable drug release from the encapsulating nanohydrogel particles. For instance, thermoresponsive hydrogels experience a sol-gel phase transformation after their contact with the ocular tissues, thus increasing the retention rate in the precorneal region as well as the availability of the anti-inflammatory agents. Nanohydrogel-composite hydrogel constructs have also been found efficient in salivary gland reconstruction due to their ability to facilitate stem cell viability along with sustained delivery of the cytokines. Furthermore, such nanogels can serve as artificial extracellular matrices for facilitating epithelial restoration and minimizing immune-mediated tissue damage.[135–137] The representative nanoplatforms used in SS for modulation of autoimmune microenvironments are given in Table 1, whereas the advantages, limitations, and clinical stages of platforms like liposomes, PLGA NPs, exosomes, nanoceria, and hydrogels are summarized in Table 2.

Nanotechnology for Salivary Gland Regeneration

The salivary gland disorder that causes SS is caused by the chronic autoimmune destruction of epithelial cells, gland fibrosis, oxidative stress, and continued lymphocyte invasion. There have been recent innovations in nanomedicine that show great promise in restoring the function and structure of the glands via stem cell delivery, tissue engineering, growth factor release, and immune modulation. Nanotechnology platforms offer better bioavailability, controlled drug release, and targeted tissue delivery.[161,162]

The salivary gland epithelium is not a passive target for immune mediated injury, as should be considered in SS. Acinar and ductal epithelial cells actively participate in the modification of the local autoimmune microenvironment via altered secretory function, epithelial stress responses, metabolic dysfunction, impaired ion/water transport, mitochondrial dysfunction, oxidative stress and endoplasmic reticulum stress. Acinar cell injury can lead to a decrease in saliva output, and ductal injury can affect electrolyte transport, epithelial barrier function, antigen presentation, and recruitment of immune cells via chemokines. Furthermore, neuroepithelial regulation is necessary for glandular secretion, since the autonomous signaling plays a role in acinar fluid secretion, protein release and epithelial homeostasis. A disruption of these epithelial and neural regulatory pathways could thus enhance the hypofunction of the glands and the activation of the local immune system.[161–163]

Table 2 A Summary of the Advantages, Limitations, and Clinical Stages of Platforms, Including Liposomes, PLGA Nanoparticles, Exosomes, Nanoceria, and Hydrogels

Platform	Main Advantages	Main Limitations	Potential Relevance to SS	Translational Stage	References
Liposomes	• Biocompatible lipid vesicles • Can encapsulate hydrophilic and lipophilic agents • Surface modification possible • Can reduce systemic toxicity and improve drug distribution	• Cargo leakage • Stability issues • Rapid clearance by the mononuclear phagocyte system • Variable tissue targeting • Manufacturing and storage constraints	Local or systemic delivery of: • Anti-inflammatory drugs • Nucleic acids • Immunomodulatory molecules targeting cytokine signaling • B-cell pathways • Epithelial inflammation	• Clinically established in several non-SS indications • SS-specific therapeutic use remains unvalidated	[151,152]
PLGA nanoparticles	• Biodegradable and biocompatible polymer • Controlled/sustained release • Tunable size, charge, and degradation rate • Suitable for small molecules, proteins, peptides, and nucleic acids	• Initial burst release • Formulation-dependent immunogenicity or inflammation • Scale-up complexity • Potential low loading efficiency for some cargos	• Sustained delivery to salivary or lacrimal tissues • Possible modulation of IFN signaling, BAFF-mediated B-cell activation, oxidative stress, epithelial injury, or local inflammation	• Broad preclinical and translational use in drug delivery • Some PLGA-based systems are clinically used in other contexts • No established SS-specific clinical application	[153,154]
Exosomes	• Natural intercellular communication vehicles • Carry proteins, lipids, mRNA, miRNA, and other bioactive cargo • Potential immune-modulatory and regenerative effects • May cross biological barriers	• Heterogeneous composition • Difficult standardization • Scalability challenges • Unclear biodistribution • Batch-to-batch variability • Safety and regulatory concerns	• Potential delivery of miRNAs, proteins, or immunomodulatory cargo • Possible relevance to epithelial repair, immune regulation, gland regeneration, and biomarker-driven therapy	• Active preclinical and early clinical investigation in several fields • No FDA-approved exosome products • SS-specific evidence remains limited	[155,156]
Nanoceria	• Redox-active nanoparticles • ROS-scavenging and enzyme-mimetic properties • Potential anti-inflammatory and cytoprotective effects • May reduce oxidative tissue injury	• Long-term safety uncertain • Possible pro-oxidant effects depending on pH, dose, surface chemistry, and biological context • Biodistribution and clearance concerns	Potential reduction of: • Oxidative stress • Epithelial injury • Inflammatory amplification • Tissue damage in salivary gland microenvironments	• Mainly preclinical for oxidative stress, inflammation, tissue injury, and regenerative applications • Not clinically validated in SS	[157,158]
Hydrogels	• Injectable or implantable local delivery systems • High water content • Tissue-like mechanical properties • Can retain drugs, cells, exosomes, growth factors, or nanoparticles at target sites • Useful for tissue engineering	• Mechanical instability • Variable degradation kinetics • Limited diffusion depending on formulation • Possible inflammatory response • Optimization needed for glandular delivery	• Local retention of immunomodulatory or regenerative agents in salivary tissue • Scaffold support for epithelial repair, glandular regeneration, or sustained release of therapeutic cargo	• Clinically used in selected biomedical applications and widely studied in tissue engineering • Salivary gland/SS applications remain experimental	[159,160]

https://doi.org/10.2147/IJN.S625156

If such strategies based on nanotechnology are tailored to work in this glandular epithelial niche, they may prove to be particularly relevant. These may include different nanocarriers for targeting the epithelium for local delivery of anti-inflammatory agents, antioxidant nanoparticles to counteract oxidative and mitochondrial stress, nucleic-acid delivery systems to intervene with interferon or chemokine related pathways, and hydrogel based local depots to maintain therapeutic exposure in salivary or lacrimal tissue. But these strategies are largely conceptual in SS and need to be assessed in disease-specific models incorporating not only an assessment of immune suppression, but also epithelial viability, acinar and ductal function, salivary secretion, neuroepithelial signaling, biodistribution, and long-term safety.[144,164,165]

Stem Cell Delivery via Nanocarriers

Regenerative treatment using stem cells appears to be an effective approach to repair salivary glands in SS patients based on the ability of MSCs, SG progenitor cells, and iPSCs to self-renew and exert immunomodulatory effects. The conventional stem cell transplantation often encounters problems related to poor survival rate, rapid clearance by immune cells, and inability to adapt to inflammatory surroundings. This has led to the development of nanoparticulates such as poly(lactic-co-glycolic acid) nanoparticles, chitosan nanoparticles, and hyaluronic acid derivatives that will increase the success rate of the stem cells.[166] The use of magnetic nanoparticles for the effective delivery of stem cells has increased efficiency due to the localization of these cells, which are attracted to specific locations using magnetic navigation. This ensures that stem cells accumulate around the glands that have inflammation. In addition, the use of exosome nanotherapy, which relies on mesenchymal stem cells, is effective for regeneration and immunomodulation, since exosomes have bioactive compounds such as lipids, miRNAs, and proteins that promote epithelial cell repair and inflammatory mediator inhibition.[162]

Growth Factor Encapsulation Strategies

Epithelial growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and keratinocyte growth factor (KGF) play important roles in the regeneration process for epithelial cells, angiogenesis, and tissue remodeling. The use of these growth factors in clinical settings is restricted due to their quick metabolic degradation and biological instability. Various nanotechnology strategies, including liposomes, polymer-based nanoparticles, nanogels, and hydrogels, have been developed to deliver regenerative agents locally in damaged salivary glands.[161] Controlled release systems can protect growth factors from enzymatic breakdown, allowing them to maintain therapeutic levels over extended periods of time. One of the most viable methods for achieving tissue regeneration through the use of nanosystems that have been injected includes the use of hydrogels and nanoparticles as they help provide mechanical stability and ensure sustained delivery of the regenerative compounds. The gene-activated nanocarriers that are able to deliver plasmid DNA or messenger RNA encoding regenerative compounds are another novel method for tissue regeneration.[162]

