The Critical Role of B Cells and BAFF in Sjögren's Disease Pathogenesis

Featuring expert insights from

Alfred Kim, MD, PhD

> ***Modulating the pathogenic effects of hyperactive B cells and dysregulated BAFF levels may be the most effective approach to modifying systemic disease processes. By restoring B-cell homeostasis, this method could safely reduce the symptom burden and improve quality of life in patients with Sjögren's disease by targeting the root cause of systemic disease pathogenesis.***
>
> —Alfred Kim, MD, PhD

Dr Kim was compensated for his time by Novartis Pharmaceuticals Corporation.

Sjögren's is a systemic disease that can be progressive with no approved therapies to target its pathogenesis or progression[1–4]

Most current treatments help to manage the condition, but they do not stop the progression of the disease. These treatments feel like 'band-aid' solutions because they merely mask the symptoms…I hope that new treatments will target the root cause and the systemic nature of the disease, so we're not just addressing the symptoms but actually treating the disease itself.

—Paula, Real Patient With Sjögren's Disease

Paula was compensated for her time by Novartis Pharmaceuticals Corporation.

97% of patients report wanting more treatment options[5,*]

Patients often have to rely on "borrowed" immunosuppressive treatments, such as hydroxychloroquine, belimumab, and rituximab, which are not specifically approved for the systemic manifestations of Sjögren's disease.[2,4,6]

Current symptomatic treatments primarily manage symptoms such as dry mouth and eyes without altering disease progression. As the disease affects internal organs, nonspecific therapies are used, albeit with limited data. Symptom relief does not change the disease course, allowing progression and affecting quality of life.

—Alfred Kim, MD, PhD

*Based on the "Living with Sjögren's disease" survey assessing demographics, symptoms, quality of life, cost, and treatment in adult patients with Sjögren's disease (N=2961), includes respondents that "somewhat agreed" or "strongly agreed."

The critical role of B cells in Sjögren's disease[7-10]

B-cell hyperactivity plays a key role in systemic inflammation among patients with Sjögren's disease[7,8,10-13]

Sjögren's disease involves more than just dryness—its core pathology is thought to include **perpetual activation of B cells, with B-cell activating factor (BAFF) signaling** (Figure 1) contributing to a pathological cycle of immune activation, **which may lead to chronic inflammation and potential irreversible tissue destruction.**[8-12]

