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Are lupus animal models useful for understanding and developing new therapies for human SLE?

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Abstract

Systemic lupus erythematosus is a systemic autoimmune disease driven by a complex combination of genetic, environmental, and other immunoregulatory factors. The development of targeted therapies is complicated by heterogeneous clinical manifestations, varying organ involvement, and toxicity. Despite advances in understanding the mechanisms contributing to SLE, only one biologic drug, belimumab, is FDA-approved. The identification and development of potential therapies have largely been driven by studies in lupus animal models. Therefore, direct comparison of both the therapeutic and immunological findings in human and murine SLE studies is critical and can reveal important insights into indeed how useful and relevant are murine studies in SLE drug development. Studies involving belimumab, mycophenolate mofetil, abatacept, rituximab, and anti-interferon strategies generally demonstrated analogous findings in the attenuation of SLE manifestations and modulation of select immune cell populations in human and murine SLE. While further basic and translational studies are needed for identifying SLE patient subsets likely to respond to particular therapeutic modalities and in dissecting complex mechanisms, we believe that despite some inherent weaknesses SLE mouse models will continue to be integral in developing targeted SLE therapies.

Keywords

Systemic lupus erythematosus; murine SLE models; autoimmunity; CyTOF

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Conflict of Interest

The authors have no conflict of interest to report.

1. Introduction

1.1 SLE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that primarily affects women, particularly those of childbearing age.[1] In the US, approximately 20 to 150 people out of 100,000 will be diagnosed with SLE, with increased frequency in Asian, African American, African Caribbean, and Hispanic American populations.[2] Patients may present with a wide array of clinical manifestations ranging from mild arthralgia and rash to more severe features including renal disease, hematologic abnormalities, and neuropsychiatric involvement.

A complex combination of genetic, environmental, hormonal, and other immunoregulatory factors contribute to the loss of tolerance and formation of anti-nuclear autoantibodies observed in SLE. Collectively, evidence implicates an imbalance between the production and clearance of apoptotic material causing activation of toll-like receptors or other nucleic acid recognition receptors that trigger an inflammatory response. This inflammatory response leads to the subsequent upregulation of Type I and II interferons, activation of autoreactive T and B cells, chemokine and cytokine release, and formation of pathogenic autoantibodies, leading in concert to tissue injury and damage in target organs.[3]

1.2 Challenges in the Treatment of SLE

Current SLE treatments are limited given their incomplete effectiveness, non-curative nature, and toxic side effects. However, developing targeted therapies for SLE patients is challenging given the multiple associated immune abnormalities, the variety of organs that can be involved, and the many potential clinical manifestations. Furthermore, SLE patients are often diagnosed at a relatively advanced stage from an immunological perspective, at which point many immune cell subsets including dendritic cells, myeloid cells, and T and B cells have already been aberrantly activated and memory lymphocytes have been formed. While there is a heritable component observed in SLE, usually limited genetic information is available during the initiation and subclinical stages of the disease prior to the formal diagnosis. Despite these well-recognized challenges, understanding the underlying contributing mechanisms should allow for the development of more precise treatments for affected patients with improved efficacy and less toxicity.

1.3 SLE Animal Models

To study the pathogenesis of SLE, researchers have traditionally utilized mouse models to examine mechanisms contributing to disease. Table 1 summarizes the key clinical features of some commonly used lupus animal models in comparison to human disease. These are also highlighted in several excellent review articles.[4–6] Briefly, the classical spontaneous models include the NZB/W F1 and derived congenic strains (e.g. B6.SLE1.SLE), MRL/lpr, and BXSB/Yaa strains, which are genetically predisposed to develop prototypical SLE-like symptoms including high serum anti-nuclear antibody (ANA) levels and immune complex-mediated nephritis. The pristane-induced and the nephrotoxic nephritis models are both useful induced models to study strong type I interferon (IFN) responses and lupus nephritis, respectively. Table 2 calls attention to several key differences between murine lupus models

in widespread use and emphasizes some of the characteristics which have contributed to preferential use of one model over the other, depending on the particular study and the scientific question being asked. Additional details, which are not the focus of this paper, can be found elsewhere.[4–8]

Both spontaneous and induced models are considered to be useful in studying the etiology and mechanisms involved in SLE. The involvement of T cells, B cells, antigen presenting cells, and macrophages in these mouse models has facilitated the subsequent identification of drug targets theoretically translatable to human disease. Furthermore, genetically manipulating mouse strains has provided strong and convincing evidence supporting genetic contributions to mechanisms of disease in SLE. Genetic studies have identified susceptibility loci in spontaneous SLE mouse models, validated susceptibility genes found by GWAS approaches in human lupus patients in the pathogenesis of the disease (i.e. PTPN22, STAT4), and have functionally characterized the contributions of individual proteins and/or pathways in the development of clinical manifestations.[9–11] A fuller description of the genetic contributions to mouse and human lupus is outside the scope of the current review and can be found elsewhere.[10,11] It is important to note that while many of the genes driving autoimmunity in mouse models don't have exact parallels in human disease (e.g. Fas mutations in humans are primarily associated with a non-lupus phenotype), nevertheless mice expressing such susceptibility loci can be valuable tools by accelerating the loss of tolerance and making many studies more feasible.[5] However, these and other important differences between the mouse and human immune systems raise potentially significant concerns regarding the usefulness of SLE mouse models in the development of effective mechanism-driven therapeutics.[12]

1.4 Purpose of Review

This review seeks to determine how helpful SLE animal models have actually been in the development and success of novel drugs in SLE patients. At first glance, it is discouraging as only one drug has been FDA approved in the past 60 years, despite advances in technology and in our understanding of disease. Nevertheless, many drugs are used off-label for lupus and several more are currently under active investigation. Therefore, whether or not the effects of such medications in lupus animal models is applicable and relevant to human disease is a key question with important implications for drug development and clinical research. In this review, the therapeutic and immunological effects of treatments including belimumab, abatacept, mycophenolate mofetil, rituximab, and anti-IFNs will be compared between human and mouse studies, with particular focus on lupus nephritis. By carefully evaluating the successes and failures of these therapies, we can assess the utility of SLE mouse models in the development of effective therapies for human lupus patients.

2. Belimumab

2.1 Introduction

Belimumab, commercially known as Benlysta, was the first targeted biologic approved for the treatment of lupus.[13] Belimumab is a human IgG1λ. recombinant monoclonal antibody targeting BAFF (B cell-activating factor, also referred to as B Lymphocyte Stimulator

(BLyS)). BAFF promotes B cell survival and differentiation and can bind to three potential receptors, BAFF Receptor 3, TACI, and B-cell maturation antigen.[13] BAFF is upregulated in a number of autoimmune diseases, including rheumatoid arthritis,[14] Sjogren's,[15] and SLE.[16–19]

2.2 BAFF Inhibition in Human SLE

2.2.1 Therapeutic effects—Two prominent multi-centric Phase III clinical trials, BLISS-52 and BLISS-76, evaluated the efficacy of intravenous belimumab in SLE patients over the course of 52 and 76 weeks respectively.[20,21] In both trials, belimumab treatment was associated with improvements in disease activity, reduced incidence and severity of disease flares, and steroid-sparing effects.[20–22] Further post hoc univariate and multivariate analyses of pooled data from these two trials demonstrated that belimumab was effective, based on SRI (SLE Responder Index) responses at weeks 52 and 76. These analyses also identified baseline factors associated with increased benefit including more severe disease, low complement levels, anti-dsDNA positivity, and baseline corticosteroid use.[23] Mucocutaneous, musculoskeletal, and immunological domains showed a significant reduction in disease activity in the belimumab-treated groups.[24]