Tissue Engineering and Nanoscaffolds

Nanotechnology-assisted tissue engineering has brought about remarkable progress in regenerative medicine of salivary glands owing to the capacity of forming biologically inspired scaffolds which mimic natural extracellular matrix. Nanofibrous structures, peptide-based nanoparticles, collagen-based matrices, and hydrogel nanocomposites offer highly porous three-dimensional environments that promote cellular activities such as attachment, growth, migration, and acinar differentiation. Nanoscaffolds may also be used to deliver various therapeutic agents including growth factors, anti-inflammatory drugs, and antioxidants to regenerate tissues.[166] Electrospinning methods have allowed for the development of nanofiber constructs employing biomaterials like collagen, gelatin, silk fibroin, chitosan, and polycaprolactone, all of which possess desirable biocompatibility and mechanical characteristics. Injectable nanocomposites with hydrogel matrices are particularly beneficial since they can adapt to glandular abnormalities while sustaining hydrated conditions that promote epithelial development and stem cell viability. Emerging innovations in the realm of three-dimensional bioprinting with nanomaterials might eventually result in the production of functional salivary gland replacements that can restore normal secretion in SS sufferers with severe glandular damage.[167]

Regenerative Immunomodulation

Salivary gland regeneration therapy in SS is possible only if chronic inflammation caused by autoimmunity is controlled. Thus, immunomodulatory approaches have been widely researched in recent years as a key element of nanomedicine applications. Nanoparticles can be designed to introduce anti-inflammatory cytokines, immunosuppressive substances, antioxidants, and tolerance-inducing components into glandular tissues invaded by lymphoid aggregates while simultaneously activating regenerative pathways.[161] Nanomaterials with immunomodulating and inherent antioxidant characteristics like CeO_2 nanoparticles and biomimetic extracellular vesicles have been found promising for lowering oxidative stress, preventing inflammatory cytokine secretion, and shifting macrophages towards an anti-inflammatory M2 type. This leads to improved epithelial defense, remodeling of the extracellular matrix, and the recovery of the normal function of glands. As a result, nanotherapy for regenerative medicine involves tissue engineering, immunomodulation, and drug delivery systems that can enhance the results of SS treatment significantly.[162]

Preclinical and Clinical Advances

Advancements made in the use of nanotechnology in therapies for SS have helped to speed up the shift from mechanism-focused research at the lab bench level to translational medicine and early clinical applications.[4,168] The pathophysiology of the autoimmune microenvironment of SS is very complicated and entails dysfunctional interactions between the immune system and epithelium.[2,38] Hence, accurate modeling of glandular inflammation and remodeling in preclinical studies is necessary to assess the effectiveness and safety of nanotherapies.[161,169] Innovative developments in organoid fabrication, microfluidic technology, animal models, and immunomodulation using nanoparticles have led to significant advancements in the comprehension of disease progression as well as treatment strategies.[2,4]

In vitro Models of Sjögren's Microenvironment

Classic two-dimensional cultures of epithelial cells have a very poor capability for reproducing the intricate interaction between cells seen in patients of SS. Hence, more complex three-dimensional organoids, salivary gland spheroids, and chip-based organs are being used to replicate the autoimmune microenvironment. The salivary gland organoids generated using stem cells or progenitors retain the integrity of the epithelial polarity, differentiation of acinus, and secretion, thus permitting an analysis of the inflammatory pathway and kinetics of nanoparticle entry. Studies showed that the use of organoid-based model accurately replicated the interferon-induced activation of the epithelium and immune cell infiltration in salivary glands affected by SS.[2,170,171] The microfabrication techniques have also made it possible to develop salivary gland-on-a-chip models that include the extracellular matrix, endothelial cells, and immune cells. The bioengineered model mimics the flow of fluids, gradients of cytokines, and epithelial-stromal interactions linked with chronic autoimmune inflammation. The tissue engineering approach is especially beneficial in studying nanoparticle delivery, targeted drug delivery, and exosomal intercellular communication. In addition, the in vitro models help in reducing animal testing and expedite the preclinical evaluation of nanomedicines against salivary gland disorders.[38,172]

Animal Models and Nanotherapy Outcomes

Multiple murine models have been created in order to examine the immunopathogenesis of Sjögren syndrome and for evaluating the nanotechnology-based therapies for this disease. Non-obese diabetic (NOD) mice, C57BL/6. NOD-Aec1Aec2 mice, and induced models of experimental Sjögren syndrome display salivary gland infiltration of lymphocytes, decreased salivary flow, the presence of autoantibodies, and epithelial cell death, similar to human Sjögren syndrome. These animal models have been widely employed in the assessment of immunotherapy and regenerative strategies utilizing nanoparticles. Targeted delivery by nanoparticles results in increased uptake by inflamed salivary glands, hence minimizing side effects.[173,174]

Exosomes from mesenchymal stem cells and polymeric nanoparticles containing anti-inflammatory drugs have resulted in successful results when tested on animals through inhibition of Th1/Th17 cell reactions, decrease in pro-inflammatory cytokine levels, and restoration of glandular secretion capacity. Lipid and hydrogel nanoparticles have also been used for delivery of growth factors responsible for regenerating the epithelium and acinar cells in glands.

Nanoparticles have also been seen to control the polarity of macrophages and inhibit hyperactivity of B-cells in salivary glands.[82,175]

Moreover, the application of nanotech biomaterials has also been combined with approaches in regenerative medicine to boost the engraftment capacity of salivary gland cells. It has been observed that in vivo studies using biomimetic scaffolds containing either nanofibers or an extracellular matrix-like scaffold increase the process of vascularization, differentiation, and integration post-transplantation. These findings indicate that through the use of nanotechnology, many challenges faced by existing systemic immunosuppressive approaches can be avoided.[176]

Ongoing and Completed Clinical Trials

The clinical application of nanotechnology in the treatment of SS is still at an early stage. However, some potential therapies based on nanotechnology are currently advancing through the preclinical and clinical testing process. The ongoing clinical trials mainly comprise biologics, B-cell inhibitors, stem cell therapies, and exosomes targeting modulation of the immune response and gland repair. Nanotechnology has increasingly become a part of these therapies, which use innovative drug delivery methods, biomarker detection devices, and regenerative tissue scaffolds. Some studies have been conducted using extracellular vesicles produced by mesenchymal stem cells, as they have the ability to modulate the immune response and regenerate damaged tissue. The size of the exosomes themselves is within the range of nanotechnology, providing effective tissue penetration and microRNA delivery. Moreover, there are diagnostic tools utilizing nanoparticles for detecting salivary autoantibodies and inflammatory mediators.[38,82] A number of biological agents that target B cell activation factor, CD40 pathway, and Fc receptor pathway have demonstrated promising outcomes in recent clinical trials of SS patients. These treatments, however, are not strictly restricted to nanotechnology. Their combination with nanocarrier technology is likely to increase pharmacokinetic properties and tissue targeting ability in the future. Moreover, increasing research in personalized treatment will make nanotechnology even more important in autoimmune diseases.[2,176]

Translational Challenges

Despite significant advances made thus far, several translational bottlenecks still persist and hinder the practical application of nanotechnology within SS. First, one of the critical challenges is associated with the heterogeneity in the presentation and immune phenotypes of patients, resulting in problems of uniform patterns of response to treatment. The other important concern relates to limited understanding of nanoparticle biodistribution, safety, immunogenicity, and clearance. Variations in the parameters of nanoparticles, such as size, chemistry, and synthesis method, can significantly influence the safety and efficacy of nanoparticles.[177,178] Inability to properly mimic the human autoimmune condition in currently available animal models constitutes another essential limitation, making it difficult to predict the effectiveness of nanoparticles in human subjects. The scalability, regulation, and reproducibility of multifunctional nanoparticles are also major barriers in this field. Finally, the interaction between nanoparticles and the immune system should be carefully optimized to prevent unwanted inflammation or immunosuppression.[175,176] Any future success would most probably rely on the collaboration of researchers across different disciplines, including immunology, biomaterials science, rheumatology, and bioengineering. Artificial intelligence, precision nanomedicine, and use of patient-specific organoids could also make the process more efficient and personalized.