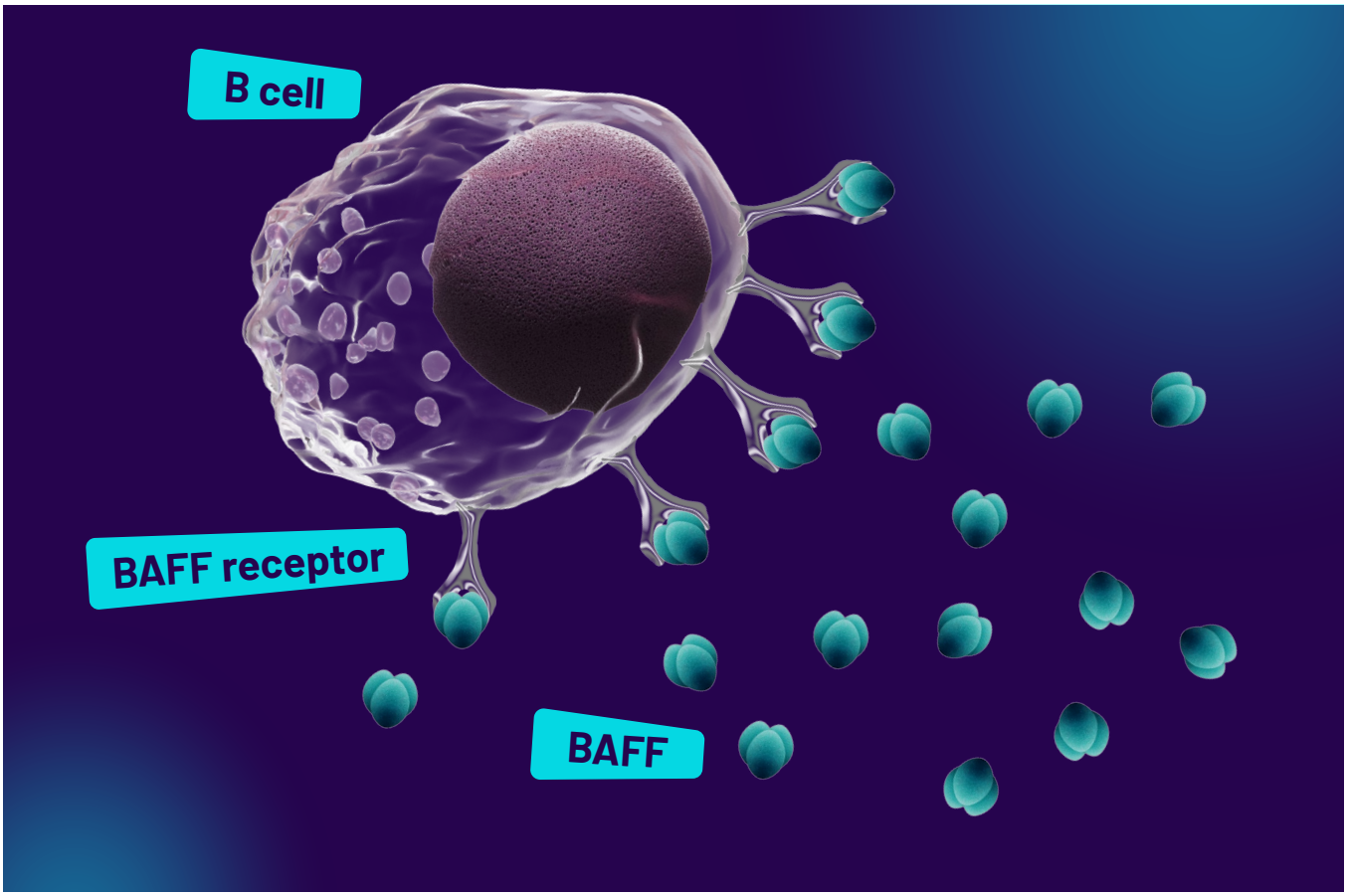


Figure 1 B cells are maintained by activating factors, including BAFF.[11]

B-cell dysfunction may be triggered by environmental factors[14,15]

Activation of epithelial cells contributes to the autoantibody-mediated B-cell hyperactivity characteristic of Sjögren's disease[14,15]

Dysregulation of the innate immune system may occur years before clinical symptoms of Sjögren's appear.[6] As epithelial cells form the first line of defense against external pathogens, they play a crucial role in immunity.[16,17]

Once activated by an environmental trigger like a virus (Figure 2), epithelial and immune cells in susceptible individuals may release numerous chemokines and proinflammatory cytokines, including BAFF.[12,16] **Activated epithelial cells release autoantigens, such as SSA/Ro and SSB/La, that trigger an autoimmune response initially in the salivary glands and may later affect other organ systems, including the skin, joints, and lymph nodes.**[12,18]