2.2.2 2nd Generation Clinical Trials—A number of second generation BAFF modulating therapies have been explored as additional B cell-modulating therapies. However, compared to the success in the belimumab trials, second generation therapies including blisibimod, tabalumab, and atacicept yielded mixed results.[25–28] Recently, a Phase II atacicept trial concluded that while primary endpoints were not met, there was a trend for increased response rates with atacicept, particularly in patients with high disease activity at baseline.[28]

2.2.3 Immunological Activity—Exploratory studies in a Phase II belimumab trial found that SLE patients with continuous belimumab treatment had significant median percentage reductions in the CD19+, CD20+, naïve (CD20+ CD27-), activated (CD20+ CD69+), and plasmacytoid (CD20+ CD138+) B cell subsets. However, there were no changes in plasma cells. Memory B cells were found be significantly increased at Day 28 but returned to baseline by week 52. Decreased serum IgG, IgA, IgM, and IgE, as well as anti-dsDNA titers, were also observed in the belimumab-treated groups.[29] Additional serological findings and cytometry by time-of-flight (CyTOF, also known as mass cytometry) confirmed that the initial B cell number reduction resulted from the preferential decrease in naïve and transitional B cells.[30] However, with prolonged belimumab treatment, non-class-switched memory B cells and plasma cells decreased after 18 months while BAFF-independent B cells, including class-switched CD27+ IgD- memory B cells, decreased after >7 years of treatment.[31,32] CyTOF immunophenotyping additionally revealed that CD11c+ CD21- B cell clusters, which resemble age-associated B cells, significantly decreased with belimumab treatment.

Despite depletion of approximately 90% of naïve B cells with belimumab, no differences were observed in V, D, or J family gene usage in unmutated IgM heavy chain sequences with treatment. While belimumab had minimal effects on the naïve B cell repertoire,

expression of VH4–34, an immunoglobulin heavy chain gene commonly overrepresented in SLE patients, was lower in plasmablasts of patients treated chronically with belimumab.[32] Multiple studies, however, found no significant changes in the number or proportion of T cells or monocytes in belimumab-treated SLE patients.

2.3 The Role of BAFF in Murine SLE

2.3.1 Therapeutic Effects—Several mouse studies have demonstrated the therapeutic potential of targeting BAFF in SLE. Similar to human SLE disease, circulating BAFF levels were elevated in both NZBWF1 and MRL/lpr strains with disease onset and progression.[33] Furthermore, constitutive overexpression of BAFF either in non-autoimmune mice[33–35] or in autoimmune-prone mice[36] led to SLE-like manifestations, including hypergammaglobulinemia, increased anti-dsDNA antibodies and circulating immune complexes, splenomegaly, and accelerated development of renal pathology.

The first *in vivo* studies for belimumab were not performed in mice due to its lower affinity for murine BAFF.[37] However, alternative methods to inhibit BAFF pathways were utilized by blocking either the specific BAFF receptor (BAFF-R) or the nonspecific receptor, TACI. In NZBWF1 mice, treatment with TACI-Ig resulted in reduced proteinuria, increased survival, and a significant decrease in peripheral B cells. However, no differences were observed in anti-dsDNA titers between TACI-Ig and PBS groups.[33] In NZM2410, selective BAFF-R blockade and nonspecific TACI blockade both delayed disease onset and induced remission after proteinuria development.[38] In BXSB mice, BAFF-R-Ig treatment led to increased survival, decreased renal disease, and reduced autoantibody production.[39]

Recent studies in mice offer additional insight into the requirement of BAFF in SLE manifestations. BAFF was not be required in the development of SLE-like disease as long as B cell survival was independently preserved.[40] This BAFF-independent SLE mouse model provides at least a partial explanation for the heterogeneity of responses with BAFF antagonists, and implies that resistant B cells may continue to promote SLE despite BAFF blockade.

2.3.2 Immunological Activity—In regard to the belimumab's mechanism of action in murine SLE, BAFF blockade in the NZM2410 strain resulted in reduced splenomegaly with significant depletion in T2, marginal zone, follicular B cells, and plasma cells.[38] While TACI blockade had more profound plasma cell depletion, particularly IgG-secreting bone marrow cells, no significant differences were seen in serum IgG levels.[38] In both this study and in the BXSB mice, activation and expansion of T cells was not affected by BAFF-R blockade.[38,39]

3. Mycophenolate Mofetil

3.1 Introduction

Mycophenolate Mofetil, also referred to as MMF or Cellcept, is an immunosuppressant prodrug of mycophenolic acid (MPA). MPA is an inosine monophosphate dehydrogenase (IMPDH) inhibitor, and therefore exerts a cytostatic effect on T and B lymphocytes which have increased dependence on IMPDH for de novo guanosine nucleotide synthesis. Initially

used to prevent acute allograft rejection, MMF has subsequently been used to treat multiple rheumatic diseases, including inducing and maintaining SLE remission.[41]

3.2 MMF in human SLE

3.2.1 Therapeutic Effects—Both ACR and EULAR recommendations position MMF as the first line drug of choice for the treatment of proliferative LN.[42] In systematic reviews and meta-analyses, MMF was found to be associated with higher response rates and fewer adverse events of leukopenia, alopecia, and ovarian failure in induction therapy compared to cyclophosphamide (CYC). For maintenance therapy, comparisons between MMF- and CYC-treated patients revealed that while those receiving MMF had a decreased rate of relapse and leukopenia compared to azathioprine (AZA), there was no difference in the rate of end-stage kidney disease or mortality between the two groups.[43]

In regard to non-renal manifestations, MMF has been found to improve systemic disease activity, and flares were rarely observed.[44] Furthermore, MMF treatment was associated with clinical improvement and remission of mucocutaneous, cardiovascular, vasculitis, and musculoskeletal manifestations.[44,45] These non-renal effects are seen in patients with or without lupus nephritis.[46]

3.2.2 Immunological Activity—MMF treatment has a significant effect on circulating B cell subsets, particularly $CD27^{high}CD38^{high}$ antibody-secreting cells (ASCs). Of those ASCs, a marked decrease was observed in the HLA-DR^{high} population, typically the predominant ASC population in flaring lupus patients, compared to the HLA-DR^{low}, which saw only a moderate change. Correlated to this depletion, MMF treatment also affected serum IgG levels, as compared to the AZA-treated or non-immunosuppressive treatment groups which had elevated ASCs.[47] Additional studies demonstrated that MMF directly inhibits both the proliferation and differentiation of ASCs. Moreover, significantly elevated numbers and percentages of transitional and naïve B cells were noted in the MMF group compared to the AZA group.[47]

With CyTOF immunophenotyping, a significant reduction in the total number of B cells in almost all B cell subsets was observed with MMF treatment, with the exception of IgD^{-} $CD27^{-}$ double-negative memory B cells. Additionally, T cells, particularly T_h17 and T_{reg}, were found to be significantly decreased, perhaps in response to MMF modulating STAT3 pathways.[48] Expression of VEGF, PDGF-BB, CXCL12, and CXCL9 was significantly reduced in MMF-treated patients, inferred to be the result of B cell and STAT3 pathway modulation.[48]