Future Perspectives

Future efforts towards the development of nanotechnology-based therapy against SS will rely on the combination of the principles of artificial intelligence (AI), precision medicine, biologics-based therapy, and multifunctional nanoparticle engineering.[179] The current approaches toward treatment are limited by the failure to effectively address the specific aspects that underlie the disease, providing only symptom alleviation and general suppression of the immune response instead of selective reprogramming of the autoimmune microenvironment. Nanomedicine techniques developed in this context aim at achieving targeted action on affected tissues, increasing treatment efficiency, and restoring physiological function of the salivary glands without causing systemic adverse effects.[180,181]

AI-Guided Nanomedicine Design

The applications of AI and machine learning (ML) have been viewed as revolutionary tools for the synthesis of nanomedicine. The application of AI computational modeling would enable the analysis of multidimensional data acquired through the application of technology such as transcriptomics, proteomics, and immune profiling to elucidate the pathways related to the pathogenesis of SS. So, it is feasible to optimally modify nanoparticle characteristics like size, charge, ligand density, and drug cargo content, leading to an increase in targeting effectiveness and pharmacokinetics. Furthermore, ML can provide information on biodistribution, cell uptake, and immunotoxicity of nanoparticles, thus reducing time in experimental procedures.[182]

Personalized and Precision Nanotherapy

The enormous heterogeneity present in SS requires the synthesis of a customized therapeutic approach to address the specific immune dysfunctions that occur with SS. The use of precision nanomedicine enables regulating the therapy according to the patient-specific information available through the use of molecular biomarkers, inflammation markers, and glandular alterations identified by means of omics approaches and single-cell sequencing. Eventually, salivary gland organoids from the patients themselves along with immune profiling could facilitate testing nanotherapies prior to their clinical administration.[183,184] The nanocarriers modified with tissue-targeting ligands may be able to selectively localize to the inflamed salivary glands or pathogenic immune cells, resulting in high local drug concentrations and decreased systemic toxicity. Moreover, biomarker-activated nanocarriers, which have the capacity to release their therapeutic cargo in response to inflammation or oxidative stress, allow for spatiotemporally controlled drug delivery. Exosome-mediated and RNA-containing nanoparticles are novel nanotherapies with potential use in autoimmune diseases.[185]

Combination Therapies (Nanotechnology and Biologics)

A combination of nanotechnology and biologic therapies would be considered a promising strategy for treating SS in the coming years. Biologic treatments against B cells, cytokines, and immune costimulation have shown some success in the treatment of autoimmunity, but their use has been hampered by poor tissue penetration, toxicity issues, and heterogeneous patient response. The use of nanoparticle formulations would help address these issues in terms of biologic stability, controlled release, and targeted delivery.[186,187] In future, nano-biologics would incorporate a mixture of monoclonal antibodies, anti-inflammatory agents, nucleic acid sequences, and growth factors to modulate the autoimmune microenvironment effectively. This approach would aim at inhibition of inflammatory signaling and stimulation of tissue repair, with the goal of stimulating secretory function in the salivary glands. Furthermore, injection of hydrogel nanocomposites for sustained drug delivery locally might be more effective.[188]

Conclusion

The SS is a multifactorial autoimmune condition marked by complicated interplays between immune cells, epithelium, cytokines, and metabolism within the autoimmune microenvironment. Current treatments only offer symptomatic relief and immunosuppressive action; therefore, there is an immediate need for effective treatments that directly affect the autoimmune process. The application of nanotechnology can be considered an effective tool for modulating the pathogenic autoimmune microenvironment via selective delivery, modulation of immune cells, regulation of cytokines, reduction of oxidative stress, and restoration of immune tolerance. Moreover, innovations related to bioinspired nanoparticles, exosomes, nanovehicles, and stimulus-responsive approaches open new possibilities for salivary gland tissue regeneration. The combination of artificial intelligence technologies and precision nanomedicine with multifunctional smart nanosystems might advance SS treatments significantly.

Current evidence points to the involvement of pathogenic mechanisms including defective epithelial barrier, interferon activation, B-cell hyperactivity, imbalance of cytokines, oxidative stress, ectopic lymphoid organization and defective tissue repair in disease development. However, the majority of the nanotechnology based strategies have not yet been translated into the clinic, nor into disease specific experimental models of SS. Thus, their effectiveness in the clinic is still not known. The focus of future research should be on preclinical models relevant to SS, targeted delivery to the salivary and lacrimal tissue, evaluation of biodistribution and toxicity, use of pharmacodynamic endpoints in the

immune system, biomarker-based patient stratification and well-designed translation studies. As long as such evidence is not provided, nanotechnology should be considered as a hopeful conceptual platform for future research in SS.

Data Sharing Statement

No data were used for the research described in the article.

Funding

This study was supported by the Jilin Provincial Department of Science and Technology (No. 20210101361JC).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ramos-Casals M, Baer AN, Brito-Zerón MDP, et al. 2023 International Rome consensus for the nomenclature of Sjögren disease. *Nat Rev Rheumatol*. 2025;21(7):426–437. doi:10.1038/s41584-025-01268-z
2. Verstappen GM, Pringle S, Bootsma H, Kroese FG. Epithelial–immune cell interplay in primary Sjögren syndrome salivary gland pathogenesis. *Nat Rev Rheumatol*. 2021;17(6):333–348. doi:10.1038/s41584-021-00605-2
3. Negrini S, Emmi G, Greco M, et al. Sjögren's syndrome: a systemic autoimmune disease. *Clin Exp Med*. 2022;22(1):9–25. doi:10.1007/s10238-021-00728-6
4. Baldini C, Fulvio G, La Rocca G, Ferro F. Update on the pathophysiology and treatment of primary Sjögren syndrome. *Nat Rev Rheumatol*. 2024;20(8):473–491. doi:10.1038/s41584-024-01135-3
5. Beydon M, McCoy S, Nguyen Y, Sumida T, Mariette X, Seror R. Epidemiology of Sjögren syndrome. *Nat Rev Rheumatol*. 2024;20(3):158–169. doi:10.1038/s41584-023-01057-6
6. Brito-Zerón P, Baldini C, Bootsma H, et al. Sjögren syndrome. *Nat Rev Dis Primer*. 2016;2(1):1–20. doi:10.1038/nrdp.2016.47
7. Thurtle E, Grosjean A, Steenackers M, Strege K, Barcelos G, Goswami P. Epidemiology of Sjögren's: a systematic literature review. *Rheumatol Therapy*. 2024;11(1):1–17. doi:10.1007/s40744-023-00611-8
8. Mardale D-A, Opriş-Belinski D, Bojincă V, et al. The physical and psychosocial impact of fatigue among patients with Sjogren's syndrome: a systematic review. *J Clin Med*. 2024;13(6):1537. doi:10.3390/jcm13061537
9. Maślińska M, Przygodzka M, Kwiatkowska B, Sikorska-Siudek K. Sjögren's syndrome: still not fully understood disease. *Rheumatol Int*. 2015;35(2):233–241. doi:10.1007/s00296-014-3072-5
10. Maleki-Fischbach M, Kastsianok L, Koslow M, Chan ED. Manifestations and management of Sjögren's disease. *Arthritis Res Therapy*. 2024;26(1):43. doi:10.1186/s13075-024-03262-4
11. Moseley CE, Sagan S, Boquett JA, et al. Sjögren syndrome candidate autoantigen AQP5 triggers AQP4 CNS autoimmunity through self-antigen mimicry. *Neurol Neuroimmunol Neuroinflamm*. 2026;13(1):e200517. doi:10.1212/nxi.0000000000200517
12. Krett JD, Filippatou AG, Barreras P, Pardo CA, Gelber AC, Sotirchos ES. "Lupus Myelitis" revisited: a retrospective single-center study of myelitis associated with rheumatologic disease. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(1):e200329. doi:10.1212/nxi.0000000000200329
13. Seror R, Nocturne G, Mariette X. Current and future therapies for primary Sjögren syndrome. *Nat Rev Rheumatol*. 2021;17(8):475–486. doi:10.1038/s41584-021-00634-x
14. He S-H, Xuan -Y-Y, Liang X, et al. Investigative biological therapies for primary Sjögren's syndrome. *Arch Med Sci*. 2020;20(2):506. doi:10.5114/aoms.2020.97288
15. Chowdhury F, Tappuni A, Bombardieri M. Biological therapy in primary Sjögren's syndrome: effect on salivary gland function and inflammation. *Front Med*. 2021;8:707104. doi:10.3389/fmed.2021.707104
16. Low HZ, Witte T. Aspects of innate immunity in Sjögren's syndrome. *Arthritis Res Therapy*. 2011;13(3):218. doi:10.1186/ar3318
17. Imgenberg-Kreuz J, Rasmussen A, Sivils K, Nordmark G. Genetics and epigenetics in primary Sjögren's syndrome. *Rheumatology*. 2021;60(5):2085–2098. doi:10.1093/rheumatology/key330
18. Imgenberg-Kreuz J, Sandling JK, Nordmark G. Epigenetic alterations in primary Sjögren's syndrome–an overview. *Clin Immunol*. 2018;196:12–20. doi:10.1016/j.clim.2018.04.004
19. Thorlacius GE, Björk A, Wahren-Herlenius M. Genetics and epigenetics of primary Sjögren syndrome: implications for future therapies. *Nat Rev Rheumatol*. 2023;19(5):288–306. doi:10.1038/s41584-023-00932-6
20. Cheng Z, Fobian S-F, Gurrieri E, et al. Lipid-based nanosystems: the next generation of cancer immune therapy. *J Hematol Oncol*. 2024;17(1):53.
21. Kusumoputro S, Au C, Lam KH, et al. Liver-targeting nanoplatforms for the induction of immune tolerance. *Nanomaterials*. 2023;14(1):67. doi:10.3390/nano14010067
22. Benne N, Ter Braake D, Stoppelenburg AJ, Broere F. Nanoparticles for inducing antigen-specific T cell tolerance in autoimmune diseases. *Front Immunol*. 2022;13:864403. doi:10.3389/fimmu.2022.864403
23. Zhao J, An Q, Zhu X, et al. Research status and future prospects of extracellular vesicles in primary Sjögren's syndrome. *Stem Cell Res Ther*. 2022;13(1):230. doi:10.1186/s13287-022-02912-1
24. Nocturne G, Mariette X. Advances in understanding the pathogenesis of primary Sjögren's syndrome. *Nat Rev Rheumatol*. 2013;9(9):544–556. doi:10.1038/nrrheum.2013.110