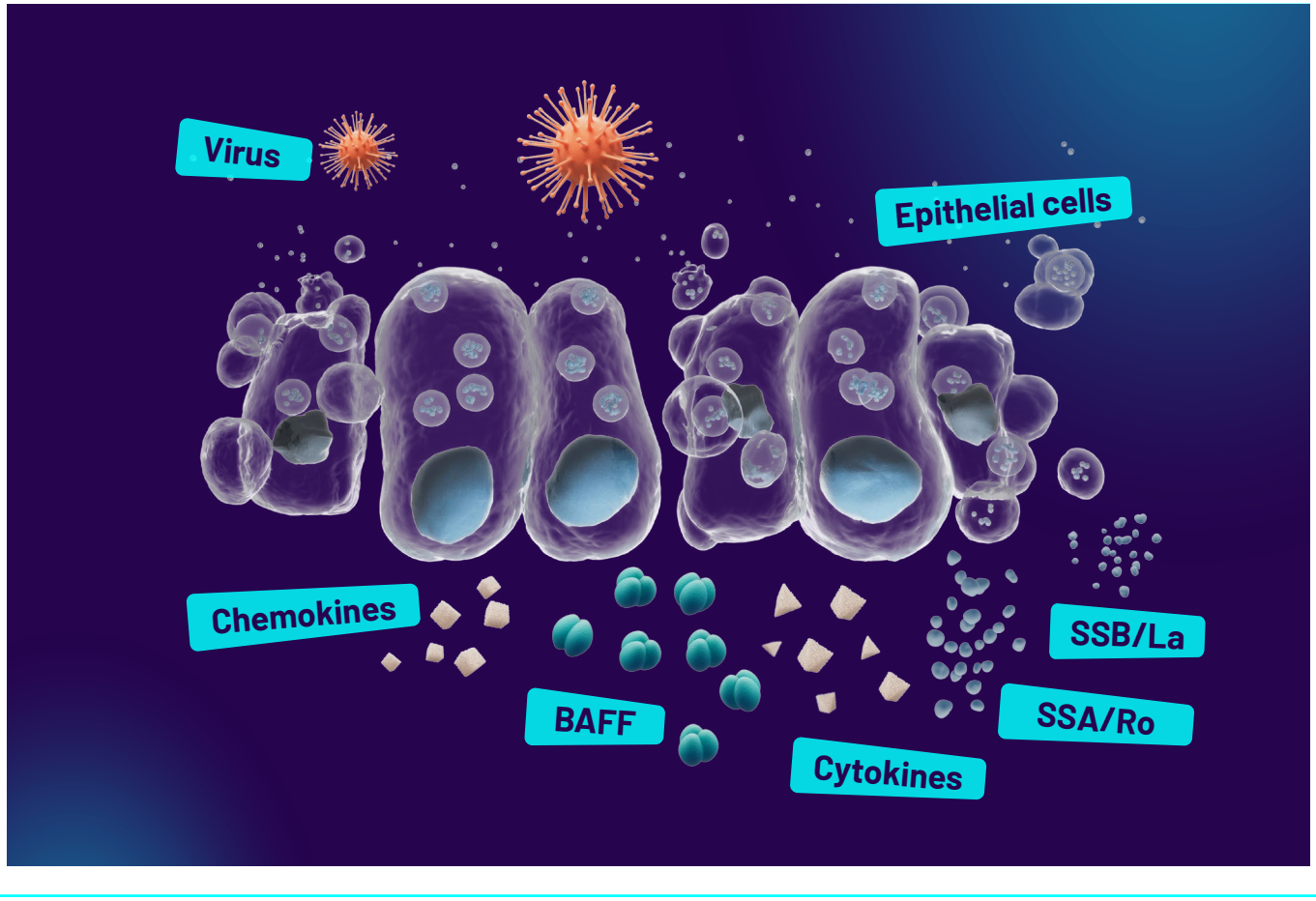


Figure 2 Epithelial and immune cell activation leads to the release of numerous chemokines and proinflammatory cytokines.[14,16]

SSA, Sjögren's syndrome antigen A; SSB, Sjögren's syndrome antigen B.

BAFF is central to B-cell survival and activation[6,14]

B-cell maturation starts in the bone marrow, where B cells are initially developed. Immature naive B cells then exit the bone marrow to complete their maturation in secondary lymphoid tissues. Normally, autoreactive B cells are eliminated through immune tolerance processes to prevent autoimmunity.[10,12]

Maintaining B-cell tolerance is crucial to prevent antibodies from targeting self-proteins. However, **elevated levels of BAFF allow autoreactive B cells, which should otherwise be eliminated, to survive.** Central and peripheral mechanisms are vital for B-cell tolerance, and their disruption can lead to autoimmune diseases, like Sjögren's disease.[10]

In addition to B cells, other immune cells, such as T cells, also play a role in the pathogenesis of Sjögren's, contributing to an autoimmune cascade and chronic inflammation (Figure 3).[12,19]

