An update on lupus animal models

Wei Li, Anton A. Titov, and Laurence Morel

Purpose of review
The complexity and heterogeneity of the clinical presentation in systemic lupus of erythematosus (SLE), combined to the inherent limitations of clinical research, have made it difficult to investigate the cause of this disease directly in patients. Various mouse models have been developed to dissect the cellular and genetic mechanisms of SLE, as well as to identify therapeutic targets and to screen treatments. The purpose of this review is to summarize the major spontaneous and induced mouse models of SLE and to provide an update on the major advances they have contributed to the field.

Recent findings
Mouse models of SLE have continued to contribute to understand the cellular, signaling and metabolic mechanisms contributing to the disease and how targeting these pathways can provide therapeutic targets. Whenever possible, we discuss the advantage of using one model over the others to test a specific hypothesis.

Summary
Spontaneous and induced models of lupus models are useful tools for the study of the cause of the disease, identify therapeutic targets and screen treatments in preclinical studies. Each model shares specific subsets of attributes with the disease observed in humans, which provides investigators a tool to tailor to their specific needs.

Keywords
B cells, mouse models, systemic lupus of erythematosus, T cells, therapeutic targets

INTRODUCTION
Systemic lupus of erythematosus (SLE) is a chronic disorder that is characterized by the over-production of antinuclear autoantibodies (ANA) resulting in the formation of immune complexes that induce tissue inflammation and destruction in multiple organs, including the kidneys [1]. The exact cause of SLE is still unknown, but there is a strong evidence that a combination of environmental exposures, genetic predisposition, cellular dysfunctions and hormonal factors lead to the development of SLE [2]. Given the high degree of clinical heterogeneity in SLE patients, preclinical mouse models summarized below (Table 1) have been very valuable to investigate the cause of SLE as well as to identify and validate therapeutic targets.

These mouse models of SLE are either spontaneous or induced, but none of them fully represents the entire clinical spectrum found in SLE patients. However, each model presents an overlapping subset of human lupus phenotypes and offers specific features of interest to address specific preclinical purposes. In addition to polygenic models, a number of mouse models are based on a single gene knock-out or transgenic expression of genes which result in lupus-like phenotypes [11]. These strains have been instrumental in delineating functional pathways in SLE as well as the involvement of specific genes in maintaining systemic immune tolerance and preventing immune complex-induced inflammation. There have been numerous reviews of mouse models of SLE starting from the foundational work published over 30 years ago [12] that has been followed by many updates. Many reviews have focused on specific aspects of these models, such as the genetic links between human and mouse SLE [11], or the mechanisms leading to systemic autoimmunity and clinical lupus in these models [13]. The present review will briefly summarize the most common mouse of SLE,
stressing their unique features. We will then provide an update on the major advances they have contributed to the field, and whenever possible, we will discuss the advantage of using one model over the others to test a specific hypothesis.

**SPONTANEOUS MOUSE MODELS OF SYSTEMIC LUPUS OF ERYTHEMATOSUS**

**NZB/W F1**

In 1960s, the NZB/W F1 model of lupus referred to the F1 hybrid between the NZB and NZW strains [3]. NZB mice show limited hemolytic autoimmune anemia, whereas NZW mice are nonautoimmune. However, their F1 hybrids develop severe lupus-like phenotypes, including a strong female bias, splenomegaly, elevated serum ANA mostly directed against DNA. Immune complex-mediated nephritis develops by 5–6 months of age, leading to renal failure and death at 10–12 months of age [12]. Overall, NZB/W F1 is a classic model used to study the genetic underpinning of SLE [11] as well as drug responses in many preclinical studies, including the inhibition of B cell activating factor (BAFF) [14], the role of type 1 interferon [15] and the identification of biomarkers of lupus nephritis [16].