3.3 MMF in Murine SLE

3.3.1 Therapeutic Effects—Similar to humans, an increased dependence to IMPDH is observed in mouse lymphocytes.[49] In the MRL/lpr and NZBWF1 strains, MMF treatment significantly improved survival and decreased albuminuria and serum anti-dsDNA levels.[50–55] Glomerulonephritis in these two strains were ameliorated, with decreased immune complex deposition and glomerulosclerosis.[51,52,54,56] Furthermore, MMF decreased kidney and salivary infiltrates in MRL/lpr mice[57] and dermal infiltration in NZBWF1.[58] In the

NZBWF1 strain, mice treated with MMF were protected from leukopenia or anemia.[54] Furthermore, studies have implicated MMF in attenuating premature atherosclerosis in murine SLE.[59,60]

3.3.2 Immunological Activity—Further analyses have not yielded a unifying mechanism of action for MMF in murine SLE. In the MRL/lpr strain, conflicting trends were observed in the effect of MMF on nitric oxide and inducible nitric oxide synthetase production, urine nitrate excretion,[51,56] and number of splenocyte T cells.[52,57] Additional comparisons revealed significantly decreased percentages of circulating double-negative T cells, increased serum levels of IL-12, and increased IFNγ and IL-10 expression in the spleen.[57] In MMF-treated NZBWF1 mice, no differences were observed in the percentage of CD4, CD8, or IgM positive splenocytes. However, the expression of VLA-4 and ICAM-1 was significantly decreased in CD4+ T cells in treated mice. When immunized, the MMF-treated NZBWF1 mice could not mount a prominent antibody response but cytokine production was unchanged.[55] Additional studies revealed that the inhibited expression of urokinase receptor in podocytes[61] and/or abrogated expression of protein kinase C and fibronectin deposition in the glomeruli and interstitium[62] could be contributing to the benefit of MMF in lupus nephritis.

4. Abatacept

4.1 Introduction

Abatacept, commercially referred to as Orencia, is the soluble form of two CTLA-4 molecules fused to an immunoglobulin constant region.[63] Cytotoxic T lymphocyte Antigen-4 (CTLA-4) is an inhibitory costimulatory molecule that competes to bind CD80 (B7–1) and CD86 (B7–2), thereby playing a critical role in tolerance mechanisms. In addition, CTLA-4 has been shown to play a role in T_{reg} function. Abatacept is FDA-approved for rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis.[64] In SLE patients, soluble plasma CTLA-4 concentrations are significantly elevated compared to healthy controls and are positively correlated to SELENA-SLEDAI disease activity scores.[65]

4.2 Abatacept in Human SLE

4.2.1 Therapeutic Effects—The efficacy of abatacept in human SLE was evaluated in three randomized, double-blind trials: two evaluating lupus nephritis[66,67] and the third evaluating non-life threatening manifestations.[68] The primary outcome for the 12-month lupus nephritis study was the time to confirmed complete response. Despite being well tolerated, the abatacept arm did not meet its primary outcome, although improvements from baseline in anti-dsDNA, C3, and C4 levels were observed in the abatacept group.[66] In the second lupus nephritis trial (the ACCESS trial) similar findings were observed, with the abatacept group not achieving the desired impact on the proportion of subjects who achieve complete renal response at week 24.[67] However, in a reanalysis, the abatacept-treated patients had a >20% response rate compared to the 6% rate in the placebo group, using the rituximab LUNAR trials' definition for response.[69] While this alone does not prove abatacept's efficacy, recent evidence provides support for potentially revisiting abatacept

controlled trials as a small cohort of refractory lupus patients saw improvement in SLEDAI scores and articular involvement.[70]

4.2.2 2nd Generation Clinical Trials—While no formal studies have been performed with belatacept, a second generation CTLA-4 biologic inhibitor, belatacept was initiated for renal indications in six SLE patients. In this cohort, five patients observed creatinine level stabilization after 6 months of therapy, and three patients saw improvements in SLEDAI-2KG, anti-dsDNA, and C3 levels. This retrospective study provides at least preliminary support for exploring the use of belatacept as an alternative therapy to calcineurin inhibitors and their associated toxicities.[71]

4.2.3 Immunological Activity—Limited information is available in regard to abatacept's mechanistic effects in human SLE. However, baseline samples collected in the abatacept trial for non-life threatening SLE manifestations revealed four immunophenotypic clusters of SLE patients.[72] Notably, in SLE patients characterized by high levels of plasma cells, activated dendritic cells, neutrophils, and natural killer cells, abatacept treatment was associated with improvement in BILAG scores, time to flare, and C3 and C4 levels. However, in patients characterized by B and T cell abnormalities at baseline, abatacept treatment was not associated with disease improvement.

4.3 Abatacept in Murine SLE

4.3.1 Therapeutic Effects—Initial SLE mouse model studies demonstrated the potential efficacy of CTLA-4 inhibition in mitigating SLE disease.[73] CTLA-4Ig suppressed the production of autoantibodies, attenuated lupus nephritis, and prolonged life when given preventatively and as treatment in the NZBWF1 mice.[74] Interestingly, the benefits of CTLA-4Ig in NZBWF1 mice extended beyond treatment as anti-dsDNA levels were suppressed 3 months after therapy cessation. Furthermore, combination therapy of CTLA-4Ig with CYC in NZBWF1 mice was effective in achieving nephritis remission.[75] Similar trends in disease attenuation were seen in the MRL/lpr mice, as well as improvements in end organ disease in the kidney and salivary glands.[76] In the BXSB model, CTLA-4Ig treated mice showed a similar suppression of glomerulonephritis and autoantibody production (both during and after treatment cessation).[77]

4.3.2 Immunological Activity—In non-SLE mice, the role of CTLA-4 in regulating immune responses has been well- documented. Indeed, homozygous CTLA-4 deficiency is fatal around 4 weeks of age due to multi-organ lymphocyte infiltration and tissue damage (e.g., severe myocarditis and pancreatitis).[78,79] In mouse transplantation studies, CTLA-4Ig not only alters T cell activation and proliferation, but also subsequently affects B cell activation as antibody production to T cell-dependent antigens is impaired.[80,81] In B6.MRL/lpr mice, CTLA-4Ig treatment significantly decreased ANA, anti-dsDNA, and IL-17A levels, particularly with the co-administration of IL-10 expressing dendritic cells.[82] Furthermore, a similar significant trend was observed the proportion of T_h17 to T_{reg} cells in treated mice.