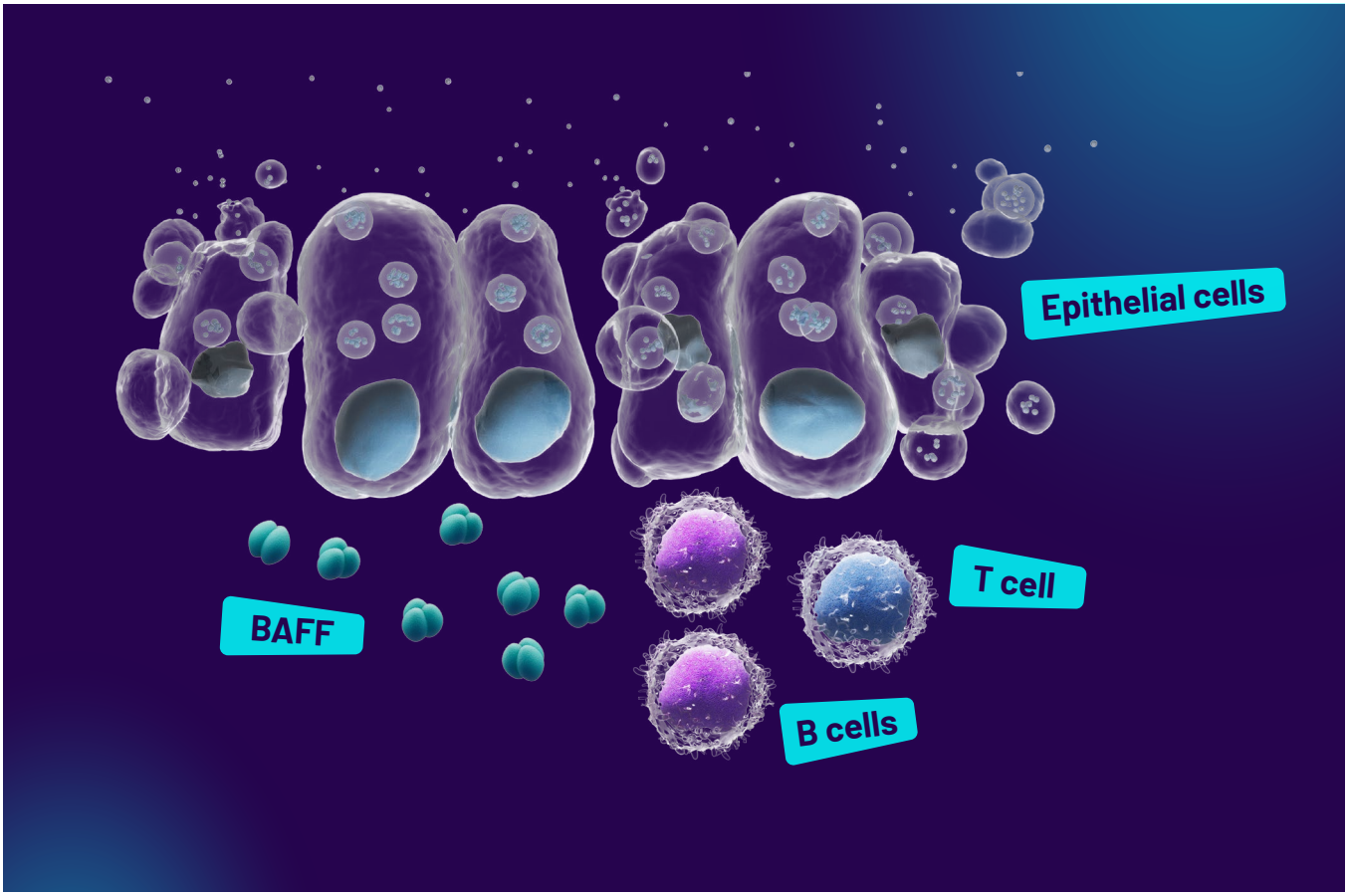


Figure 3 The inflamed tissue environment and release of BAFF attracts and promotes the proliferation of immune cells.[6,16]

Ectopic germinal centers promote chronic activation of B cells[16]

Ectopic germinal centers facilitate the proliferation and differentiation of mature B cells[14,16]

Immune cell gatherings in secondary lymphoid tissues form "germinal centers," promoting B-cell proliferation and differentiation. When such clusters form outside these tissues, like in salivary and lacrimal glands, they are often referred to as "germinal center–like structures" or "ectopic germinal centers" (Figure 4).[14,16] These centers can disrupt gland function. Additionally, elevated BAFF levels can lead to persistent B-cell activation, **boosting autoantibody production and immune complex formation, which may contribute to extraglandular manifestations.**[10]

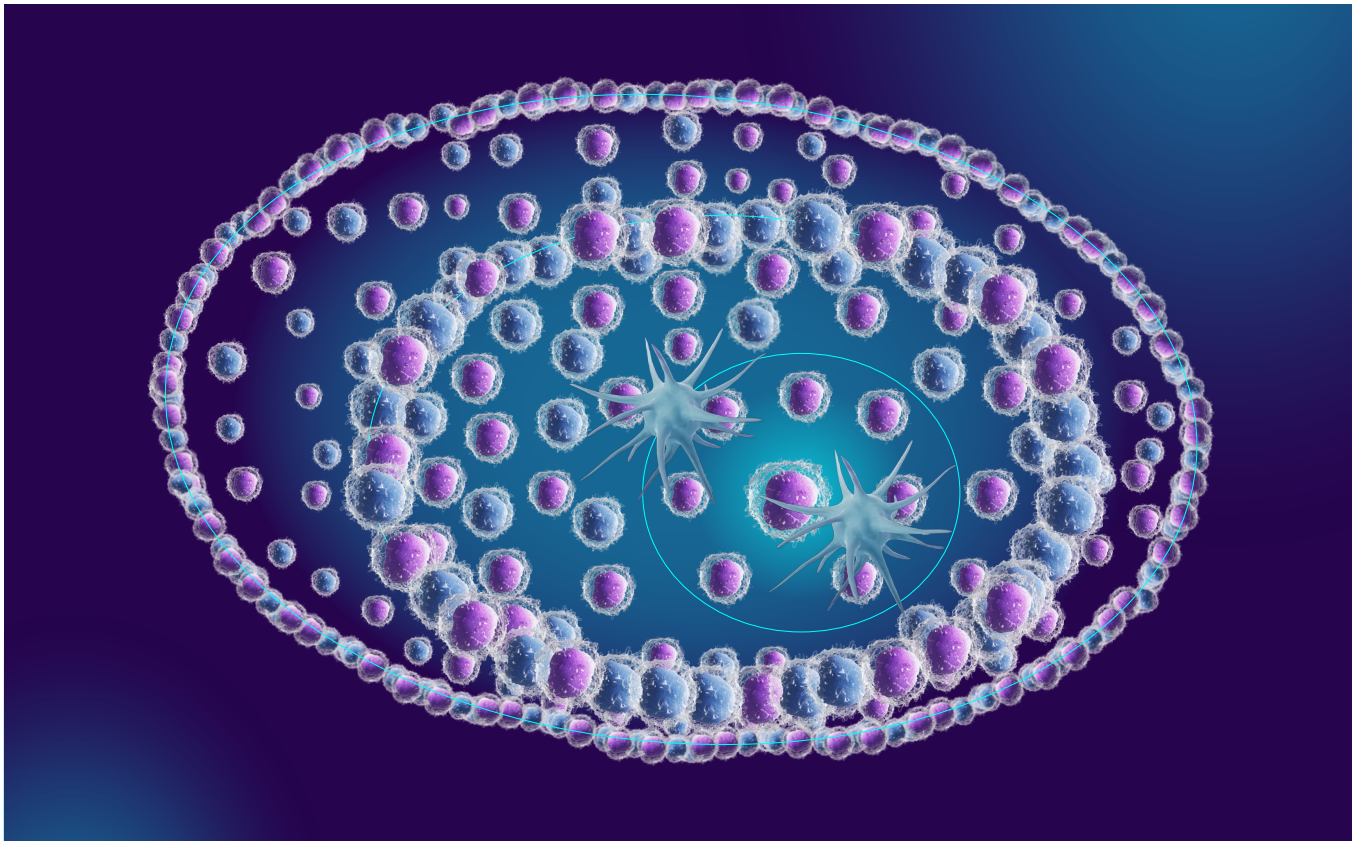


Figure 4 Clusters of immune cells, including B cells, T cells, macrophages, and follicular dendritic cells, lead to the formation of "ectopic germinal centers."[12,14]