**New Zealand Mixed**

An accidental backcross between NZB/W F1 and NZW followed by brother–sister mating generated 27 different recombinant inbred strains of New Zealand Mixed (NZM) mice among which NZM2328 and NZM2410 are now used as lupus models [4–6]. The clinical manifestations in NZM strains are similar to that of NZB/W F1 mice, whereas there are some differences in renal disorder [16,17] and the response to BAFF inhibition [18]. The main advantage of the NZM strains over NZB/W F1 is that they have homozygous genomes, which has facilitated genetic analyses [11]. From the NZM2410 strain, a novel congenic model has been produced that combines the three susceptibility loci, Sle1, Sle2 and Sle3, that are necessary and sufficient to induce a lupus phenotype on a nonautoimmune C57BL/6 (B6) genetic background [19]. The B6.NZM2410.Sle1.Sle2.Sle3 has the unique advantage to share 95% of its genome with B6, providing a robust control for immunological and genetic studies. The corresponding single (mostly Sle1) and bicongenic (Sle1.Sle3) are

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**Table 1. Classical mouse models of lupus**

<table>
<thead>
<tr>
<th>Mouse model</th>
<th>Generation/protocol</th>
<th>Sex bias</th>
<th>Main clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous models</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZB/W F1 [3]</td>
<td>F1 hybrid between NZB and NZW strains</td>
<td>Female</td>
<td>Lymphadenopathy, splenomegaly, anti-dsDNA IgG, IC-mediated GN</td>
</tr>
<tr>
<td>NZM2410/2328 [4–6]</td>
<td>Backcross between NZB/W F1 and NZW followed by brother–sister mating</td>
<td>Female</td>
<td>Overlaps with NZB/W F1</td>
</tr>
<tr>
<td>MRL/lpr [7]</td>
<td>lpr mutation in Fas gene on MRL background</td>
<td>Both</td>
<td>Lymphadenopathy due to accumulation of DN B220+ T cells, DNA and RNA-directed autoantibodies, IC-mediated GN and dermatitis</td>
</tr>
<tr>
<td>BXSB/Yaa [8]</td>
<td>Backcross of (B6 X SB/Le) F1 to SB/Le</td>
<td>Male</td>
<td>Lymphadenopathy, anti-DNA, RNA and gp70 autoAbs, monocyctosis, IC mediated GN</td>
</tr>
<tr>
<td>Induced models</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pristane-induced lupus [9]</td>
<td>i.p. injection of pristine</td>
<td>Female</td>
<td>Type I interferon mediated, autoAb, GN, arthritis, anemia, serositis (strain dependent)</td>
</tr>
<tr>
<td>cGVHD [10]</td>
<td>(1) DBA → BDF1 (injection of spleen cells)</td>
<td>Female</td>
<td>AutoAb, GN, polyclonal B-cell and T-cell activation, proteinuria (CD8+ T cell dependent)</td>
</tr>
<tr>
<td></td>
<td>(2) B6 → B6.Bm12 (injection of spleen cells)</td>
<td>Female</td>
<td>AutoAb, GN, polyclonal B-cell and T-cell activation, proteinuria (donor CD4+ T-cell dependent)</td>
</tr>
</tbody>
</table>

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cGVHD, chronic graft-versus-host disease; IC, immune complexes.
well suited to breed to B6-based gene knockouts. For instance, deletion of the plasmacytoid dendritic cells (pDC)-specific transcription factor Tcf4 in B6.Sle1.Sle3 mice provided genetic evidence that pDCs are critically involved in the development of SLE [20*].

