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Targeting TNFSF4 in the Management of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disorder that remains a significant challenge for both healthcare providers and researchers. Despite advances in understanding its mechanisms, finding effective therapies is still difficult. This review highlights a potential therapeutic target in SLE research: tumor necrosis factor superfamily member 4 (TNFSF4), also referred to as OX40L. We explore how TNFSF4 contributes to SLE development, looking at its role in immune system regulation and how its dysfunction may lead to disease progression. Current SLE treatments are discussed, highlighting both their strengths and limitations, which underscores the need for new therapeutic approaches. Recent studies targeting the TNFSF4-OX40 pathway have shown potential in managing SLE. We examine both laboratory and clinical research, considering their methods, results, and implications for future work. Early evidence suggests that inhibiting TNFSF4-OX40 interactions might help normalize immune responses in SLE patients, potentially improving their health outcomes. Looking ahead, the TNFSF4-OX40 pathway represents a promising avenue for SLE treatment. Future research should focus on refining these therapies, understanding their long-term effects, and identifying which patients might benefit most. By deepening our understanding of TNFSF4's role in SLE, we may open the door to more targeted and effective treatments, ultimately improving the lives of those living with this challenging disease.

Keywords: TNFSF4, OX40L, systemic lupus erythematosus (SLE), immune regulation, therapeutic target.

INTRODUCTION

Systemic lupus erythematosus (SLE), classified as a persistent autoimmune disorder, is principally defined by the aberrant production of autoantibodies, the development of immune complexes within diverse tissues, and the consequent inflammatory reactions that affect multiple organ systems across the body. The wide array of clinical symptoms associated with this condition significantly complicates both the diagnostic process and the formulation of effective treatment strategies [1]. Epidemiological studies indicate that SLE impacts an estimated population ranging from 20 to 150 individuals for every 100,000 globally, with a notable increase in prevalence observed among certain ethnic demographics, alongside a striking female-to-male incidence ratio of approximately 9:1 [2, 3]. The etiology of this complicated disease is fundamentally multifactorial, involving a confluence of genetic risks, environmental provocations that may elicit the condition, and hormonal dynamics that can worsen the immune response [4]. The effective management of SLE necessitates meticulous consideration of various safety parameters, primarily due to the potential for severe involvement of multiple organs as well as complications arising from the treatments

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administered [5]. Ongoing and systematic surveillance of various elements of disease activity, organ performance, and potential drug toxicity is not solely necessary but also involves a comprehensive range of assessments, including renal function tests, detailed blood counts, liver function evaluations, cardiovascular risk assessments, bone density measurements, and ophthalmic examinations [6, 7].

Despite the significant advancements made in our understanding of the underlying mechanisms contributing to SLE, the existing therapeutic modalities frequently fall short of achieving sustained remission over the long term, as well as failing to adequately prevent the damage incurred by affected organs. Traditional therapeutic approaches, which generally encompass corticosteroids and a range of immunosuppressive agents, are linked to significant adverse effects and fail to adequately target the underlying mechanisms of the immune dysregulation characteristic of this condition [8]. Among these, TNFSF4, commonly referred to as OX40 ligand (OX40L), has surfaced as a compelling candidate for therapeutic intervention specifically aimed at treating SLE. The interaction between TNFSF4 and its receptor, OX40 (CD134), is crucial in regulating T cell activation, differentiation, and survival-markedly dysregulated in SLE [9, 10]. The TNFSF4-OX40 signaling pathway has been implicated in numerous critical elements of the pathogenesis of systemic lupus erythematosus (SLE), which includes the promotion of autoreactive T cell responses, the enhancement of B cell activation in conjunction with the production of autoantibodies, and the regulation of the activities of regulatory T cells [11].

This review aims to rigorously investigate the complex role of TNFSF4 in the pathogenesis of SLE while also highlighting its potential as a feasible therapeutic target, thus analyzing the diverse biological functions linked to this ligand, the dysregulation observed in SLE, and the fundamental justification for focusing on this specific pathway. The review will also consider the significant obstacles encountered in the development of TNFSF4-targeted therapies, encompassing challenges related to target specificity, the potential for off-target effects, and the intrinsic complexity of SLE as a heterogeneous condition.