25. Voulgarelis M, Tzioufas AG. Pathogenetic mechanisms in the initiation and perpetuation of Sjögren's syndrome. *Nat Rev Rheumatol*. 2010;6(9):529–537. doi:10.1038/nrrheum.2010.118
26. Nordmark G, Alm GV, Rönnblom L. Mechanisms of disease: primary Sjögren's syndrome and the type I interferon system. *Nat Clin Pract Rheumatol*. 2006;2(5):262–269. doi:10.1038/ncprheum0173
27. Stott DI, Hiepe F, Hummel M, Steinhauser G, Berek C. Antigen-driven clonal proliferation of B cells within the target tissue of an autoimmune disease. The salivary glands of patients with Sjögren's syndrome. *J Clin Invest*. 1998;102(5):938–946. doi:10.1172/jci3234
28. Moseley CE, Sabatino JJ, Zamvil SS. B-cell antigen presentation in central nervous system autoimmunity. *Curr Opinion Immunol*. 2025;96:102647. doi:10.1016/j.coi.2025.102647
29. Kwok S-K, Lee J, Yu D, et al. A pathogenetic role for IL-21 in primary Sjögren syndrome. *Nat Rev Rheumatol*. 2015;11(6):368–374. doi:10.1038/nrrheum.2014.225
30. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. *Nat Rev Rheumatol*. 2018;14(3):133–145. doi:10.1038/nrrheum.2018.1
31. Zhan Q, Zhang J, Lin Y, Chen W, Fan X, Zhang D. Pathogenesis and treatment of Sjogren's syndrome: review and update. *Front Immunol*. 2023;14:1127417. doi:10.3389/fimmu.2023.1127417
32. Youinou P, Pers J-O. Disturbance of cytokine networks in Sjögren's syndrome. *Arthritis Res Therapy*. 2011;13(4):227. doi:10.1186/ar3348
33. Rios-Rios WJ, Sosa-Luis SA, Torres-Aguilar H. T cells subsets in the immunopathology and treatment of Sjogren's syndrome. *Biomolecules*. 2020;10(11):1539. doi:10.3390/biom10111539
34. Blinova VG, Vasilyev VI, Rodionova EB, Zhdanov DD. The role of regulatory T cells in the onset and progression of primary Sjögren's syndrome. *Cells*. 2023;12(10):1359. doi:10.3390/cells12101359
35. Hao H, Nakayamada S, Tanaka Y. Differentiation, functions, and roles of T follicular regulatory cells in autoimmune diseases. *Inflammat Regenerat*. 2021;41(1):14. doi:10.1186/s41232-021-00164-9
36. Phillips R. T cell differentiation in Sjögren syndrome is regulated by TOX. *Nat Rev Rheumatol*. 2022;18(8):432.
37. Verstappen GM, Corneth OB, Bootsma H, Kroese FG. Th17 cells in primary Sjögren's syndrome: pathogenicity and plasticity. *J Autoimmun*. 2018;87:16–25. doi:10.1016/j.jaut.2017.11.003
38. Tan Z, Wang L, Li X. Composition and regulation of the immune microenvironment of salivary gland in Sjögren's syndrome. *Front Immunol*. 2022;13:967304. doi:10.3389/fimmu.2022.967304
39. Zandonella Callegher S, Giovannini I, Zenz S, et al. Sjögren syndrome: looking forward to the future. *Therapeutic Adv Musculoskeletal Dis*. 2022;14:1759720X221100295. doi:10.1177/1759720X221100295
40. Jonsson R. Disease mechanisms in Sjögren's syndrome: what do we know? *Scandinavian J Immunol*. 2022;95(3):e13145. doi:10.1111/sji.13145
41. Mielle J, Tison A, Cornec D, Le Pottier L, Daien C, Pers J-O. B cells in Sjögren's syndrome: from pathophysiology to therapeutic target. *Rheumatology*. 2021;60(6):2545–2560. doi:10.1093/rheumatology/key332
42. Varin -M-M, Le Pottier L, Youinou P, Saulep D, Mackay F, Pers J-O. B-cell tolerance breakdown in Sjögren's syndrome: focus on BAFF. *Autoimmunity Rev*. 2010;9(9):604–608. doi:10.1016/j.autrev.2010.05.006
43. Yao Y, Liu Z, Jallal B, Shen N, Rönnblom L. Type I interferons in Sjögren's syndrome. *Autoimmunity Rev*. 2013;12(5):558–566. doi:10.1016/j.autrev.2012.10.006
44. Apostolou E, Tzioufas AG. Type-III interferons in Sjögren's syndrome. *Clin Exp Rheumatol*. 2020;38(Suppl 1):245–252.
45. Chivasso C, Sarrand J, Perret J, Delporte C, Soyfoo MS. The involvement of innate and adaptive immunity in the initiation and perpetuation of Sjögren's syndrome. *Int J Mol Sci*. 2021;22(2):658. doi:10.3390/ijms22020658
46. Reizis B, Bunin A, Ghosh HS, Lewis KL, Sisirak V. Plasmacytoid dendritic cells: recent progress and open questions. *Ann Rev Immunol*. 2011;29(1):163–183. doi:10.1146/annurev-immunol-031210-101345
47. Tang -Y-Y, Wang D-C, Wang Y-Q, Huang A-F, Xu W-D. Emerging role of hypoxia-inducible factor-1α in inflammatory autoimmune diseases: a comprehensive review. *Front Immunol*. 2023;13:1073971. doi:10.3389/fimmu.2022.1073971
48. Chen P-S, Chiu W-T, Hsu P-L, et al. Pathophysiological implications of hypoxia in human diseases. *J Biomed Sci*. 2020;27(1):63. doi:10.1186/s12929-020-00658-7
49. Bombardieri M, Lewis M, Pitzalis C. Ectopic lymphoid neogenesis in rheumatic autoimmune diseases. *Nat Rev Rheumatol*. 2017;13(3):141–154. doi:10.1038/nrrheum.2016.217
50. Corsiero E, Nerviani A, Bombardieri M, Pitzalis C. Ectopic lymphoid structures: powerhouse of autoimmunity. *Front Immunol*. 2016;7:430. doi:10.3389/fimmu.2016.00430
51. Sarkar I, Davies R, Aarebrot AK, et al. Aberrant signaling of immune cells in Sjögren's syndrome patient subgroups upon interferon stimulation. *Front Immunol*. 2022;13:854183. doi:10.3389/fimmu.2022.854183
52. Verstappen GM, Kroese FG. A leading role for interferon as a treatment target in Sjögren syndrome. *Nat Rev Rheumatol*. 2023;19(8):468–469. doi:10.1038/s41584-023-00991-9
53. Mcbride DA, Jones RM, Bottini N, Shah NJ. The therapeutic potential of immunoengineering for systemic autoimmunity. *Nat Rev Rheumatol*. 2024;20(4):203–215. doi:10.1038/s41584-024-01084-x
54. Lee NK, Kim S-N, Park CG. Immune cell targeting nanoparticles: a review. *Biomater Res*. 2021;25(1):44. doi:10.1186/s40824-021-00246-2
55. Lu Q, Kou D, Lou S, et al. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. *J Hematol Oncol*. 2024;17(1):16.
56. Raju GSR, Pavitra E, Varaprasad GL, et al. Nanoparticles mediated tumor microenvironment modulation: current advances and applications. *J Nanobiotechnol*. 2022;20(1):274. doi:10.1186/s12951-022-01476-9
57. Bombardieri M, Pitzalis C. Ectopic lymphoid neogenesis and lymphoid chemokines in Sjogren's syndrome: at the interplay between chronic inflammation, autoimmunity and lymphomagenesis. *Current Pharm Biotechnol*. 2012;13(10):1989–1996. doi:10.2174/138920112802273209
58. Antonioli L, Fornai M, Pellegrini C, Masi S, Puxeddu I, Blandizzi C. Ectopic lymphoid organs and immune-mediated diseases: molecular basis for pharmacological approaches. *Trends Mol Med*. 2020;26(11):1021–1033. doi:10.1016/j.molmed.2020.06.004
59. Wei X, Niu X. T follicular helper cells in autoimmune diseases. *J Autoimmun*. 2023;134:102976. doi:10.1016/j.jaut.2022.102976
60. Gensous N, Charrier M, Duluc D, et al. T follicular helper cells in autoimmune disorders. *Front Immunol*. 2018;9:1637. doi:10.3389/fimmu.2018.01637