**MRL/lpr**

The MRL strain was developed by crossing several strains, including LG/J, C3H/Di, C57BL/6 and AKR/J [12]. One of the MRL substrains carrying a spontaneous mutation named lpr for lymphoproliferation developed an SLE-like phenotype characterized by accumulation of double negative (CD4−CD8−) B220+ T cells. Double negative T cells are autoreactive [21] and expanded in SLE patients [22], making this model specifically relevant to SLE pathogenesis. Lpr corresponds to nonfunctional transcripts of the Fas gene, a major regulator of apoptosis in immune cells [23]. Both male and female MRL/lpr mice are affected and produce autoantibodies against dsDNA and Sm, leading to large amounts of immune complex that induce renal and skin disorder [7]. MRL/lpr mice develop a massive lymphadenopathy that is not observed in SLE patients. However, in addition to expanded double negative T cells, this model has the advantage of a rapid and severe disease development as compared with the other spontaneous models. Notably, the MRL/lpr strain has been used to dissect the role of toll-like receptor 7 and TLR9 in lupus development directly in a nonautoimmune strain, such the protective effect of TLR9 evaluated in BALB/c mice after pristane injections. Pristane-treated mice also have immune complex deposition in the kidney causing severe nephritis [32]. Strain differences in the response to pristane have been observed [33], illustrating the role of gene/environment interactions in lupus susceptibility. Pristane-induced lupus is more severe in females than in males, at least in the SJL strain [34]. Pristane-induced lupus is driven by a strong type 1 interferon response [35], and this model is, therefore, well suited to investigate the type 1 interferon signature present in many SLE patients, but much weaker in spontaneous mouse models of this disease. This model is also useful to test the impact of a specific gene on lupus development directly in a nonautoimmune strain, such the protective effect of TLR9 evaluated in BALB/c.Th9−/− mice treated with pristane [36*].

**BSXB/Yaa**

A recombinant inbred strain derived from the backcross of (B6 X SB/Le) F1 to SB/Le, termed BSXB/Mp (BSXB/Yaa), develops a lupus-like disease with lymphoid hyperplasia, immune complex-mediated nephritis, ANA and high-serum retroviral glycoprotein gp70 titers [7,28]. Nephritis leads to the death of BSXB/Yaa males in about 5 months and BSXB females in 14 months. The rapid-onset disease in males is attributable to the Y-autoimmune accelerator (Yaa) locus, which is due to a translocation from the X to the Y chromosome, duplicates 16 genes, including TLR7 [29,30]. TLR7 regulates the activation of the type 1 interferon pathway by RNA complexes, a critical pathway in SLE pathogenesis [31]. Therefore, in spite of its presentation in males, the BSXB/Yaa strain is uniquely suited to model the consequences of an overreactive TLR7/Type 1 interferon pathway.

**INDUCED MOUSE MODELS OF SYSTEMIC LUPUS OF ERYTHEMATOSUS**

**Pristane-induced lupus**

Pristane is an isoprenoid alkane found at high concentration in mineral oil. Intraperitoneal injection of pristane is a standard method to obtain ascitic fluid enriched in mAbs. Antiribonucleoprotein, anti-DNA and antihistone autoantibodies are found in BALB/c mice after pristane injections. Pristane-treated mice also have immune complex deposition in the kidney causing severe nephritis [32]. Strain differences in the response to pristane have been observed [33], illustrating the role of gene/environment interactions in lupus susceptibility. Pristane-induced lupus is more severe in females than in males, at least in the SJL strain [34]. Pristane-induced lupus is driven by a strong type 1 interferon response [35], and this model is, therefore, well suited to investigate the type 1 interferon signature present in many SLE patients, but much weaker in spontaneous mouse models of this disease. This model is also useful to test the impact of a specific gene on lupus development directly in a nonautoimmune strain, such the protective effect of TLR9 evaluated in BALB/c.Th9−/− mice treated with pristane [36*].

**Chronic graft-versus-host disease models**

Induced chronic graft-versus-host disease (cGVHD) models require injections of donor lymphocytes into a semiallogenic recipient to induce a lupus-like syndrome. In the parent→F1 model, DBA/2 strain spleen cells are injected into (C57BL/6 X DBA/2) F1 (BDF1) recipients, whereas in the other, B6 spleen cells are injected into class II major histocompatibility complex-mismatched B6.bm12 recipients or reversely. In both models, donor CD4+ T cells react to host B cells triggering the polyclonal activation of autoreactive B cells, and eventually, lupus-like syndrome [10]. Compared with the other models, cGVHD is easy to control, adjustable to investigator’s needs and generally presents with a reduced interindividual variability. In addition, autoimmune and clinical manifestations of SLE develop relatively rapidly over a period of weeks, instead of months for the other models. Finally, because the activation and expansion of donor T cells play an essential role in cGVHD response, it is easy to track them relative to host cells by flow cytometry.
These models also allow the study of the effect of treatments or genetic modifications in donor cells to alter the course of the cGVHD response. The bm12 model is particularly useful to test the effect of single genes or alleles on the development of systemic autoimmunity on a B6 genetic background. This approach has been used to evaluate Slamt6 isoforms as lupus susceptibility alleles for the Sle1b locus [37,38], and to identify the association of a naturally occurring polymorphism in the G-CSF gene with resistance to autoimmune activation [39,40].