In the CTLA-4Ig-treated BXSB male mice, the predominant CD4+ T cell population was found to be a naïve T cell phenotype ($CD44^{low}$ $CD45RB^{high}$ $CD62L^{high}$), compared to the control mice that had predominantly activated/memory T cell characteristics ($CD44^{high}$ $CD45RB^{low}$ $CD62L^{low}$).[77] In NZBWF1 mice, the injection of a CTLA-4Ig-expressing adenoviral vector led to a decreased expansion of both IgM and IgG autoreactive B cells, inhibited immunoglobulin class switching, altered pattern of somatic hypermutation, and decreased activated CD69+ CD4 T cell numbers.[83] Bone marrow IgG-secreting B cells were unaffected by CTLA-4Ig, likely not requiring T cell-mediated help. In the pristane-induced lupus model, treatment with a B7–1 short hairpin RNA lentivirus or a neutralizing anti-B7–1 antibody led to a significant reduction of serum ANA, IFNγ, and IL-4 levels as well as attenuating the expression of CD11b, CD11c, Gr1, CD21, CD86, MHC II in splenic B cells.[84]

5. Rituximab

5.1 Introduction

Rituximab, commercially known as Rituxan, is a murine-human chimera anti-CD20 monoclonal antibody designed to deplete cells expressing CD20+, [85] which is an identifying B cell surface marker. CD20 is widely expressed in most B cell subsets except for pro-B cells and terminally differentiated plasmablasts and plasma cells.[86] The extensive role of B cells in SLE has been widely documented, both the expansion of abnormal B cells and the role of B cells in the pathogenesis. [87,88]

Despite being the first B cell differentiation antigen discovered, the function and/or regulation of CD20 has not been fully elucidated. CD20 is believed to be involved in the regulation of B cell activation and proliferation[89,90], as well as to constitute part of the multimeric cell surface complex that regulates Ca^{2+} transport across the plasma membrane.[91,92] The use of rituximab has been FDA approved in rheumatoid arthritis[93], granulomatosis with polyangiitis, and microscopic polyangiitis.[94]

5.2 CD20 Inhibition in Human SLE

5.2.1 Therapeutic Effects—Quite a few trials have been conducted to determine the efficacy of rituximab in SLE, albeit with mixed success.[86,95–105] EXPLORER and LUNAR were randomized, double-blind clinical trials that evaluated the efficacy and safety of rituximab in SLE patients with moderately-to-severely active extrarenal disease[106] or proliferative lupus nephritis,[107] respectively. In both these trials, there were no significant differences between the rituximab-treated and the placebo groups in their respective primary or secondary outcomes, despite robust depletion of CD19+ cells by 2 weeks after initial infusions. Nevertheless, in the LUNAR trial statistical improvements in anti-dsDNA titers and complement levels were seen in the rituximab-treated group.[107] Similarly, a post hoc analysis revealed a reduction in anti-cardiolipin antibodies and an increase in serum complement and BAFF levels in the rituximab-treated group.[108]

5.2.2 2nd Generation Clinical Trial Findings—A second generation of anti-CD20 therapies have been designed to be more effective, better tolerated, and less immunogenic.

[109] These antibodies include ocrelizumab, obinutuzumab, and ofatumumab, which is fully human. Trials using the fully humanized ocrelizumab were halted either due to a lack of response or an increased risk of severe infections.[109] There is a phase II trial for obinutuzumab currently underway that shows promise for lupus nephritis. Early findings are that 34.9% of obinutuzumab-receiving patients meet the trial's primary outcome and 91% of obinutuzumab-receiving patients have no detectable B cells by flow cytometry at 52 weeks.[110–112] A single-center retrospective case series described the potential for the use of ofatumumab as a potential alternative agent, with initial evidence of safety and efficacy in B cell depletion.[113]

5.2.3 Immunological Activity—Analyzing immune cells population may elucidate rituximab's effects in human SLE, particularly those B cells resistant to depletion. The resistant B cells were memory, double negative (IgD- CD27-), and CD5+ phenotype, suggested to be CD19+ plasmablasts with little to no CD20 expression.[114] Furthermore, rituximab treatment was associated with decreased expression of the costimulatory molecules CD40 and CD80 on B cells. This down-regulation could impact T cells and their activation. However, significant increases in activated CD4+, CD8+, and T regulatory cells were observed with rituximab treatment in two separate studies.[99,114]

The role of CD20 in Murine SLE

5.3.1 Therapeutic Effects—In the MRL/lpr and its congenic control, MRL/+, B cell deficiency was achieved by inhibiting heavy chain formation and subsequently B cell maturation. Both B cell-deficient strains were protected from development of glomerulonephritis and interstitial nephritis, and had lower serum IgG and anti-dsDNA levels.[115] Additionally, anti-CD20 approaches ameliorated clinical disease in MRL/lpr,[116] NZBWF1,[116,117] and pristane-accelerated NZBWF1 strains.[118] However, in NZBWF1 mice, anti-CD20 failed to decrease anti-dsDNA or total IgG levels.[117]

5.3.2 Immunological Activity—For B cell deficient MRL/lpr and MRL/+ strains, additional immunological changes included reduced activated and memory T cell populations, while the percentage of naïve T cells increased in these strains.[115] In MRL/lpr mice, a depleting anti-CD20 antibody similarly substantially reduced B cell subsets, which in turn diminished T cell activation.[116] However, resistant B cells were found in secondary lymphoid tissue, which was also a feature in MRL/+ and NZBWF1 mice treated with anti-CD20 antibody. Unless treatment was maintained for a long period of time, splenic B cells in MRL/lpr mice were recalcitrant to depletion.[116] In NZBWF1 mice, these findings were corroborated but also demonstrated that mice with more severe nephritis had increased resistance to B cell depletion. The residual B cells in the spleen were found to be predominantly marginal zone ($CD21^{high}$, $CD23^{low}$) and T2 B cells ($CD21^{high}$, $CD23^{high}$).[117] In combination, these findings infer that B cell intrinsic factors in autoimmune mice contribute to the survival of select resistant B cell subsets.

6. Anti-IFN

6.1 Introduction

Anifrolumab is a fully human monoclonal antibody that binds to the Interferon-α receptor 1 (IFNAR) and prevents signaling from all type I interferons.[119] As a hallmark of SLE, 60–80% of adult SLE patients have a Type I interferon (IFN) signature, defined as a collection of interferon-stimulated genes upregulated in PBMCs.[120–122] Plasmacytoid dendritic cells and their production of Type I IFN are considered to be critical players in the pathogenesis of SLE.[123] Not only have genetic and epigenetic studies identified multiple IFN loci associated with SLE susceptibility, but in some studies the IFN signature correlated with disease activity.[120–122] Furthermore, patients with hepatitis C or melanoma who received IFNα therapeutically have experienced SLE-like manifestations including high ANA titers and arthritis.[124]

6.2 Anti-IFN in Human SLE

6.2.1 Therapeutic Effects—Both the MUSE and TULIP Anifrolumab clinical trials illustrate the potential of anti-IFN biologics in SLE. As a phase IIb, randomized, double-blind study, the MUSE trial met its primary outcome, the percentage of patients achieving a SRI response by 24 weeks of treatment with sustained reduction of corticosteroid use.[125] At 52 weeks of treatment, anifrolumab-treated patients had significant improvements in SRI response and in organ-specific disease such as cutaneous lupus and arthritis manifestations.[126] Furthermore, patients with a high IFN signature at screening experienced greater efficacy with anifrolumab.