61. Lim ZFS, Hoi AY, Vincent FB, et al. Regulatory T cell therapy for Sjögren's disease: from pathogenesis to targeted treatment. *J Trans Autoimmun*. 2025;11:100311. doi:10.1016/j.jtauto.2025.100311
62. Ming B, Zhu Y, Zhong J, Dong L. Regulatory T cells: a new therapeutic link for Sjögren syndrome? *Rheumatology*. 2023;62(9):2963–2970. doi:10.1093/rheumatology/kead070
63. Saei A, Hadjati J. Tolerogenic dendritic cells: key regulators of peripheral tolerance in health and disease. *Int Arch Allergy Immunol*. 2013;161 (4):293–303. doi:10.1159/000350328
64. Maldonado RA, LaMothe RA, Ferrari JD, et al. Polymeric synthetic nanoparticles for the induction of antigen-specific immunological tolerance. *Proc Natl Acad Sci*. 2015;112(2):E156–E165. doi:10.1073/pnas.1408686111
65. Li H, Yang Y-G, Sun T. Nanoparticle-based drug delivery systems for induction of tolerance and treatment of autoimmune diseases. *Front Bioeng Biotechnol*. 2022;10:889291. doi:10.3389/fbioe.2022.889291
66. Jomova K, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch Toxicol*. 2024;98 (5):1323–1367. doi:10.1007/s00204-024-03696-4
67. Chen Y, Luo X, Deng C, et al. Immunometabolic alteration of CD4+ T cells in the pathogenesis of primary Sjögren's syndrome. *Clin Exp Med*. 2024;24(1):163. doi:10.1007/s10238-024-01429-6
68. Wei D, Sun Y, Zhu H, Fu Q. Stimuli-responsive polymer-based nanosystems for cancer theranostics. *ACS nano*. 2023;17(23):23223–23261. doi:10.1021/acsnano.3c06019
69. Meng X, Shen Y, Zhao H, Lu X, Wang Z, Zhao Y. Redox-manipulating nanocarriers for anticancer drug delivery: a systematic review. *J Nanobiotechnol*. 2024;22(1):587. doi:10.1186/s12951-024-02859-w
70. Liu J, Jia B, Li Z, Li W. Reactive oxygen species-responsive polymer drug delivery systems. *Front Bioeng Biotechnol*. 2023;11:1115603. doi:10.3389/fbioe.2023.1115603
71. Avgoustakis K, Angelopoulou A. Biomaterial-based responsive nanomedicines for targeting solid tumor microenvironments. *Pharmaceutics*. 2024;16(2):179. doi:10.3390/pharmaceutics16020179
72. Aljabali AA, Obeid MA, Gammoh O, et al. Nanomaterial-driven precision immunomodulation: a new paradigm in therapeutic interventions. *Cancers*. 2024;16(11):2030. doi:10.3390/cancers16112030
73. Pande S. Liposomes for drug delivery: review of vesicular composition, factors affecting drug release and drug loading in liposomes. *Artif Cells Nanomed Biotechnol*. 2023;51(1):428–440. doi:10.1080/21691401.2023.2247036
74. Bose RJ, Lee S-H, Park H. Lipid-based surface engineering of PLGA nanoparticles for drug and gene delivery applications. *Biomater Res*. 2016;20(1):34. doi:10.1186/s40824-016-0081-3
75. Wang J, Li B, Qiu L, Qiao X, Yang H. Dendrimer-based drug delivery systems: history, challenges, and latest developments. *J Biol Eng*. 2022;16(1):18. doi:10.1186/s13036-022-00298-5
76. Zewail MB, Doghish AS, El-Husseiny HM, et al. Lipid-based nanocarriers: an attractive approach for rheumatoid arthritis management. *Biomater Sci*. 2024;12(24):6163–6195. doi:10.1039/D4BM01058B
77. Gan J, Huang D, Che J, Zhao Y, Sun L. Biomimetic nanoparticles with cell-membrane camouflage for rheumatoid arthritis. *Matter*. 2024;7 (3):794–825. doi:10.1016/j.matt.2023.12.022
78. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov*. 2021;20(2):101–124. doi:10.1038/s41573-020-0090-8
79. Tu Z, Zhong Y, Hu H, et al. Design of therapeutic biomaterials to control inflammation. *Nature Rev Mater*. 2022;7(7):557–574. doi:10.1038/s41578-022-00426-z
80. Yoo J, Park C, Yi G, Lee D, Koo H. Active targeting strategies using biological ligands for nanoparticle drug delivery systems. *Cancers*. 2019;11(5):640. doi:10.3390/cancers11050640
81. Álvarez K, Rojas M. Nanoparticles targeting monocytes and macrophages as diagnostic and therapeutic tools for autoimmune diseases. *Heliyon*. 2023;9(9):e19861. doi:10.1016/j.heliyon.2023.e19861
82. Cui X, Liu L, Duan C, et al. A review of the roles of exosomes in salivary gland diseases with an emphasis on primary Sjögren's syndrome. *J Dental Sci*. 2025;20(1):1–14. doi:10.1016/j.jds.2024.10.001
83. Gulfam M, Sahle FF, Lowe TL. Design strategies for chemical-stimuli-responsive programmable nanotherapeutics. *Drug Discovery Today*. 2019;24(1):129–147. doi:10.1016/j.drudis.2018.09.019
84. Liu G, Lovell JF, Zhang L, Zhang Y. Stimulus-responsive nanomedicines for disease diagnosis and treatment. *Int J Mol Sci*. 2020;21(17):6380. doi:10.3390/ijms21176380
85. Tang B, Xie X, Lu J, et al. Designing biomaterials for the treatment of autoimmune diseases. *Appl Mater Today*. 2024;39:102278.
86. Egbuna C, Parmar VK, Jeevanandam J, et al. Toxicity of nanoparticles in biomedical application: nanotoxicology. *J Toxicol*. 2021;2021 (1):9954443. doi:10.1155/2021/9954443
87. Inglut CT, Sorrin AJ, Kuruppu T, et al. Immunological and toxicological considerations for the design of liposomes. *Nanomaterials*. 2020;10 (2):190. doi:10.3390/nano10020190
88. El-Hammadi MM, Arias JL. Recent advances in the surface functionalization of PLGA-based nanomedicines. *Nanomaterials*. 2022;12(3):354. doi:10.3390/nano12030354
89. Li J, Li W, Zhuang L. Natural biomimetic nano-system for drug delivery in the treatment of rheumatoid arthritis: a literature review of the last 5 years. *Front Med*. 2024;11:1385123. doi:10.3389/fmed.2024.1385123
90. Huijser E, Versnel MA. Making sense of intracellular nucleic acid sensing in type I interferon activation in Sjögren's syndrome. *J Clin Med*. 2021;10(3):532. doi:10.3390/jcm10030532
91. Nasrullah M, Meenakshi Sundaram DN, Claerhout J, Ha K, Demirkaya E, Uludag H. Nanoparticles and cytokine response. *Front Bioeng Biotechnol*. 2023;11:1243651. doi:10.3389/fbioe.2023.1243651
92. Liu J, Liu Z, Pang Y, Zhou H. The interaction between nanoparticles and immune system: application in the treatment of inflammatory diseases. *J Nanobiotechnol*. 2022;20(1):127. doi:10.1186/s12951-022-01343-7
93. Kiaie SH, Majidi Zolbanin N, Ahmadi A, et al. Recent advances in mRNA-LNP therapeutics: immunological and pharmacological aspects. *J Nanobiotechnol*. 2022;20(1):276. doi:10.1186/s12951-022-01478-7