**RECENT INVESTIGATIONS OF THERAPEUTIC TARGETS WITH MOUSE MODELS OF LUPUS**

Table 2 lists recent treatments or genetic approaches that have been used in mouse models of lupus.

### Table 2. Treatments tested in mouse models of systemic lupus of erythematosus

<table>
<thead>
<tr>
<th>Gene target</th>
<th>Cell target</th>
<th>Model</th>
<th>Treatment</th>
<th>Main manifestations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-cell targets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular metabolism</td>
<td>CD4 T cells</td>
<td>B6.Sle1, Sle2, Sle3 BWF1 B6.lpr</td>
<td>Metformin, 2-deoxyglucose</td>
<td>AutoAb, GN, Immune activation</td>
<td>[41**,42**]</td>
</tr>
<tr>
<td>Cellular metabolism</td>
<td>CD4 T cells</td>
<td>cGVHD</td>
<td>Isogarcinol</td>
<td>Proteinuria, autoAb, GN</td>
<td>[43]</td>
</tr>
<tr>
<td>Cellular metabolism</td>
<td>CD4 T cells</td>
<td>cGVHD</td>
<td>Quercitrin</td>
<td>Proteinuria, autoAb, GN</td>
<td>[44]</td>
</tr>
<tr>
<td>B7-1</td>
<td>T-cell-APC interaction</td>
<td>Pristane-induced</td>
<td>B7-1 shRNA and anti-B7-1 mAb</td>
<td>ANA, anti-dsDNA IgG</td>
<td>[45,46]</td>
</tr>
<tr>
<td>ICOS-B7RP-1</td>
<td>Tfh</td>
<td>BWF1</td>
<td>Anti-ICOS-B7RP-1</td>
<td>Proteinuria, anti-dsDNA IgG</td>
<td>[47]</td>
</tr>
<tr>
<td>ICOS-B7RP-1</td>
<td>Tfh</td>
<td>MRL/lpr</td>
<td>Ablation of ICOS ligand in CD11c+ cells</td>
<td>Kidney/lung inflammation</td>
<td>[48**,49]</td>
</tr>
<tr>
<td>IL-21</td>
<td>Tfh</td>
<td>B6.Sle1, Yaa</td>
<td>Anti-IL-21 MAb</td>
<td>GC B cells, CD138hi IgG2c, autoantibodies</td>
<td>[49]</td>
</tr>
<tr>
<td>IL-21</td>
<td>Tfh</td>
<td>cGVHD</td>
<td>IL-21</td>
<td>Host B cell, autoantibody, renal disease</td>
<td>[50**]</td>
</tr>
<tr>
<td>IL-21</td>
<td>Tfh</td>
<td>MRL/lpr, BWF1, BXSB</td>
<td>IL-21RFc</td>
<td>IgG, proteinuria, anti-dsDNA</td>
<td>[51,52**,53]</td>
</tr>
<tr>
<td><strong>B-cell targets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAFF</td>
<td>B cells</td>
<td>MRL/lpr</td>
<td>BAFF-R Fc</td>
<td>Tertiary lymphoid structures and nephritis</td>
<td>[54]</td>
</tr>
<tr>
<td>BAFF</td>
<td>B cells</td>
<td>NZM2328 KO BCR3 with TACI or BCMA</td>
<td>BAFF-BCMA and/or BAFF-TACI combinations contribute to SLE</td>
<td>[55]</td>
<td></td>
</tr>
<tr>
<td>BTK</td>
<td>B cells</td>
<td>BWF1, MRL/lpr, pristane-induced, BXSB</td>
<td>Proteasome inhibitor</td>
<td>ANA, GN, Survival</td>
<td>[62]</td>
</tr>
<tr>
<td>miR-148</td>
<td>B cells</td>
<td>MRL/lpr</td>
<td>Increased miR148</td>
<td>GN</td>
<td>[60**,61]</td>
</tr>
<tr>
<td>miR-155</td>
<td>B cells</td>
<td>MRL/lpr</td>
<td>miR155 KO</td>
<td>ANA, B-cell signaling</td>
<td>[61]</td>
</tr>
<tr>
<td>Proteasome</td>
<td>Plasma cells</td>
<td>BWF1, MRL/lpr</td>
<td>Proteasome inhibitor</td>
<td>ANA, GN, Survival</td>
<td>[62]</td>
</tr>
<tr>
<td><strong>Other targets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLRP3</td>
<td>Macrophages</td>
<td>BWF1</td>
<td>NLRP3 inhibitor</td>
<td>ROS, NAPDH, COX-2, GN</td>
<td>[63]</td>
</tr>
<tr>
<td>NLRP3</td>
<td>Macrophages</td>
<td>Pristane-induced</td>
<td>NLRP3 gain-function</td>
<td>Proteinuria and GN</td>
<td>[64]</td>
</tr>
<tr>
<td>IRAK4</td>
<td>TLR pathway</td>
<td>BWF1, MRL/lpr</td>
<td>IRAK4 inhibitor</td>
<td>Proteinuria, dsDNA, GN</td>
<td>[65]</td>
</tr>
<tr>
<td>Topoisomerase I</td>
<td>dsDNA binding</td>
<td>MRL/lpr</td>
<td>Topoisomerase I inhibitor</td>
<td>Nephritis and skin lesions</td>
<td>[66]</td>
</tr>
</tbody>
</table>