UNDERSTANDING SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): A COMPLEX AUTOIMMUNE DISEASE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the immune system's misguided attack on the body's own tissues and organs. This condition can affect multiple organ systems, leading to a wide range of symptoms and complications [1]. The hallmark of SLE is the production of autoantibodies, particularly antinuclear antibodies (ANAs), which target various cellular components, resulting in inflammation and damage. The clinical presentation of SLE is highly variable, with some individuals experiencing mild symptoms such as fatigue and joint pain, while others may face severe manifestations involving the skin, kidneys, heart, lungs, and central nervous system. Notably, SLE is more prevalent in women of childbearing age, indicating a potential hormonal influence on its pathogenesis [3].

The etiology of SLE is complex and multifactorial, involving genetic predispositions that interact with environmental triggers such as infections, ultraviolet light exposure, and certain medications. These factors can lead to a breakdown in immune tolerance, causing the immune system to mistakenly identify self-antigens as threats. Dysregulation of both innate and adaptive immune responses plays a critical role in the disease's progression. In SLE patients, T-lymphocytes and B-lymphocytes exhibit abnormal signaling and activation patterns, perpetuating the autoimmune response. As a result, SLE can lead to significant morbidity due to its unpredictable course and potential for severe organ damage, underscoring the need for ongoing research into its pathogenesis and treatment options [1, 2].

TNFSF4 AND ITS ROLE IN SLE PATHOGENESIS

TNFSF4, which is alternatively referred to as OX40L, is classified as a significant member of the extensive tumor necrosis factor superfamily, and it is recognized for its indispensable contribution to the facilitation of immune responses that are mediated by T cells. The receptor associated with TNFSF4,

known as OX40 (CD134), is predominantly found on T cells that have undergone activation, while the expression of TNFSF4 is notably observed in antigen-presenting cells (APCs), which encompasses various cell types such as B cells, dendritic cells, and macrophages, thereby illustrating the intricate cellular interactions involved in immune responses [12].

The interaction between TNFSF4 and OX40 provides essential costimulatory signals that are instrumental in the processes of T cell activation, cellular proliferation, and the survival of these immune cells, which highlights the significance of this signaling pathway in relation to the generation and sustained presence of memory T cells, which are crucial for long-term immune protection [13].

The pathway connecting OX40 and its corresponding ligand TNFSF4 plays a vital role in the pathogenesis associated with systemic lupus erythematosus (SLE), exerting its influence through several intricate mechanisms. The signaling cascade initiated by TNFSF4-OX40 interaction significantly enhances the survival rates of activated CD4+ T cells by promoting the expression of anti-apoptotic proteins, such as Bcl-xL and Bcl-2, which could ultimately lead to the prolonged existence of autoreactive T cells that contribute to autoimmune pathology. In conjunction with this, the signaling pathway also facilitates the differentiation and functional capabilities of T follicular helper (Tfh) cells, which are essential for orchestrating B cell responses and the subsequent production of autoantibodies, thereby potentially worsening the autoantibody-mediated pathological manifestations typical of SLE. While there exists the capacity for this signaling to augment the proliferation of regulatory T cells (Treg), it is important to note that TNFSF4-OX40 signaling may simultaneously compromise their suppressive functions, thereby contributing to a significant imbalance between effector T cells and regulatory T cells within the immune system. Furthermore, TNFSF4, when expressed on B cells, engages with OX40 found on T cells, thus facilitating a bidirectional signaling mechanism that promotes B cell activation, cellular proliferation, and the production of antibodies, ultimately leading to the heightened autoantibody generation that characterizes SLE. Lastly, genome-wide association studies (GWAS) have successfully identified various polymorphisms within the TNFSF4 gene as notable risk factors associated with the development of systemic lupus erythematosus, with these identified genetic variants being correlated with an upregulation of TNFSF4 expression, thereby further emphasizing the gene's pivotal role in the susceptibility to this autoimmune disease [12–14].

The important role of TNFSF4 in these disease processes makes it a promising target for treating SLE. By adjusting this process, it might be feasible to lessen abnormal T-cell reactions, decrease autoantibody generation, and reinstate immune balance [13].