The TULIP program was comprised of two phase III clinical trials, titled TULIP 1 and 2. Based on the belimumab trials and success in the MUSE trial, the primary outcome for both were originally identified to be a SRI response. However, mixed success was observed in the TULIP 1 trial as the primary outcome was not met and yet the secondary end points suggested treatment efficacy.[127] Subsequently, the TULIP 2 trial protocol was amended, prior to data analysis, designating BICLA response as its primary endpoint. Notably, it was recently published that the latter primary outcome as well as some secondary end points including improved skin disease and glucocorticoid use were met in the TULIP 2 trial.[128] Overall, improvements in the BICLA response, skin disease, and flare reduction were observed in all three trials, with a SRI response observed only in the TULIP-2 and MUSE trials.[126–128]

6.2.2 Additional Anti-IFN therapies—Additional anti-IFN therapies have been explored in SLE, including rontalizumab and sifalimumab, human anti-IFN-α monoclonal antibodies, and AMG811, a human anti-IFNγ antibody. Similar to the anifrolumab trials, sifalimumab met its primary outcome in a phase IIb randomized, double-blind trial, reducing organ-disease manifestations and other disease activity composites.[129] In contrast, rontalizumab trials have been discontinued after the rontalizumab ROSE phase II study failed to meet either primary or secondary outcomes even in SLE patients with high IFN signature metric scores.[130] Initial data in Phase Ib AMG811 SLE trials demonstrated

efficacy and reduced IFNγ-associated biomarkers but yielded no evidence for clinical improvement.[131]

6.2.3 Immunological Activity—Anifrolumab treatment rapidly and sustainably reversed SLE-associated neutropenia, lymphopenia, monocytopenia, and thrombocytopenia.[132] Specifically, significant increases in class-switched memory B cells and in a number of T cell subsets including CD4, CD8, and CXCR5+/− memory cells were observed in anifrolumab-treated patients. Furthermore, T and B cell-targeting chemokines were significantly decreased including CXCL13, BAFF, CCL19, and endothelial cell markers (i.e. VCAM-1). However, for patients with low interferon signature scores, no significant differences were observed in lymphocyte or neutrophil numbers or subsets. The ability of anifrolumab to suppress plasmacytoid dendritic cell-driven Type 1 interferon production was evaluated in healthy controls.[133]

6.3 Anti-IFN in Murine SLE

6.3.1 Therapeutic Effects—Numerous studies have been performed in SLE mouse models to elucidate the role of interferons in the pathogenesis of murine SLE. IFNAR-deficient NZBWF1, B6/MRL-lpr, and NZM2328 mice showed reduced nephritis and less kidney IgG deposition, as well as reduced anti-dsDNA levels.[134–136] In BXSB male mice treated with anti-IFNAR antibodies, similar improvements in glomerulonephritis and kidney deposits were observed.[137] However, inconsistent results have been observed in the MRL/lpr strain. A transient therapeutic effect was noted with anti-IFNAR treatment as anti-RNA autoantibodies and proteinuria were significantly reduced at 12 weeks of age but not at 16 weeks.[137] In genetic studies however[138], the Type I IFN receptor deficiency worsened lymphoproliferation, autoantibody production, and end organ damage, while the Type II IFN receptor deficiency protected MRL/lpr mice from autoimmune manifestations. Some of the variability in the murine studies has been attributed to the fact that different from human SLE, IFN signatures vary in SLE animal models, ranging from low/weak (MRL/lpr and NZBWF1) to strong (pristane-induced).[139]

6.3.2 Immunological Activity—In the IFNAR −/− NZBWF1 mice, significant decreases in T, B cells, and macrophages were identified, correlating with the observed decrease in splenomegaly. While generally the proportions of these populations were not affected, the frequency of activated CD19+ CD69+ B cells were reduced with IFNAR deficiency which correlated to decreased levels of autoantibodies. Furthermore, IFNAR deficient mice had decreased proliferative in vitro and in vivo responses of B and T cells.[134] Comparatively, in IFNAR −/− NZM2328 mice, both the percentage and number of activated $CD40^{hi}$ plasmacytoid dendritic cells were reduced in the renal lymph node compared to the control NZM2328 mice at 2 months of age, suggesting an early IFNAR-dependent response.[135] At 5 months of age, splenic dendritic cells were reduced in IFNAR deficient NZM mice and had decreased CD40 expression.

In the BXSB mice treated with anti-IFNAR antibody, the decrease in splenic B cells correlated with the attenuated splenomegaly observed.[137] Furthermore, the percent of

activated CD69+ CD4 and CD8 T cells, number of CD11b+ CD11c- monocytes, and MHC I expression in cDCs were reduced in these mice.

7. Discussion

Many challenges limit the development of targeted therapies for SLE, including the heterogeneous manifestations observed in SLE patients and the complex immunological mechanisms underlying this disease. The development of mechanism-driven therapies has been predominantly based on evidence in human SLE patients (i.e. the expansion of autoreactive B cells and/or Type I IFN signature) as well as immunological aberrations in SLE mouse models. However, a number of biologics and immunosuppressants have been tested in SLE clinical trials with little success.

Comparisons between human and mouse SLE findings, particularly the immunological effects, provide insights into the successes and failures of the drugs evaluated in this review. These findings are summarized in Table 1. For the most part, similar therapeutic effects were observed between mouse SLE studies and corresponding clinical trials, including decreased autoantibody production and improved kidney disease. Furthermore, both depleted and resistant immune populations in the treated SLE patient populations were similarly reflected in the mouse studies. This is notable as mouse models could potentially identify enduring cell populations that can potentiate disease manifestations despite treatment. For example, immunological changes associated with belimumab and rituximab treatment revealed not only varied effects between B cell-mediated therapies, but also identified similar populations of B cells resistant to depletion in both mouse and human SLE. Therefore, while the varied clinical responses in treated SLE patients sometimes appear discordant with the more uniform beneficial effects reported in mouse studies, it further demonstrates the complexity of mechanisms driving SLE.

While no singular SLE mouse model perfectly recapitulates human SLE disease, the flexibility of genetic mouse studies can shed some light not only on the potential efficacy of novel drug targets, but also in discerning nuanced mechanisms after a clinical trial. For example, recent mouse studies have revealed the potential redundancy of BAFF in the pathogenesis of SLE-like manifestations, and therefore a possible explanation for a lack of response observed in select SLE patients.

An important facet in the development of a drug from mouse studies to clinical trials is deciding, in advance, on the primary outcomes of a trial, which as we have seen can greatly affect the overall success or failure of a novel drug. There are multiple examples of post hoc and meta-analyses of lupus trials in which previously unrecognized but significant differences were elucidated between the treatment and placebo groups. Recent clinical trial findings in the anifrolumab TULIP trials further highlight the importance of selecting the most appropriate primary outcome.

Recent technology advances are poised to further expand our understanding of both murine and human SLE. For the spontaneous SLE models, the use of the CRISPR/Cas9 system can increase the ease and feasibility of studies in the spontaneous SLE models with their unique

genetic backgrounds. Additionally, immunophenotyping techniques, such as CyTOF, have revealed clusters of SLE patients who were more likely to respond to various treatment strategies. Moreover, single cell RNA sequencing methodologies can provide intricately detailed gene expression information from minute amounts of human biopsy tissue obtained for clinical indications.[140–142] Future clinical trials may benefit from these and other methodological advances and improvements in classification criteria in identifying subsets of SLE patients who will more likely benefit from more precise and targeted therapies.

In summary, the comparisons revealed that SLE mouse models are not only integral in demonstrating potential efficacy, but also in detailing possible mechanisms of action for both the success and failure of treatments after clinical trial completion. While no one single mouse model replicates the human SLE immune system in all its variability and complexity, we believe that lupus animal models are enormously valuable, are currently irreplaceable, and are likely to remain a cornerstone of drug development efforts for human SLE for years to come.