94. An Q, Zhao J, Zhu X, et al. Exploiting the role of T cells in the pathogenesis of Sjögren's syndrome for therapeutic treatment. *Front Immunol*. 2022;13:995895. doi:10.3389/fimmu.2022.995895
95. Yousefpour P, Ni K, Irvine DJ. Targeted modulation of immune cells and tissues using engineered biomaterials. *Nature Rev Bioengineer*. 2023;1 (2):107–124. doi:10.1038/s44222-022-00016-2
96. Mao K, Wang J, Xie Q, et al. Cationic nanoparticles-based approaches for immune tolerance induction in vivo. *J Control Release*. 2024;366:425–447. doi:10.1016/j.jconrel.2023.12.044
97. Clarke J. New hope for B cell-targeting therapy in pSS. *Nat Rev Rheumatol*. 2022;18(2):61. doi:10.1038/s41584-021-00740-w
98. Parodis I, Gatto M, Sjöwall C. B cells in systemic lupus erythematosus: targets of new therapies and surveillance tools. *Front Med*. 2022;9:952304. doi:10.3389/fmed.2022.952304
99. Wang J, Yang J, Kopeček J. Nanomedicines in B cell-targeting therapies. *Acta Biomater*. 2022;137:1–19. doi:10.1016/j.actbio.2021.10.024
100. Cifuentes-Rius A, Desai A, Yuen D, Johnston AP, Voelcker NH. Inducing immune tolerance with dendritic cell-targeting nanomedicines. *Nature Nanotechnol*. 2021;16(1):37–46. doi:10.1038/s41565-020-00810-2
101. Burke JA, Zhang X, Bobbala S, et al. Subcutaneous nanotherapy repurposes the immunosuppressive mechanism of rapamycin to enhance allogeneic islet graft viability. *Nature Nanotechnol*. 2022;17(3):319–330. doi:10.1038/s41565-021-01048-2
102. Liu J, Li Y, Chen S, et al. Biomedical application of reactive oxygen species–responsive nanocarriers in cancer, inflammation, and neurodegenerative diseases. *Front Chem*. 2020;8:838. doi:10.3389/fchem.2020.00838
103. Joshi-Barr S, de Gracia Lux C, Mahmoud E, Almutairi A. Exploiting oxidative microenvironments in the body as triggers for drug delivery systems. *Antioxid Redox Signaling*. 2014;21(5):730–754. doi:10.1089/ars.2013.5754
104. Hsu P-H, Almutairi A. Recent progress of redox-responsive polymeric nanomaterials for controlled release. *J Mat Chem B*. 2021;9 (9):2179–2188. doi:10.1039/D0TB02190C
105. Rius-Pérez S, Pérez S, Martí-Andrés P, Monsalve M, Sastre J. Nuclear factor kappa B signaling complexes in acute inflammation. *Antioxid Redox Signaling*. 2020;33(3):145–165. doi:10.1089/ars.2019.7975
106. Repellin M, Guerin H, Catania G, Lollo G. ROS-based nanomedicines for anti-inflammatory therapies. *Redox Experi Med*. 2023;2023(1). doi:10.1530/REM-23-0021
107. Huang X, He D, Pan Z, Luo G, Deng J. Reactive-oxygen-species-scavenging nanomaterials for resolving inflammation. *Mater Today Bio*. 2021;11:100124.
108. Huang Y, Guo X, Wu Y, et al. Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. *Signal Transduct Target Ther*. 2024;9(1):34.
109. Mirchandani AS, Sanchez-Garcia MA, Walmsley SR. How oxygenation shapes immune responses: emerging roles for physioxia and pathological hypoxia. *Nat Rev Immunol*. 2025;25(3):161–177.
110. Gong X, Yang S-Y, Wang Z-Y, Tang M. The role of hypoxic microenvironment in autoimmune diseases. *Front Immunol*. 2024;15:1435306.
111. Yang Z, Shi C, Cheng D, et al. Biomimetic nanomaterial-facilitated oxygen generation strategies for enhancing tumour treatment outcomes. *Front Bioeng Biotechnol*. 2022;10:1007960. doi:10.3389/fbioe.2022.1007960
112. Zhang R, Jiang B, Fan K, Gao L, Yan X. Designing nanozymes for in vivo applications. *Nature Rev Bioengineer*. 2024;2(10):849–868.
113. Cao W, Jin M, Yang K, et al. Fenton/Fenton-like metal-based nanomaterials combine with oxidase for synergistic tumor therapy. *J Nanobiotechnol*. 2021;19(1):325. doi:10.1186/s12951-021-01074-1
114. Ren X, Chen D, Wang Y, et al. Nanozymes-recent development and biomedical applications. *J Nanobiotechnol*. 2022;20(1):92. doi:10.1186/s12951-022-01295-y
115. Taylor CT, Colgan SP. Regulation of immunity and inflammation by hypoxia in immunological niches. *Nat Rev Immunol*. 2017;17 (12):774–785. doi:10.1038/nri.2017.103
116. Saleem M, Shahzad KA, Marryum M, et al. Exosome-based therapies for inflammatory disorders: a review of recent advances. *Stem Cell Res Ther*. 2024;15(1):477. doi:10.1186/s13287-024-04107-2
117. Xu K, Liu Q, Wu K, et al. Extracellular vesicles as potential biomarkers and therapeutic approaches in autoimmune diseases. *J Transl Med*. 2020;18(1):432. doi:10.1186/s12967-020-02609-0
118. Duan W, Zhang W, Jia J, Lu Q, Eric Gershwin M. Exosomal microRNA in autoimmunity. *Cell Mol Immunol*. 2019;16(12):932–934. doi:10.1038/s41423-019-0319-9
119. Zheng A, Liu H, Yin G, Xie Q. Macrophage-derived exosomes in autoimmune diseases: mechanistic insights and therapeutic implications. *Immunol Res*. 2025;73(1):171. doi:10.1007/s12026-025-09723-5
120. Mori T, Giovannelli L, Bilia AR, Margheri F. Exosomes: potential next-generation nanocarriers for the therapy of inflammatory diseases. *Pharmaceutics*. 2023;15(9):2276. doi:10.3390/pharmaceutics15092276
121. Saadh MJ, Allela OQB, Al-Hussainy AF, et al. Exosomal non-coding RNAs: gatekeepers of inflammation in autoimmune disease. *J Inflam*. 2025;22(1):18. doi:10.1186/s12950-025-00443-z
122. Mirzaei R, Zamani F, Hajibaba M, et al. The pathogenic, therapeutic and diagnostic role of exosomal microRNA in the autoimmune diseases. *J Neuroimmunol*. 2021;358:577640. doi:10.1016/j.jneuroim.2021.577640
123. Ji Y, Mi L, Zhao M, et al. Innovative diagnosis and therapeutic modalities: engineered exosomes in autoimmune disease. *Int J Nanomed*. 2024;19:3943–3956. doi:10.2147/IJN.S452184
124. Huang Y, Li R, Ye S, Lin S, Yin G, Xie Q. Recent advances in the use of exosomes in Sjögren's syndrome. *Front Immunol*. 2020;11:1509. doi:10.3389/fimmu.2020.01509
125. Li N, Li Y, Hu J, et al. A link between mitochondrial dysfunction and the immune microenvironment of salivary glands in primary Sjogren's syndrome. original research. *Front Immunol*. 2022;13. doi:10.3389/fimmu.2022.845209
126. Tang X, Hu J, Fan X, et al. Salivary gland cell senescence in Sjögren's syndrome: current research and novel therapeutic directions. *Immunity Ageing*. 2025;22(1):45. doi:10.1186/s12979-025-00541-9
127. Zhou J, Pathak JL, Liu Q, et al. Modes and mechanisms of salivary gland epithelial cell death in Sjogren's syndrome. *Adv Biol*. 2023;7 (12):2300173. doi:10.1002/adbi.202300173
128. Lee J, Roh J-L. Ferroptosis in salivary gland disorders: mechanisms, biomarkers, and therapeutic perspectives. *Apoptosis*. 2026;31(2):70. doi:10.1007/s10495-026-02285-3