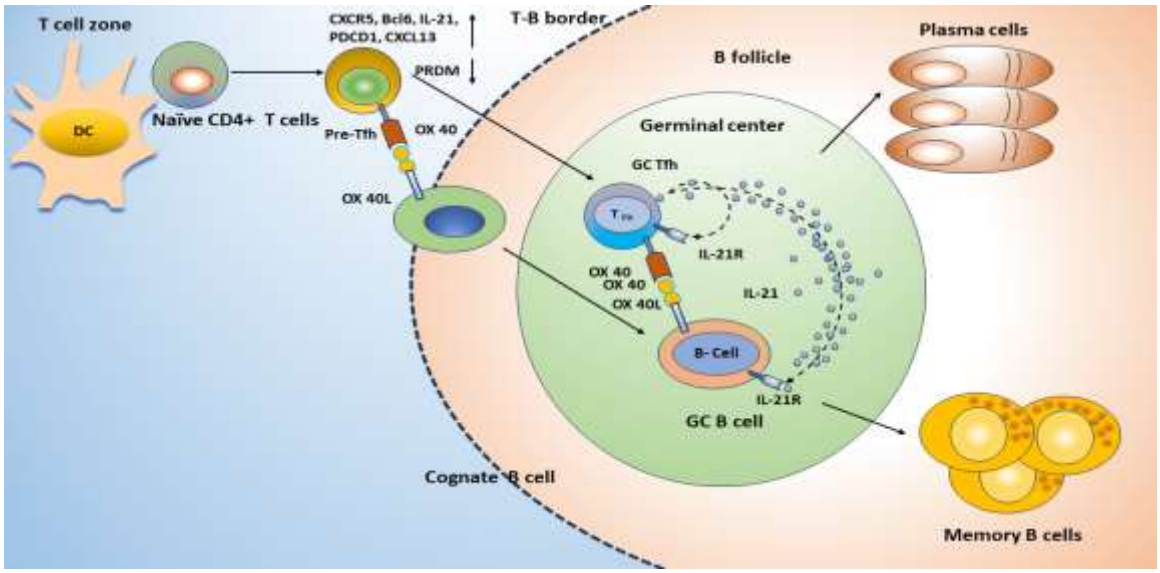

Figure 1. TNFSF4-OX40 signaling in SLE pathogenesis.

Figure 1 is the author's original work, illustrating TNFSF4-OX40 signaling in the pathogenesis of systemic lupus erythematosus (SLE).

CURRENT THERAPEUTIC APPROACHES IN SLE

The management of Systemic Lupus Erythematosus (SLE) involves a multi-faceted approach tailored to disease severity and organ involvement. Conventional immunosuppressants form the backbone of treatment. Corticosteroids, such as prednisone, are widely used for rapid control of disease flares but are associated with significant side effects when used long-term, including osteoporosis, diabetes, and increased cardiovascular risk. Antimalarials, particularly hydroxychloroquine, are considered a cornerstone of SLE treatment, effective in managing mild disease, preventing flares, and improving long-term outcomes [15, 16]. Other immunosuppressants like azathioprine, mycophenolate mofetil, and methotrexate are commonly used for maintenance therapy and organ-specific manifestations, especially lupus nephritis. In recent years, targeted biologics have emerged as important additions to the SLE treatment [17]. B cell-targeted therapies have shown promise, with belimumab (an anti-BAFF monoclonal antibody) approved for SLE treatment, demonstrating efficacy in reducing disease activity and preventing flares. Rituximab, an anti-CD20 monoclonal antibody, is used off-label in refractory cases, particularly for severe lupus nephritis or neuropsychiatric manifestations. Additionally, interferon pathway inhibitors like anifrolumab, which targets the type I interferon receptor, have shown encouraging results in clinical trials, addressing the interferon signature characteristic of SLE [18].