> ***Ectopic germinal centers play a role in Sjögren's disease by perpetuating B-cell dysfunction.***
>
> —Alfred Kim, MD, PhD

BAFF bridges the innate and adaptive immune systems and is key to supporting B-cell survival and activation[11]

By binding to receptors on B-cell subtypes, BAFF enhances the proliferation and differentiation of B cells into memory B cells and plasmablasts[11,20]

Activation of BAFF receptors (BAFF-R) extends B-cell lifespan by regulating survival functions such as protein synthesis and energy metabolism.[20] Elevated levels of BAFF also have been shown to correlate with persistent autoantibodies—a key factor in tissue damage in Sjögren's disease.[11] **Inhibition of BAFF receptors could provide effective and sustained B-cell modulation, offering therapeutic potential against the autoantibody-driven damage in Sjögren's disease**.[7,21]

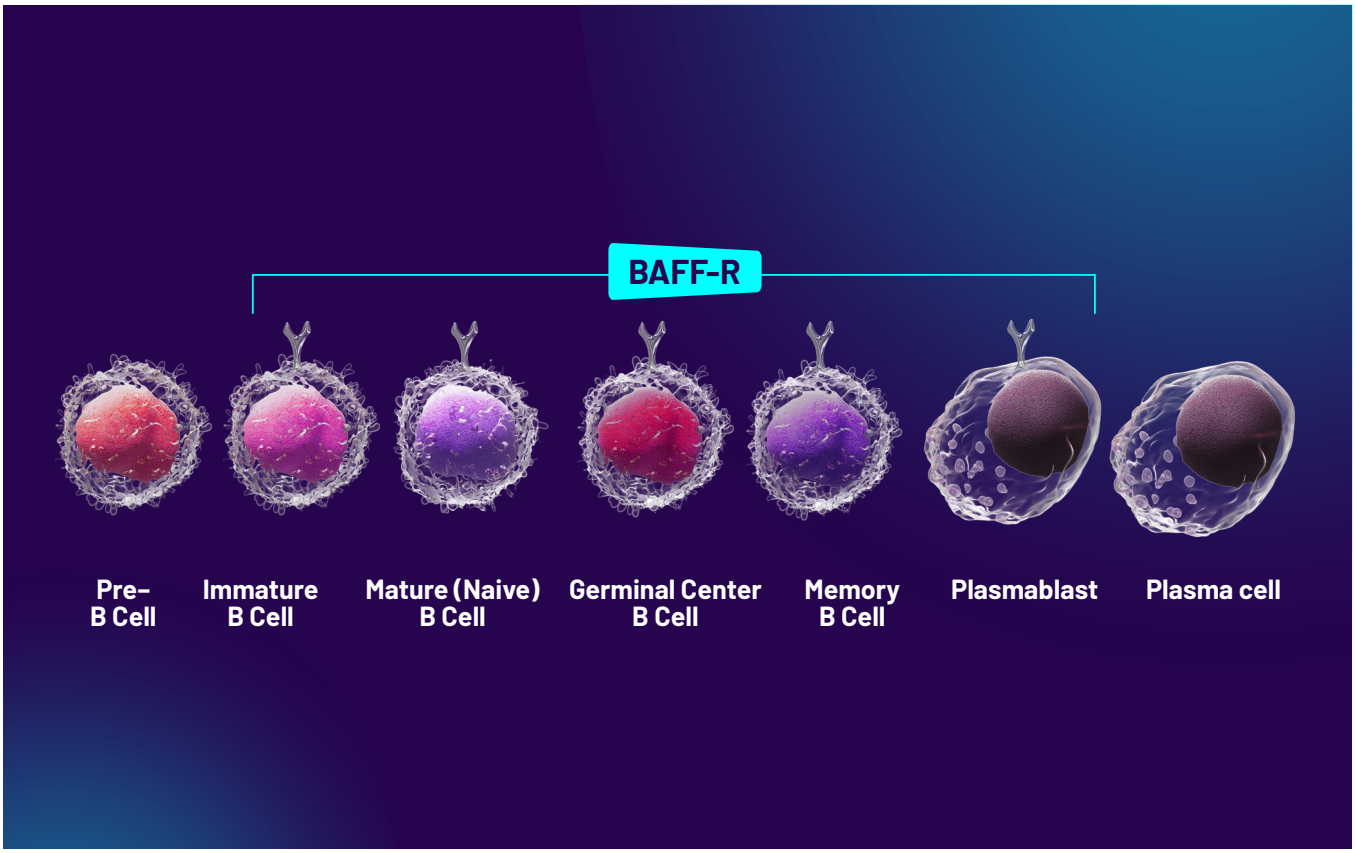


Figure 5 Expression of cell-surface antigens throughout B-cell maturation.[22]