129. Bairagi RD, Reon RR, Hasan MM, et al. Ocular drug delivery systems based on nanotechnology: a comprehensive review for the treatment of eye diseases. *Discover Nano*. 2025;20(1):75. doi:10.1186/s11671-025-04234-6
130. Silva AM, Siopa JR, Martins-Gomes C, et al. Chapter 6 - new strategies for the treatment of autoimmune diseases using nanotechnologies. In: Shegokar R, Souto EB, editors. *Emerging Nanotechnologies in Immunology*. Elsevier; 2018. 135–163.
131. Wen J, Moloney EB, Canning A, et al. Synthesized nanoparticles, biomimetic nanoparticles and extracellular vesicles for treatment of autoimmune disease: comparison and prospect. *Pharmacol Res*. 2021;172:105833. doi:10.1016/j.phrs.2021.105833
132. Singh AP, Biswas A, Shukla A, Maiti P. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. *Signal Transduct Target Ther*. 2019;4(1):33. doi:10.1038/s41392-019-0068-3
133. Nasra S, Bhatia D, Kumar A. Recent advances in nanoparticle-based drug delivery systems for rheumatoid arthritis treatment. *Nanoscale Adv*. 2022;4(17):3479–3494. doi:10.1039/D2NA00229A
134. Cai R, Zhang L, Chi H. Recent development of polymer nanomicelles in the treatment of eye diseases. *Front Bioeng Biotechnol*. 2023;11:1246974. doi:10.3389/fbioe.2023.1246974
135. Sahu DK, Pradhan D, Biswasroy P, Kar B, Ghosh G, Rath G. Recent trends in nanocarrier based approach in the management of dry eye disease. *J Drug Delivery Sci Technol*. 2021;66:102868. doi:10.1016/j.jddst.2021.102868
136. Farjadian F, Ghasemi S, Akbarian M, Hoseini-Ghahfarokhi M, Moghoofei M, Doroudian M. Physically stimulus-responsive nanoparticles for therapy and diagnosis. *Front Chem*. 2022;10:952675. doi:10.3389/fchem.2022.952675
137. Afarid M, Mahmoodi S, Baghban R. Recent achievements in nano-based technologies for ocular disease diagnosis and treatment, review and update. *J Nanobiotechnol*. 2022;20(1):361. doi:10.1186/s12951-022-01567-7
138. Hameed S, Bhattarai P, Dai Z. Cerasomes and bicelles: hybrid bilayered nanostructures with silica-like surface in cancer theranostics. *Front Chem*. 2018;6:127. doi:10.3389/fchem.2018.00127
139. Maccarone R, Tisi A, Passacantando M, Ciancaglini M. Ophthalmic applications of cerium oxide nanoparticles. *J Ocul Pharmacol Ther*. 2020;36(6):376–383. doi:10.1089/jop.2019.0105
140. Lord MS, Berret JF, Singh S, Vinu A, Karakoti AS. Redox active cerium oxide nanoparticles: current status and burning issues. *Small*. 2021;17(51):2102342. doi:10.1002/smll.202102342
141. Baldim V, Yadav N, Bia N, et al. Polymer-coated cerium oxide nanoparticles as oxidoreductase-like catalysts. *ACS Appl Mater Interfaces*. 2020;12(37):42056–42066. doi:10.1021/acsami.0c08778
142. Fang RH, Gao W, Zhang L. Targeting drugs to tumours using cell membrane-coated nanoparticles. *Nat Rev Clin Oncol*. 2023;20(1):33–48. doi:10.1038/s41571-022-00699-x
143. Kroll AV, Fang RH, Zhang L. Biointerfacing and applications of cell membrane-coated nanoparticles. *Bioconjugate Chem*. 2017;28(1):23–32. doi:10.1021/acs.bioconjchem.6b00569
144. Tian B, Li Q, Chang B, Zhao S. Bioengineered anti-EpCAM–guided exosome nanocarriers delivering Foxp3 agonist butyrate achieve tissue-specific immunomodulation in autoimmune Sjögren's syndrome. *J Nanobiotechnol*. 2026;24(1):546. doi:10.1186/s12951-026-04373-7
145. Shah M, Edman MC, Janga SR, et al. A rapamycin-binding protein polymer nanoparticle shows potent therapeutic activity in suppressing autoimmune dacryoadenitis in a mouse model of Sjögren's syndrome. *J Control Release*. 2013;171(3):269–279. doi:10.1016/j.jconrel.2013.07.016
146. Garrós N, Mallandrich M, Beirampour N, et al. Baricitinib liposomes as a new approach for the treatment of Sjögren's syndrome. *Pharmaceutics*. 2022;14(9):1895. doi:10.3390/pharmaceutics14091895
147. Thanuja M, Ranganath SH, Bonanno JA, Srinivas SP. Nanoliposomes for sensing local osmolarity of the tear film on the corneal surface. *J Ocul Pharmacol Ther*. 2022;38(8):549–560. doi:10.1089/jop.2022.0044
148. Peng X, Hou L, Wu X, et al. The plasma exosomes from patients with primary Sjögren's syndrome contain epithelial cell–derived proteins involved in ferroptosis. *J Mol Med*. 2023;101(10):1289–1304. doi:10.1007/s00109-023-02361-0
149. Prencipe G, Tabakman SM, Welsher K, et al. PEG branched polymer for functionalization of nanomaterials with ultralong blood circulation. *J Am Chem Soc*. 2009;131(13):4783–4787. doi:10.1021/ja809086q
150. Rui K, Hong Y, Zhu Q, et al. Olfactory ecto-mesenchymal stem cell-derived exosomes ameliorate murine Sjögren's syndrome by modulating the function of myeloid-derived suppressor cells. *Cell Mol Immunol*. 2021;18(2):440–451. doi:10.1038/s41423-020-00587-3
151. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. *Pharmaceutics*. 2017;9(2):12. doi:10.3390/pharmaceutics9020012
152. Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. *Molecules*. 2022;27(4). doi:10.3390/molecules27041372
153. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. *J Control Release*. 2012;161(2):505–522. doi:10.1016/j.jconrel.2012.01.043
154. Marquina S, Ozgul M, Robertson-Brown K, Kenney MC. A review on PLGA particles as a sustained drug-delivery system and its effect on the retina. *Exp Eye Res*. 2023;235:109626. doi:10.1016/j.exer.2023.109626
155. Koh HB, Kim HJ, Kang SW, Yoo TH. Exosome-Based drug delivery: translation from bench to clinic. *Pharmaceutics*. 2023;15(8):2042. doi:10.3390/pharmaceutics15082042
156. Serrano DR, Juste F, Anaya BJ, et al. Exosome-Based drug delivery: a next-generation platform for cancer, infection, neurological and immunological diseases, gene therapy and regenerative medicine. *Pharmaceutics*. 2025;17(10):1336. doi:10.3390/pharmaceutics17101336
157. Das S, Dowding JM, Klump KE, McGinnis JF, Self W, Seal S. Cerium oxide nanoparticles: applications and prospects in nanomedicine. *Nanomedicine*. 2013;8(9):1483–1508. doi:10.2217/nnm.13.133
158. Rajeshkumar S, Naik P. Synthesis and biomedical applications of Cerium oxide nanoparticles - A Review. *Biotechnol Rep*. 2018;17:1–5. doi:10.1016/j.btre.2017.11.008
159. Liu J, Du C, Huang W, Lei Y. Injectable smart stimuli-responsive hydrogels: pioneering advancements in biomedical applications. *Biomater Sci*. 2024;12(1):8–56.
160. Mohapatra S, Mirza MA, Hilles AR, et al. Biomedical application, patent repository, clinical trial and regulatory updates on hydrogel: an extensive review. *Gels*. 2021;7(4):207. doi:10.3390/gels7040207