Despite these available options, there remains a significant unmet need for SLE treatment. Many patients fail to achieve sustained remission or experience inadequate responses to current therapies. Prolonged immunosuppression may result in severe side effects, such as a higher chance of infections and cancerous growth. This has spurred the exploration of novel approaches to expand the treatment armamentarium [19]. JAK inhibitors, such as tofacitinib and baricitinib, which modulate multiple cytokine pathways implicated in SLE pathogenesis, have shown potential in early-phase trials [20]. Complement inhibitors, including eculizumab and other agents targeting various components of the complement cascade, are being studied for lupus nephritis and other severe manifestations [21]. Other areas of active research include targeting plasma cells (e.g., proteasome inhibitors), modulating T cell co-stimulation (e.g. abatacept), and exploring combination therapies to achieve synergistic effects [22]. Creating biomarkers to anticipate how patients will respond to treatment and direct personalized therapy is also a major priority. The persistent challenges in SLE management, including the heterogeneity of the disease and the need for safer, more effective treatments, underscore the importance of exploring new therapeutic targets like TNFSF4. Such novel approaches hold promises for expanding treatment options, improving long-term outcomes, and potentially achieving disease remission in a greater proportion of patients with this complex and challenging autoimmune disease [23].

TARGETING TNFSF4: RATIONALE AND MECHANISMS

The rationale for targeting TNFSF4 in SLE management is rooted in its critical role in T cell-mediated immune responses and its involvement in key pathogenic mechanisms of the disease. TNFSF4, also known as OX40L, interacts with its receptor OX40 (CD134) to provide essential costimulatory signals for T cell activation, proliferation, and survival [11]. In SLE, this pathway is often dysregulated, contributing to the persistence of autoreactive T cells and the breakdown of immune tolerance. Genetic studies have further strengthened the case for TNFSF4 as a therapeutic target, with several polymorphisms in the TNFSF4 gene identified as risk factors for SLE development. These genetic variants are associated with increased TNFSF4 expression, potentially predisposing individuals to heightened T-cell responses and autoimmunity [12, 13].

The mechanisms by which TNFSF4 inhibition could benefit SLE patients are multifaceted. Firstly, blocking the TNFSF4-OX40 interaction can attenuate the activation and survival of autoreactive T cells, potentially reducing the pool of self-reactive lymphocytes. Secondly, TNFSF4 inhibition may modulate the differentiation of T follicular helper (Tfh) cells, which play a crucial role in supporting B cell

responses and autoantibody production in SLE. By limiting Tfh cell function, this approach could indirectly reduce the excessive autoantibody levels characteristic of the disease. Furthermore, focusing on TNFSF4 could assist in reestablishing the equilibrium between effector T cells and regulatory T cells (Tregs). While TNFSF4-OX40 signaling can enhance Treg proliferation, it may also impair their suppressive function. By fine-tuning this pathway, it may be possible to enhance Treg-mediated suppression of autoreactive responses.

Table 1. Therapeutic approaches for SLE [17–23].

Category	Medications	Mechanism of Action	Indications/Uses	Side Effects
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen, Naproxen, Celecoxib.	Reduces inflammation by inhibiting cyclooxygenase (COX) enzyme.	For mild pain and inflammation, particularly joint pain.	Gastrointestinal upset, risk of cardiovascular events.
Antimalarials	Hydroxychloroquine (Plaquenil).	Modulates the immune system and reduces flare frequency.	Skin rashes, joint pain, fatigue; often used in all stages of SLE.	Retinopathy (with long-term use), GI disturbances.
Corticosteroids	Prednisone, Methylprednisolone.	Reduces inflammation and suppresses immune response.	For moderate to severe SLE flares affecting organs.	Weight gain, osteoporosis, high blood pressure.
Immunosuppressants	Azathioprine, Methotrexate, Mycophenolate Mofetil.	Inhibits immune cell proliferation and reduces immune response.	Severe SLE or organ involvement (e.g., kidneys, lungs).	Risk of infection, liver toxicity, bone marrow suppression.
Biologics	Belimumab (Benlysta), Rituximab.	Targets specific immune system proteins to reduce autoantibody production.	For refractory SLE or those unresponsive to other therapies.	Infusion reactions, increased infection risk.
Cytotoxic agents	Cyclophosphamide.	Destroys rapidly dividing immune cells.	Severe lupus nephritis or central nervous system (CNS) involvement.	Increased infection risk, bladder toxicity, infertility.
Calcium & Vitamin D	Supplements.	Maintains bone health, often prescribed alongside corticosteroids.	Prevents osteoporosis in long-term corticosteroid use.	Rare side effects; hypercalcemia with overdose.