ANA, antinuclear autoantibodies; B7RP-1, B7-related protein-1; BAFF, B cell activating factor; COX, cyclooxygenase-2; IC, immune complexes; ICOS, Inducible T-cell COStimulator; IRAK4, IL-1R-associated kinase 4; ROS, reactive oxygen species; Tfh, T follicular help cells.
The interactions between B7-1 and 2 on the B cell/antigen presenting cell side and CD28/CTLA-4 on the T cell side are cardinal regulatory pathways of the immune response, and there have been numerous attempts to target them therapeutically [69]. Based on studies in mouse models, CTLA-4-Ig (abatacept) is now in clinical trial for the treatment of lupus nephritis [70]. In the pristane-induced lupus model, the specific blockade of the interaction between B7-1 and CD28 decreased serum ANA and antidsDNA IgG [45].

T follicular help cells (Tfh) are a CD4+ helper T-cell subset specialized for provision of help of B cells which plays an essential role in germinal center formation, affinity maturation and the development of high-affinity antibodies [71]. Tfh cells are expanded in mouse models of lupus, and the level of circulating Tfh cells correlates with disease severity in SLE patients [72]. Consequently, therapeutic targeting of Tfh cells has been proposed for SLE patients and lupus mouse models through the IL-21, Inducible T-cell COStimulator (ICOS) and OX40 pathways. Genetic approaches or a soluble IL21R-Fc protein have demonstrated that blocking the IL-21 pathway prevented or greatly ameliorated disease in several mouse strains [52*,73]. A recent preclinical study showed that treatment of B6.Sle1.Yaa mice with an anti-IL-21 antibody reduced germinal center B cells, CD138hi plasmablasts, IFN-γ-dependent IgG2c production and autoantibodies, indicating that Tfh cell-derived IL-21 is critical for pathological B cell cues in lupus [49]. However, targeting the IL-21 pathway may have unintended consequences in CD8+ T cells. In BXSB.Yaa, IL-21 signaling is essential for the maintenance of CD8+ suppressor T cells [74]. Moreover, in the parent → F1 cGVHD model, treatment with IL-21 strongly promoted donor CD8+ T-cell expansion and rescued defective donor antihost CTLs, resulting in host B-cell elimination, decreased autoantibody levels and attenuated renal disease, despite evidence of concurrently enhanced CD4+ T cell help for B cells [50*]. Another approach to eliminate Tfh cells has been to target ICOS/B7RP-1 interactions. Treatment of NZB/W F1 mice with an anti-B7RP-1 antibody decreased the number of Tfh cells and germinal center B cells and ameliorated disease manifestations [47]. It is also been reported that the selective ablation of ICOS ligand in CD11c+ cells, but not in B cells, dramatically ameliorated kidney and lung inflammation in MRL/lpr mice [48**].