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References

1. Tsokos GC. Systemic Lupus Erythematosus. New England Journal of Medicine. 2011;365(22):2110–2121. doi:10.1056/nejmra1100359 [PubMed: 22129255]
2. Lim SS, Drenkard C. Epidemiology of lupus: an update. Curr Opin Rheumatol. 2015;27(5):427–432. doi:10.1097/B0R.0000000000000198 [PubMed: 26196375]
3. Tsokos GC, Lo MS, Costa Reis P, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol. 2016;12(12):716–730. doi: 10.1038/nrrheum.2016.186 [PubMed: 27872476]
4. Li W, Titov AA, Morel L. An update on lupus animal models. Curr Opin Rheumatol. 2017;29(5):434–441. doi:10.1097/BOR.0000000000000412 [PubMed: 28537986]
5. Richard ML, Gilkeson G. Mouse models of lupus: what they tell us and what they don't. Lupus Science & Medicine. 2018;5(1):e000199. doi:10.1136/lupus-2016-000199 [PubMed: 29387435]
6. Du Y, Sanam S, Kate K, Mohan C. Animal models of lupus and lupus nephritis. Curr Pharm Des. 2015;21(18):2320–2349. doi:10.2174/1381612821666150316115727 [PubMed: 25777751]
7. Fu Y, Du Y, Mohan C. Experimental anti-GBM disease as a tool for studying spontaneous lupus nephritis. Clin Immunol. 2007;124(2):109–118. doi:10.1016/j.clim.2007.05.007 [PubMed: 17640604]
8. Chalmers SA, Doerner J, Bosanac T, et al. Therapeutic Blockade of Immune Complex-Mediated Glomerulonephritis by Highly Selective Inhibition of Bruton's Tyrosine Kinase. Sci Rep 2016;6. doi:10.1038/srep26164 [PubMed: 28442741]
9. Wither JE, Lajoie G, Heinrichs S, et al. Functional dissection of lupus susceptibility loci on the New Zealand black mouse chromosome 1: evidence for independent genetic loci affecting T and B cell activation. J Immunol. 2003;171(4):1697–1706. doi:10.4049/jimmunol.171.4.1697 [PubMed: 12902468]
10. Kono DH, Theofilopoulos AN. Genetics of SLE in mice. Springer Semin Immunopathol. 2006;28(2):83–96. doi: 10.1007/s00281-006-0030-7 [PubMed: 16972052]

11. Mohan C, Putterman C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. Nat Rev Nephrol. 2015;11(6):329–341. doi:10.1038/nrneph.2015.33 [PubMed: 25825084]
12. Mestas J, Hughes CCW. Of Mice and Not Men: Differences between Mouse and Human Immunology. The Journal of Immunology. 2004;172(5):2731–2738. doi:10.4049/jimmunol.172.5.2731 [PubMed: 14978070]
13. Treml JF, Hao Y, Stadanlick JE, Cancro MP. The BLyS Family: Toward a Molecular Understanding of B Cell Homeostasis. CellBiochem Biophys. 2009;53(1):1–16. doi:10.1007/s12013-008-9036-1
14. Cambridge G, Stohl W, Leandro MJ, Migone T-S, Hilbert DM, Edwards JCW. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis Rheum. 2006;54(3):723–732. doi:10.1002/art.21650 [PubMed: 16508933]
15. Gottenberg J-E, Busson M, Cohen-Solal J, et al. Correlation of serum B lymphocyte stimulator and beta2 microglobulin with autoantibody secretion and systemic involvement in primary Sjogren's syndrome. Ann Rheum Dis. 2005;64(7):1050–1055. doi: 10.1136/ard.2004.030643 [PubMed: 15640273]
16. Zhang J, Roschke V, Baker KP, et al. Cutting Edge: A Role for B Lymphocyte Stimulator in Systemic Lupus Erythematosus. The Journal of Immunology. 2001;166(1):6–10. doi:10.4049/jimmunol.166.1.6 [PubMed: 11123269]
17. Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. Arthritis Rheum. 2001;44(6):1313–1319. doi:10.1002/1529-0131(200106)44:6<1313::AID-ART223>3.0.CO;2-S [PubMed: 11407690]
18. Collins CE, Gavin AL, Migone T-S, Hilbert DM, Nemazee D, Stohl W. B lymphocyte stimulator (BLyS) isoforms in systemic lupus erythematosus: disease activity correlates better with blood leukocyte BLyS mRNA levels than with plasma BLyS protein levels. Arthritis Res Ther. 2006;8(1):R6. doi:10.1186/ar1855 [PubMed: 16356193]
19. Stohl W, Metyas S, Tan S-M, et al. B lymphocyte stimulator overexpression in patients with systemic lupus erythematosus: longitudinal observations. Arthritis Rheum. 2003;48(12):3475–3486. doi:10.1002/art.11354 [PubMed: 14673998]
20. Navarra SV, Guzmân RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721–731. doi:10.1016/S0140-6736(10)61354-2 [PubMed: 21296403]
21. Furie R, Petri M, Zamani O, et al. A Phase 3, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits BLyS, in Patients With Systemic Lupus Erythematosus. Arthritis Rheum. 2011;63(12):3918–3930. doi:10.1002/art.30613 [PubMed: 22127708]
22. Blair HA, Duggan ST. Belimumab: A Review in Systemic Lupus Erythematosus. Drugs. 2018;78(3):355–366. doi:10.1007/s40265-018-0872-z [PubMed: 29396833]
23. van Vollenhoven RF, Petri MA, Cervera R, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis. 2012;71(8):1343–1349. doi:10.1136/annrheumdis-2011-200937 [PubMed: 22337213]
24. Manzi S, Sânchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71(11):1833–1838. doi:10.1136/annrheumdis-2011-200831 [PubMed: 22550315]
25. Furie RA, Leon G, Thomas M, et al. A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. Annals of the Rheumatic Diseases. 2015;74(9) :1667–1675. doi:10.1136/annrheumdis-2013-205144 [PubMed: 24748629]
26. Isenberg DA, Petri M, Kalunian K, et al. Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Annals of the Rheumatic Diseases. 2016;75(2):323–331. doi:10.1136/annrheumdis-2015-207653 [PubMed: 26338095]

27. Merrill JT, Vollenhoven RF van, Buyon JP, et al. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Annals of the Rheumatic Diseases. 2016;75(2):332–340. doi:10.1136/annrheumdis-2015-207654 [PubMed: 26293163]

28. Merrill JT, Wallace DJ, Wax S, et al. Efficacy and Safety of Atacicept in Patients With Systemic Lupus Erythematosus. Arthritis Rheumatol. 2018;70(2):266–276. doi:10.1002/art.40360 [PubMed: 29073347]

29. Wallace DJ, Stohl W, Furie RA, et al. A Phase II, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Belimumab in Patients With Active Systemic Lupus Erythematosus. Arthritis Rheum. 2009;61(9):1168–1178. doi:10.1002/art.24699 [PubMed: 19714604]

30. Ramsköld D, Parodis I, Lakshmikanth T, et al. B cell alterations during BAFF inhibition with belimumab in SLE. EBioMedicine. 2018;40:517–527. doi:10.1016/j.ebiom.2018.12.035 [PubMed: 30593436]

31. Jacobi AM, Huang W, Wang T, et al. The Effect of Prolonged Treatment with Belimumab on B cells in Human SLE. Arthritis Rheum. 2010;62(1):201–210. doi:10.1002/art.27189 [PubMed: 20039404]

32. Huang W, Quach TD, Dascalu C, et al. Belimumab promotes negative selection of activated autoreactive B cells in systemic lupus erythematosus patients. JCI Insight. 2018;3(17):e122525. doi:10.1172/jci.insight.122525

33. Gross JA, Johnston J, Mudri S, et al. TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease. Nature. 2000;404(6781):995–999. doi:10.1038/35010115 [PubMed: 10801128]