Several therapeutic strategies have been suggested to block the TNFSF4-OX40 axis [24, 25]. An alternate method includes using monoclonal antibodies that target TNFSF4 or OX40. These antibodies can obstruct the connection between the ligand and receptor, halting the transfer of costimulatory signals. Another approach utilizes fusion proteins as decoy receptors, effectively trapping TNFSF4 and blocking its binding to OX40 on T cells. Investigation is also being carried out on small molecule inhibitors that can interrupt the downstream signaling pathways activated by the TNFSF4-OX40 interaction. These molecules could offer advantages in terms of oral bioavailability and tissue penetration. Furthermore, researchers are exploring the potential of combination therapies, where TNFSF4 inhibition is paired with other immunomodulatory approaches to achieve synergistic effects. As our understanding of the TNFSF4-OX40 pathway in SLE pathogenesis continues to evolve, these therapeutic strategies may be refined to offer more targeted and effective treatments for SLE patients [26, 27].

PRECLINICAL STUDIES ON TNFSF4 INHIBITION IN SLE

Preclinical studies investigating TNFSF4 inhibition in SLE have provided valuable insights into the potential efficacy and mechanisms of this therapeutic approach [28]. In murine models of lupus, such as the NZB/W F1 and MRL/lpr strains, blockade of the TNFSF4-OX40 pathway has shown promising results. One seminal study demonstrated that the administration of an anti-TNFSF4 monoclonal antibody to NZB/W F1 mice significantly reduced autoantibody production, proteinuria, and renal pathology. The treatment also decreased the numbers of activated T cells and plasma cells in these mice, suggesting a modulation of both T and B cell responses [29]. Similarly, another study reported that the OX40-Ig fusion protein, which acts as a decoy receptor for TNFSF4, delayed the onset of nephritis and

improved survival in MRL/lpr mice. These studies provided proof of concept that targeting the TNFSF4-OX40 axis could ameliorate lupus-like symptoms in animal models [30].

Further mechanistic insights have been gained from ex-vivo studies using human cells from SLE patients. Researchers have found that blocking TNFSF4-OX40 interactions in cultured peripheral blood mononuclear cells (PBMCs) from SLE patients reduced the production of inflammatory cytokines such as interferon-γ and interleukin-17 [31]. One study demonstrated that TNFSF4 blockade in vitro diminished the ability of T cells from SLE patients to provide help to B cells for autoantibody production [32]. Additionally, another research group showed that the inhibition of the TNFSF4-OX40 pathway reduced the differentiation of T follicular helper cells, which are crucial for germinal center reactions and autoantibody production in SLE [14]. These findings collectively suggest that TNFSF4 inhibition could target multiple pathogenic mechanisms in SLE, including T cell activation, B cell help, and autoantibody production. However, it is important to note that while these preclinical studies are encouraging, they also highlight the complexity of TNFSF4-OX40 signaling in immune regulation and underscore the need for careful translation of these findings to human clinical trials.

CLINICAL TRIALS AND EMERGING THERAPIES

Positive outcomes in preclinical research have opened the door for clinical experiments focusing on the TNFSF4-OX40 axis in SLE. Now, numerous treatments are at different points of clinical progress. One of the most advanced is KY1005, a fully human anti-TNFSF4 monoclonal antibody developed by Kymab (now part of Sanofi). KY1005 has completed a phase 1 trial (NCT03161288) in healthy volunteers and patients with mild SLE, demonstrating a favorable safety profile and providing early evidence of biological activity [33]. Another agent, VIB4920, a fusion protein designed to block TNFSF4-OX40 interactions, has shown promise in a phase 1b study (NCT02647866) involving patients with rheumatoid arthritis and is now being investigated for other autoimmune conditions, including SLE [34]. Additionally, several pharmaceutical companies are exploring small molecule inhibitors of the TNFSF4-OX40 pathway, although these are still in earlier stages of development. While these emerging therapies offer hope, it is important to note that larger, well-designed phase 2 and 3 trials are still needed to fully evaluate the efficacy and safety of TNFSF4-targeted therapies in SLE. These ongoing and future studies will be crucial in determining whether the promising results observed in preclinical models can translate into meaningful clinical benefits for patients with SLE.