Elevated levels of BAFF support B-cell survival and hyperactivity, further advancing disease progression[11,23]

Hyperactive B cells are responsible for the production of IgG autoantibodies that affect lacrimal and salivary glands, contributing to inflammation and activation of other signaling pathways[7,8,10]

Elevated BAFF levels induce autoreactive B-cell hyperactivity, contributing to increased IgG autoantibody production, including those against SSA (Ro) and SSB (La) (Figure 6).[7,10,14]

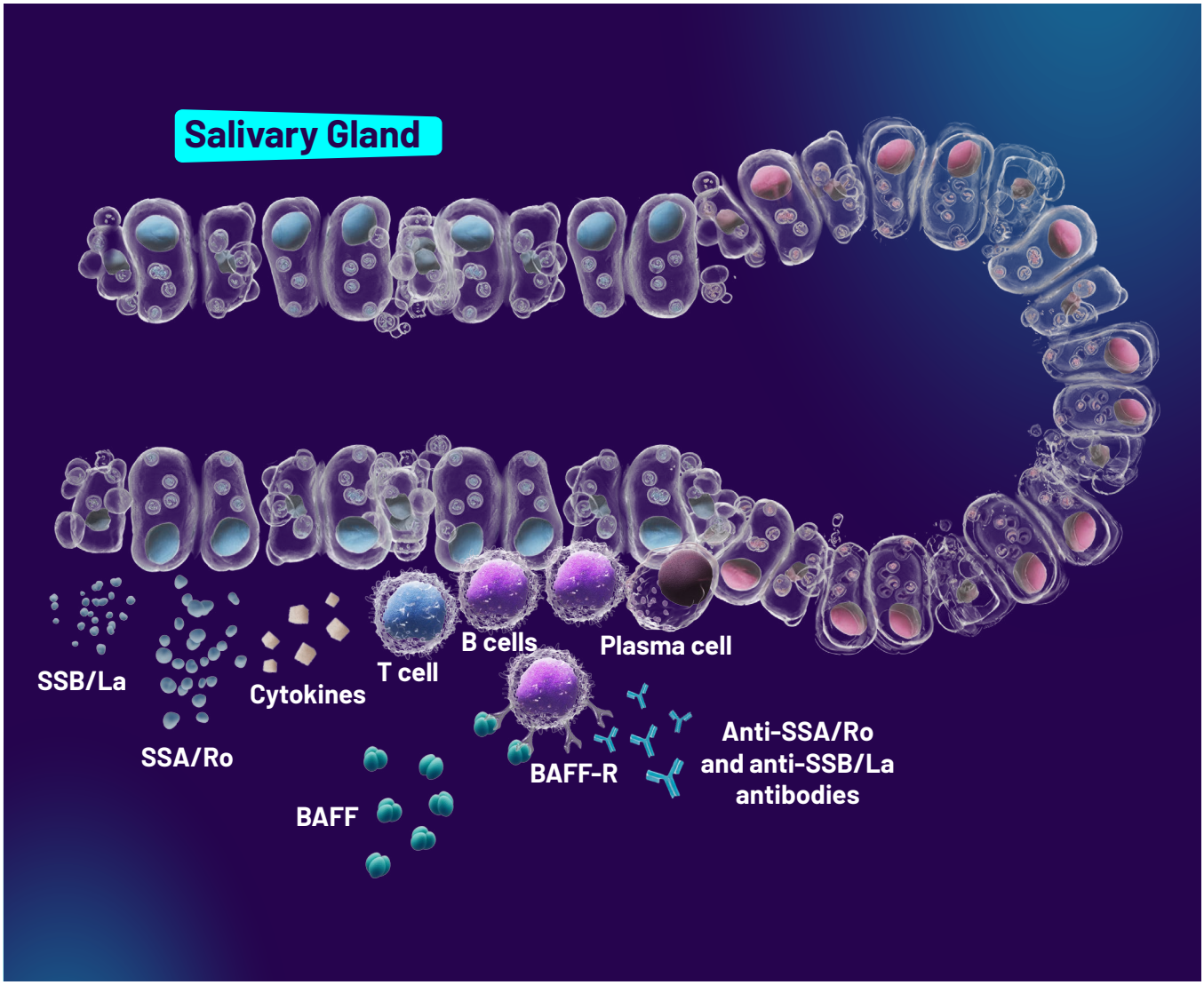


Figure 6 Elevated levels of BAFF lead to B-cell hyperactivity and autoantibody-mediated destruction of glandular tissue.[10,13,24,25]

IgG, immunoglobulin G.