**B-cell targets**

BAFF is a cytokine that is required for B-cell development and survival. Largely based on studies in mouse models [75], BAFF blockade has been the first and only biologic treatment approved to treat lupus. BAFF also plays a previously unappreciated role in lupus nephritis by inducing renal tertiary lymphoid structures and regulating the position of T cells in the glomeruli of MRL/lpr mice [54]. Moreover, genetic approaches in the NZM2328 mice demonstrated that the three BAFF/APRIL receptors (BAFF-R, TACI and BCMA) have compensatory roles, suggesting a therapeutic benefit to target multiple receptors [55].

Bruton’s tyrosine kinase (Btk) regulates signaling downstream of the B-cell receptor and Fcγ receptor, and it is also involved in TLR signaling. Treatment with Btk inhibitors alleviate lupus symptoms in MRL/lpr [56], NZB/W F1 [57,58], B6.Sle1.Sle3 [76] and BXSB.Yaa mice [59] as well as in pristane-induced lupus [59]. Overall, based on these preclinical studies, US Food and Drug Administration-approved Btk inhibitor ibrutinib has great potential as a therapeutic agent in SLE.

Finally, two miRNAs have been identified as potent regulators of B-cell tolerance. Elevated miR-148a expression impaired B-cell tolerance by promoting the survival of immature B cells after engagement of the B-cell receptor by suppressing the expression of the autoimmune suppressor Gadd45α, the tumor suppressor Phosphatase and tensin homolog (PTEN) and the proapoptotic protein Bim. Increased expression of miR-148a facilitated the development of lethal autoimmune disease in MRL/lpr mice [60**]. Reduction of miR-148a expression upregulated PTEN in the glomeruli and improved renal function in MRL/lpr mice. [77]. Conversely, miR155 is overexpressed in B cells from B6.lpr mice, and miR155 deletion decreased B-cell activation, autoantibody production, and autoimmune disorder [61].

**Other targets**

Abundant immune complexes can trigger the activation of the NLRP3 inflammasome in macrophages in SLE patients and in mouse models, leading to cell dysfunction and tissue damage [78]. In the NZB/W F1 model, a NLRP3 inhibitor termed ‘Citral’ alleviates lupus symptoms by inhibiting levels of reactive oxygen species, NAPDH and cyclooxygenase-2 [63]. In the pristane-induced model, a more severe lupus-like syndrome developed in mice carrying the Nlrp3<sup>G258W</sup> gain-of-function mutation, providing evidence that NLRP3 plays a role in the development of SLE [64]. In a related pathway, serine/threonine kinase IL-1R-associated kinase 4 (IRAK-4) is a regulator of innate immunity involved in TLR signaling. Treatment with an IRAK4 inhibitor ameliorated lupus symptom in NZB/W F1 and MRL/lpr mice [65]. Finally, it has been proposed that topoisomerase I plays a role in anti-dsDNA antibody
Systemic lupus erythematosus and sjogren syndrome

CONCLUSION
The use of murine models has led to discovery of potential therapeutic targets in diverse signaling pathways dysregulated in SLE. Immune cells, including T cells, B cells, antigen presenting cells and macrophages, are all potential targets in different models of SLE (Fig. 1). Clinical lupus is an extremely complex and diverse disease, and establishment of a mouse model with all features of the disease is very difficult. Various mouse models of SLE, spontaneous, induced or genetically engineered, have been used during the past 30 years, to answer the question of how the alteration of the immune system and target organs leads to break of tolerance to self.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


An update on lupus animal models Li et al.


This study showed that ICODIL – dendritic cells drive end organ inflammation in MRL/lpr mice independently from autoantibody production.


This study used a parent→F1-induced model of systemic lupus of erythematous (SLE) to show the dual effect of IL-21 on the disease.


This study used the NZBWF1 model for a preclinical demonstration of the efficacy of IL-21R blockade.