CHALLENGES AND FUTURE DIRECTIONS

The advancement of therapeutic interventions specifically targeting TNFSF4 for the treatment of systemic lupus erythematosus (SLE) encounters a multitude of significant challenges that necessitate thorough examination and resolution as scholarly inquiry in this domain continues to evolve and progress. One of the foremost issues that has emerged in this context is the substantial potential for off-target effects, which may lead to unintended and possibly detrimental consequences arising from the modulation of the TNFSF4-OX40 signaling pathway, a pathway that is critically involved in the regulation of normal immune responses. There exists a considerable risk that a broad-spectrum inhibition of this pathway could inadvertently compromise the protective immunity that is essential for combating various infections or could adversely affect the efficacy of vaccine responses in patients. To effectively mitigate these associated risks, it is imperative that future research endeavors prioritize the development of more selective and precise targeting strategies that can differentiate between pathogenic immune responses that contribute to disease and protective immune responses that are vital for host defense. Another paramount challenge that must be addressed pertains to the inherent patient heterogeneity and the intricate nature of SLE as a multifaceted autoimmune disorder. This disease manifests with a diverse array of clinical symptoms and varying degrees of severity among affected individuals, thereby complicating the design of treatment modalities that can be universally applied across the patient population. Therefore, future investigative directions should encompass initiatives aimed at identifying specific biomarkers that could reliably predict which patients are most likely to derive therapeutic benefit from TNFSF4-targeted interventions. Such efforts could entail the

implementation of genetic screening to identify TNFSF4 polymorphisms or the assessment of baseline concentrations of soluble TNFSF4 in the serum of patients.

The long-term repercussions associated with the inhibition of TNFSF4 remain largely speculative and will necessitate meticulous monitoring during clinical trials as well as ongoing post-marketing surveillance once therapies are approved for public use. There exists a pressing need for extensive follow-up studies that can rigorously evaluate the durability of therapeutic responses over time and identify any potential delayed adverse effects that may arise because of such interventions. Furthermore, optimizing drug delivery methods and establishing appropriate dosing regimens represent another critical avenue for future research exploration. The innovation of novel pharmaceutical formulations, including the utilization of targeted nanoparticles or the development of engineered cell therapies designed to deliver TNFSF4 inhibitors with enhanced precision to sites of inflammation, has the potential to significantly improve therapeutic efficacy while concurrently minimizing the occurrence of systemic side effects. In addition to these considerations, the implementation of personalized dosing strategies that consider individual patient characteristics and the specific activity of their disease may further enhance treatment outcomes. As our comprehension of the immune system continues to expand and advance, it is essential that future research endeavors delve into the more extensive implications of TNFSF4-OX40 signaling within the broader context of immune regulation. Such investigations could potentially unveil novel therapeutic applications that extend beyond the confines of SLE, thereby offering benefits to patients suffering from a range of other autoimmune disorders. Collaborative initiatives that involve partnerships between academic institutions, industrial entities, and regulatory agencies will be of paramount importance in effectively addressing these multifaceted challenges and propelling TNFSF4-targeted therapies from promising theoretical concepts into fully approved and viable treatment options for SLE [35].

CONCLUSION

The strategic targeting of TNFSF4 within the context of systemic lupus erythematosus (SLE) embodies a highly promising therapeutic approach aimed at the modulation of aberrant immune responses that characterize this complex autoimmune condition. A multitude of preclinical investigations and early-phase clinical trials have provided compelling evidence supporting the potential efficacy of this innovative strategy in terms of its ability to significantly reduce autoantibody production, improve the extent of tissue damage incurred during disease progression and facilitate the restoration of immune homeostasis within affected individuals. Although numerous challenges persist, including the variability among patient populations and the potential for off-target effects that may complicate treatment outcomes, the ongoing development of TNFSF4-targeted therapeutic interventions holds considerable promise for delivering more effective and individualized treatment options to patients afflicted with this debilitating condition. As research in this area continues to advance, it is anticipated that this approach may not only enhance the management of SLE but also contribute to a deeper understanding of the intricate mechanisms underlying immune regulation in the broader spectrum of autoimmune diseases.

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