34. Mackay F, Woodcock SA, Lawton P, et al. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med. 1999;190(11):1697–1710. doi:10.1084/jem.190.11.1697 [PubMed: 10587360]

35. Khare SD, Sarosi I, Xia XZ, et al. Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. Proc Natl Acad Sci USA. 2000;97(7):3370–3375. doi:10.1073/pnas.050580697 [PubMed: 10716715]

36. Stohl W, Xu D, Kim KS, et al. BAFF overexpression and accelerated glomerular disease in mice with an incomplete genetic predisposition to systemic lupus erythematosus. Arthritis & Rheumatism. 2005;52(7):2080–2091. doi:10.1002/art.21138 [PubMed: 15986357]

37. Stohl W, Hilbert DM. The discovery and development of belimumab: the anti-BLyS–lupus connection. NatBiotechnol. 2012;30(1):69–77. doi:10.1038/nbt.2076

38. Ramanujam M, Wang X, Huang W, et al. Similarities and differences between selective and nonselective BAFF blockade in murine SLE. J Clin Invest. 2006;116(3):724–734. doi: 10.1172/JCI26385 [PubMed: 16485042]

39. Ding H, Wang L, Wu X, et al. Blockade of B-cell-activating factor suppresses lupus-like syndrome in autoimmune BXSB mice. J Cell Mol Med. 2010;14(6b):1717–1725. doi:10.1111/j.1582-4934.2009.00817.x [PubMed: 19627403]

40. Stohl W, Yu N, Chalmers S, Putterman C, Jacob CO. Development of Murine Systemic Lupus Erythematosus in the Absence of BAFF. Arthritis & Rheumatology. 2020;72(2):292–302. doi:10.1002/art.41097 [PubMed: 31493335]

41. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47(2):85–118. doi: 10.1016/S0162-3109(00)00188-0 [PubMed: 10878285]

42. Mok CC. Mycophenolate mofetil for lupus nephritis: an update. Expert Rev Clin Immunol. 2015;11(12):1353–1364. doi:10.1586/1744666X.2015.1087314 [PubMed: 26364748]

43. Chen Y, Sun J, Zou K, Yang Y, Liu G. Treatment for lupus nephritis: an overview of systematic reviews and meta-analyses. RheumatolInt. 2017;37(7):1089–1099. doi:10.1007/s00296-017-3733-2

44. Ginzler EM, Wofsy D, Isenberg D, Gordon C, Lisk L, Dooley M-A. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: Findings in a multicenter, prospective, randomized, open-label, parallel-group

clinical trial. Arthritis & Rheumatism. 2010;62(1):211–221. doi:10.1002/art.25052 [PubMed: 20039429]

45. Jung UH, Kwak SG, Choe J-Y, Lee S-S, Kim S-K. The Effect of Mycophenolate Mofetil on Non-Renal Manifestations in Systemic Lupus Erythematosus: Results from Korean Lupus Network Registry. J Korean Med Sci. 2019;34(27). doi:10.3346/jkms.2019.34.e185
46. Tselios K, Gladman DD, Su J, Urowitz MB. Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study. J Rheumatol. 2016;43(3):552–558. doi:10.3899/jrheum.150779 [PubMed: 26773121]
47. Eickenberg S, Mickholz E, Jung E, Nofer J-R, Pavenstadt HJ, Jacobi AM. Mycophenolic acid counteracts B cell proliferation and plasmablast formation in patients with systemic lupus erythematosus. Arthritis Res Ther. 2012;14(3):R110. doi:10.1186/ar3835 [PubMed: 22571761]
48. Slight-Webb S, Guthridge JM, Chakravarty EF, et al. Mycophenolate mofetil reduces STAT3 phosphorylation in systemic lupus erythematosus patients. JCI Insight. 4(2). doi:10.1172/jci.insight.124575
49. Gu JJ, Stegmann S, Gathy K, et al. Inhibition of T lymphocyte activation in mice heterozygous for loss of the IMPDH II gene. J Clin Invest. 2000;106(4):599–606. [PubMed: 10953035]
50. Guo H, Leung JCK, Chan LYY, Lui SL, Tsang AWL, Lai KN. Modulation of intrapulmonary TGF-beta expression by mycophenolate mofetil in lupus prone MRL/lpr mice. Lupus. 2005;14(8):583–592. doi:10.1191/0961203305lu2170oa [PubMed: 16175929]
51. Lui SL, Tsang R, Wong D, et al. Effect of mycophenolate mofetil on severity of nephritis and nitric oxide production in lupus-prone MRL/lpr mice. Lupus. 2002;11(7):411–418. doi:10.1191/0961203302lu214oa [PubMed: 12195781]
52. Van Bruggen MC, Walgreen B, Rijke TP, Berden JH. Attenuation of murine lupus nephritis by mycophenolate mofetil. J Am Soc Nephrol. 1998;9(8):1407–1415. [PubMed: 9697662]
53. Ramos MA, Pinera C, Setién MA, et al. Modulation of autoantibody production by mycophenolate mofetil: effects on the development of SLE in (NZB x NZW)F1 mice. Nephrol Dial Transplant. 2003;18(5):878–883. doi:10.1093/ndt/gfg034 [PubMed: 12686658]
54. Corna D, Morigi M, Facchinetti D, Bertani T, Zoja C, Remuzzi G. Mycophenolate mofetil limits renal damage and prolongs life in murine lupus autoimmune disease. Kidney International. 1997;51(5):1583–1589. doi:10.1038/ki.1997.217 [PubMed: 9150476]
55. McMurray RW, Elbourne KB, Lagoo A, Lal S. Mycophenolate mofetil suppresses autoimmunity and mortality in the female NZB x NZW F1 mouse model of systemic lupus erythematosus. J Rheumatol. 1998;25(12):2364–2370. [PubMed: 9858431]
56. Yu CC, Yang CW, Wu MS, et al. Mycophenolate mofetil reduces renal cortical inducible nitric oxide synthase mRNA expression and diminishes glomerulosclerosis in MRL/lpr mice. J Lab Clin Med. 2001;138(1):69–77. doi:10.1067/mlc.2001.115647 [PubMed: 11433230]
57. Jonsson CA, Erlandsson M, Svensson L, Molne J, Carlsten H. Mycophenolate mofetil ameliorates perivascular T lymphocyte inflammation and reduces the double-negative T cell population in SLE-prone MRLlpr/lpr mice. Cell Immunol. 1999;197(2):136–144. doi:10.1006/cimm.1999.1570 [PubMed: 10607431]
58. Lee Y-F, Cheng C-C, Lan J-L, et al. Effects of mycophenolate mofetil on cutaneous lupus erythematosus in (NZB x NZW) F1 mice. J Chin Med Assoc 2013;76(11):615–623. doi:10.1016/jjcma.2013.07.010 [PubMed: 23968808]
59. Richez C, Richards RJ, Duffau P, et al. The effect of mycophenolate mofetil on disease development in the gld.apoE (−/−) mouse model of accelerated atherosclerosis and systemic lupus erythematosus. PLoSONE. 2013;8(4):e61042. doi:10.1371/journal.pone.0061042
60. van Leuven SI, Mendez-Fernandez YV, Wilhelm AJ, et al. Mycophenolate mofetil but not atorvastatin attenuates atherosclerosis in lupus-prone LDLr(−/−) mice. Ann Rheum Dis. 2012;71(3):408–414. doi:10.1136/annrheumdis-2011-200071 [PubMed: 21953346]
61. Cheng C-C, Lee Y-F, Lan J-L, et al. Mycophenolate mofetil alleviates lupus nephritis through urokinase receptor signaling in a mice model. Lupus. 2013;22(6):554–561. doi:10.1177/0961203313480398 [PubMed: 23478030]
62. Yung S, Zhang Q, Zhang CZ, Chan KW, Lui SL, Chan TM. Anti-DNA antibody induction of protein kinase C phosphorylation and fibronectin synthesis in human and murine lupus and the

effect of mycophenolic acid. Arthritis Rheum. 2009;60(7):2071–2082. doi: 10.1002/art.24573 [PubMed: 19565476]