161. Qi W, Tian J, Wang G, et al. Advances in cellular and molecular pathways of salivary gland damage in Sjögren's syndrome. *Front Immunol*. 2024;15:1405126. doi:10.3389/fimmu.2024.1405126
162. Ma D, Feng Y, Lin X. Immune and non-immune mediators in the fibrosis pathogenesis of salivary gland in Sjögren's syndrome. *Front Immunol*. 2024;15:1421436. doi:10.3389/fimmu.2024.1421436
163. Byun J-S. Role of homeostatic changes in salivary gland acinar cells in primary Sjögren's syndrome: a review. *J Oral Med Pain*. 2023;48 (2):39–44. doi:10.14476/jomp.2023.48.2.39
164. Su H, Fan X, Nie C, et al. A narrative review of salivary gland extracellular matrix and Sjögren's syndrome: research status and future prospects. *Biomolecules*. 2026;16(1):72. doi:10.3390/biom16010072
165. Wang L, Zhou Y, Wu M, et al. Functional nanocarrier for drug and gene delivery via local administration in mucosal tissues. *Nanomedicine*. 2018;13(1):69–88. doi:10.2217/nnm-2017-0143
166. Dong Y, Wang T, Wu H. The role of cytokines from salivary gland epithelial cells in the immunopathology of Sjögren's syndrome. *Front Immunol*. 2024;15:1443455. doi:10.3389/fimmu.2024.1443455
167. Park H-S, Martínez-Martínez L, Magallares López B, et al. Prognostic significance of lymphocytic foci composition in minor salivary gland biopsies for severe disease flare and severity in Sjögren's syndrome: a 3-year follow-up cohort study. *Front Immunol*. 2024;15:1332924. doi:10.3389/fimmu.2024.1332924
168. Yura Y, Hamada M. Outline of salivary gland pathogenesis of Sjögren's syndrome and current therapeutic approaches. *Int J Mol Sci*. 2023;24 (13):11179. doi:10.3390/ijms241311179
169. Hou J, Feng Y, Yang Z, et al. Primary Sjögren's syndrome: new perspectives on salivary gland epithelial cells. *Eur J Med Res*. 2024;29(1):371. doi:10.1186/s40001-024-01967-5
170. Yang T, Goudarzi N, Kroese FG, Mariette X, Pringle S, Nocturne G. Salivary gland organoids and the future of modeling autoimmune epithelitis in Sjögren's disease. *Curr Opinion Immunol*. 2026;98:102707. doi:10.1016/j.coi.2025.102707
171. Zhao C, Meng C, Cui N, Sha J, Sun L, Zhu D. Organoid models for salivary gland biology and regenerative medicine. *Stem Cells International*. 2021;2021(1):9922597. doi:10.1155/2021/9922597
172. Almansoori AA, Kim B, Lee J-H, Tran SD. Tissue engineering of oral mucosa and salivary gland: disease modeling and clinical applications. *Micromachines*. 2020;11(12):1066. doi:10.3390/mi11121066
173. 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 Therapy*. 2015;17(1):172. doi:10.1186/s13075-015-0678-2
174. 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(1):35–44. doi:10.1007/s12016-011-8288-5
175. Langthasa J, Guan L, Jinagal SL, Le Q-T. Salivary gland stem/progenitor cells: advancing from basic science to clinical applications. *Cell Regener*. 2025;14(1):4. doi:10.1186/s13619-025-00221-5
176. Fan X, Su H, Tang X, et al. Prospects and challenges of salivary gland tissue engineering in Sjögren's syndrome. *Exp Rev Mol Med*;2025. 1–44. doi:10.1017/erm.2025.10017
177. Harrison C. Patent watch. *Nat Rev Drug Discov*. 2013;12(4):256–257. doi:10.1038/nrd3995
178. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. *Nature Rev Mater*. 2016;1(5):16014. doi:10.1038/natrevmats.2016.14
179. Gandolfo S, Bombardieri M, Pers J-O, Mariette X, Ciccia F. Precision medicine in Sjögren's disease. *Lancet Rheumatol*. 2024;6(9):e636–e647. doi:10.1016/S2665-9913(24)00039-0
180. Gupta N, Shaik AR, Chettupalli AK, Bukke SPN, Goruntla N. Nanomedicine for the management of rheumatoid arthritis: current status and prospective therapeutic approaches. *Discover Med*. 2025;2(1):111. doi:10.1007/s44337-025-00316-7
181. Barakat M, Ershaid JMA, Alzaghari L, et al. Nanotechnology-Based therapies for autoimmune diseases; 2025.
182. Menegatti S, Lopez-Cobo S, Sutra Del Galy A, et al. Ablation of FAS confers allogeneic CD3–CAR T cells with resistance to rejection by T cells and natural killer cells. *Nat Biomed Eng*. 2024;8(12):1651–1664. doi:10.1038/s41551-024-01282-8
183. Rossi G, Manfrin A, Lutolf MP. Progress and potential in organoid research. *Nat Rev Genet*. 2018;19(11):671–687. doi:10.1038/s41576-018-0051-9
184. Drost J, Clevers H. Organoids in cancer research. *Nat Rev Cancer*. 2018;18(7):407–418. doi:10.1038/s41568-018-0007-6
185. Dion MZ, Artzi N. Polypeptide agonists of innate immune sensors. *Nat Biomed Eng*. 2024;8(5):495–496. doi:10.1038/s41551-024-01212-8
186. Saraux A, Nowak E, Devauchelle-Pensec V. Treatment of primary Sjögren syndrome with rituximab. *Ann Internal Med*. 2014;161(5):377–378. doi:10.7326/L14-5017-4
187. Jousse-Joulin S, Devauchelle-Pensec V, Cornec D, et al. Brief report: ultrasonographic assessment of salivary gland response to rituximab in primary Sjögren's syndrome. *Arthritis Rheumatol*. 2015;67(6):1623–1628. doi:10.1002/art.39088
188. Eidell KP, Hemann MT. FAS-less allogeneic CAR T cells. *Nat Biomed Eng*. 2024;8(12):1518–1520. doi:10.1038/s41551-024-01319-y