Autoantibodies highlight the humoral immune dysregulation in Sjögren's disease[16]

Anti-Ro/SSA and anti-La/SSB form immune complexes with autoantigens from injured epithelial cells, perpetuating immune activation[10,16]

The constant activation of B cells and autoantibody production leads to chronic inflammation and further immune activation, potentially resulting in irreversible tissue damage.[8] **Infiltration of pathogenic B cells into tissues may lead to dryness, fatigue, chronic joint pain, and systemic complications like enlarged or swollen salivary glands.**[7,13,26]

The presence of anti-SSA and anti-SSB antibodies can serve as diagnostic markers[8,27]

Clinically, patients with Sjögren's disease may produce detectable levels of antibodies, with anti-SSA prevalent in approximately 54% of cases and anti-SSB in about 37%.[8,28] Within SSA, the distinct autoantigens Ro52 and Ro60, each encoded by separate genes, may be associated with the disease's clinical features[27,29]:

Presence of Autoantibodies	Potential Association
isolated anti-Ro52+	Higher disease activity, more pronounced sicca symptoms, and increased incidence of cryoglobulinemia[30,31]
isolated anti-Ro60+	Milder clinical presentation with fewer typical glandular and sicca manifestations[30]
anti-Ro52+/anti-Ro60+	The presence of both antibodies indicates B-cell hyperactivity and glandular inflammation, and their coexistence is linked to a higher incidence of primary Sjögren's disease and mucocutaneous involvement such as sicca symptoms, malar rash, and oral ulcers[27,29,32]

Sjögren's disease involves a self-perpetuating cycle of systemic inflammation[14]

Autoreactive B cells and autoantibody production reinforces the autoimmune cycle (Figure 7), exacerbating tissue damage and immune responses.[14,16] In some patients, this process may be **associated with systemic manifestations that can impair quality of life in patients with Sjögren's disease.**[19,33,34]

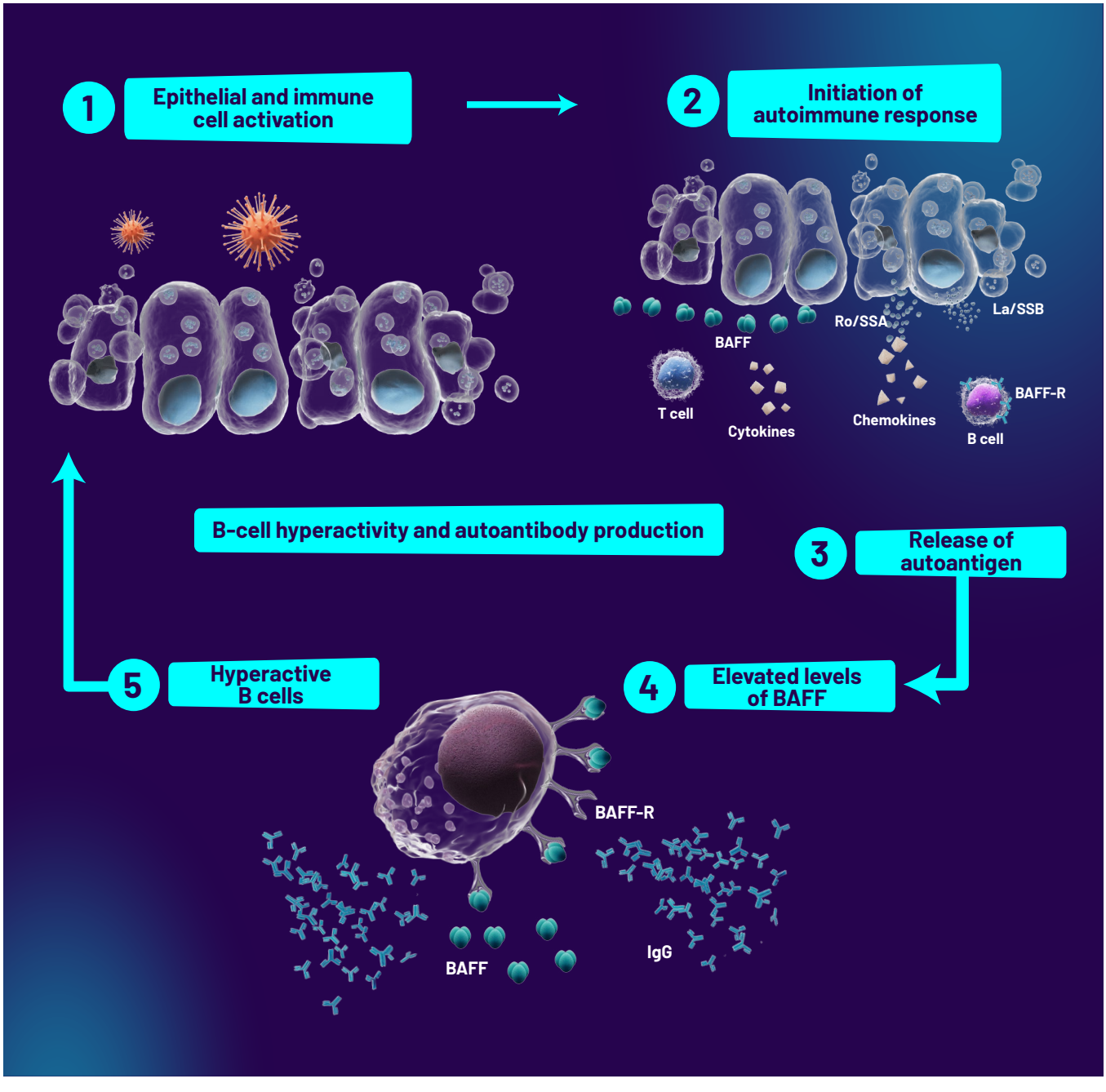


Figure 7 B-cell–driven pathological cycle of immune activation.[14]

Sustained B-cell depletion may help address the systemic nature of Sjögren's disease[7,21]

There is a need for therapies that target systemic inflammation and go beyond symptomatic relief[2]

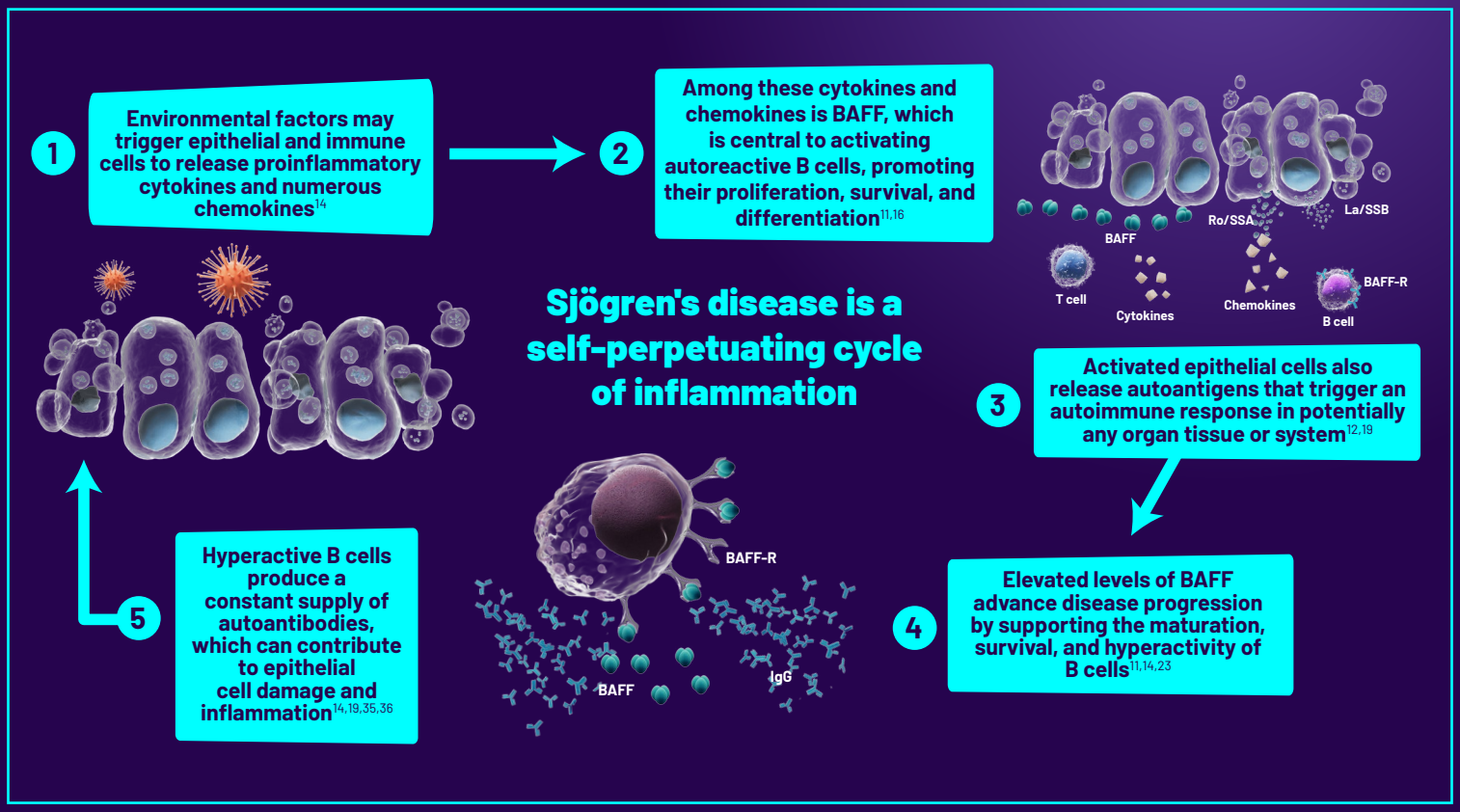
Systemic treatments, including hydroxychloroquine and rituximab, are used but have failed to demonstrate significant improvement on systemic disease outcomes in randomized clinical trials.[2] Several novel therapies for effective and sustained B-cell depletion are currently under investigation.[21]

Novartis has expanded its commitment to rheumatology by partnering with experts and universities to explore new ways to target B-cell hyperactivity and BAFF.

Continued research is critical to identify novel therapeutic targets that can effectively slow disease progression[2]

This is such an exciting time for Sjögren's disease research. There have been several important clinical trials and other research over the past few years that have been highly impactful, and this will drive further research development in the future.

—Alfred Kim, MD, PhD



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