63. Esensten JH, Helou YA, Chopra G, Weiss A, Bluestone JA. CD28 Costimulation: From Mechanism to Therapy. Immunity. 2016;44(5):973–988. doi:10.1016/j.immuni.2016.04.020 [PubMed: 27192564]
64. Orencia (abatacept) FDA Approval History. Drugs.com Accessed April 14, 2020 https://www.drugs.com/history/orencia.html
65. Wong CK, Lit LCW, Tam LS, Li EK, Lam CWK. Aberrant production of soluble costimulatory molecules CTLA-4, CD28, CD80 and CD86 in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2005;44(8):989–994. doi: 10.1093/rheumatology/keh663 [PubMed: 15870153]
66. Furie R, Nicholls K, Cheng T-T, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis & Rheumatology (Hoboken, NJ). 2014;66(2):379–389. doi:10.1002/art.38260
67. ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. Arthritis & Rheumatology (Hoboken, NJ). 2014;66(11):3096–3104. doi:10.1002/art.38790
68. Merrill JT, Burgos-Vargas R, Westhovens R, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62(10):3077–3087. doi:10.1002/art.27601 [PubMed: 20533545]
69. Wofsy D, Hillson JL, Diamond B. Comparison of alternative primary outcome measures for use in lupus nephritis clinical trials. Arthritis Rheum. 2013;65(6):1586–1591. doi:10.1002/art.37940 [PubMed: 23529285]
70. Danion F, Rosine N, Belkhir R, et al. Efficacy of abatacept in systemic lupus erythematosus: a retrospective analysis of 11 patients with refractory disease. Lupus. 2016;25(13): 1440–1447. doi:10.1177/0961203316640911 [PubMed: 27013663]
71. Carrion-Barberà I, Fajardo M, Danias G, et al. Belatacept in kidney transplant patients with systemic lupus erythematosus. Lupus SciMed. 2019;6(1):e000355. doi:10.1136/lupus-2019-000355
72. Bandyopadhyay S, Connolly SE, Jabado O, et al. Identification of biomarkers of response to abatacept in patients with SLE using deconvolution of whole blood transcriptomic data from a phase IIb clinical trial. Lupus Sci Med. 2017;4(1):e000206. doi:10.1136/lupus-2017-000206 [PubMed: 29214034]
73. Davidson A, Diamond B, Wofsy D, Daikh D. Block and tackle: CTLA4Ig takes on lupus. Lupus. 2005;14(3):197–203. doi:10.1191/0961203305lu2136oa [PubMed: 15807196]
74. Finck BK, Linsley PS, Wofsy D. Treatment of murine lupus with CTLA4Ig. Science. 1994;265(5176): 1225–1227. doi:10.1126/science.7520604 [PubMed: 7520604]
75. Cunnane G, Chan OTM, Cassafer G, et al. Prevention of renal damage in murine lupus nephritis by CTLA-4Ig and cyclophosphamide. Arthritis Rheum. 2004;50(5):1539–1548. doi:10.1002/art.20147 [PubMed: 15146424]
76. Takiguchi M, Murakami M, Nakagawa I, et al. Blockade of CD28/CTLA4-B7 pathway prevented autoantibody-related- diseases but not lung disease in MRL/Ipr mice. Laboratory investigation; a journal of technical methods and pathology. 1999;79(3):317–326. [PubMed: 10092068]
77. Chu EB, Hobbs MV, Wilson CB, Romball CG, Linsley PS, Weigle WO. Intervention of CD4+ cell subset shifts and autoimmunity in the BXSB mouse by murine CTLA4Ig. The Journal of Immunology. 1996; 156(3): 1262–1268. [PubMed: 8558006]
78. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity. 1995;3(5): 541–547. doi:10.1016/1074-7613(95)90125-6 [PubMed: 7584144]
79. Waterhouse P, Penninger JM, Timms E, et al. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. Science. 1995;270(5238):985–988. doi:10.1126/science.270.5238.985 [PubMed: 7481803]

80. Sandner SE, Salama AD, Houser SL, Palmer E, Turka LA, Sayegh MH. New TCR transgenic model for tracking allospecific CD4 T-cell activation and tolerance in vivo. Am J Transplant. 2003;3(10):1242–1250. doi:10.1046/j.1600-6143.2003.00220.x [PubMed: 14510697]
81. Judge TA, Tang A, Spain LM, Gratiot-Deans J, Sayegh MH, Turka LA. The In Vivo Mechanism of Action of CTLA4Ig. J Immunol. 1996;156(6):2294–2299. [PubMed: 8690920]
82. Huang C, Zhang L, Ling F, et al. Effect of immune tolerance induced by immature dendritic cells and CTLA4-Ig on systemic lupus erythematosus: An in vivo study. Experimental and Therapeutic Medicine. 2018;15(3):2499–2506. doi:10.3892/etm.2018.5697 [PubMed: 29456655]
83. Mihara M, Tan I, Chuzhin Y, et al. CTLA4Ig inhibits T cell-dependent B-cell maturation in murine systemic lupus erythematosus. J Clin Invest. 2000;106(1):91–101. [PubMed: 10880052]
84. HUANG L KONG Y, WANG J, SUN J, SHI Q, QIU Y-H. Reducing progression of experimental lupus nephritis via inhibition of the B7/CD28 signaling pathway. Mol Med Rep. 2015;12(3):4187–4195. doi:10.3892/mmr.2015.3953 [PubMed: 26096149]
85. Murphy G, Isenberg DA. New therapies for systemic lupus erythematosus - past imperfect, future tense. Nat Rev Rheumatol 2019;15(7):403–412. doi:10.1038/s41584-019-0235-5 [PubMed: 31165780]
86. Leandro MJ. B-cell subpopulations in humans and their differential susceptibility to depletion with anti-CD20 monoclonal antibodies. Arthritis Res Ther. 2013;15(Suppl 1):S3. doi: 10.1186/ar3908
87. Nashi E, Wang Y, Diamond B. The Role Of B Cells in Lupus Pathogenesis. Int JBiochem Cell Biol. 2010;42(4):543–550. doi:10.1016/j.biocel.2009.10.011 [PubMed: 19850148]
88. Dorner T, Giesecke C, Lipsky PE. Mechanisms of B cell autoimmunity in SLE. Arthritis Res Ther. 2011;13(5):243. doi:10.1186/ar3433 [PubMed: 22078750]
89. Tedder TF, Boyd AW, Freedman AS, Nadler LM, Schlossman SF. The B cell surface molecule B1 is functionally linked with B cell activation and differentiation. J Immunol. 1985;135(2):973–979. [PubMed: 3925015]
90. Tedder TF, Forsgren A, Boyd AW, Nadler LM, Schlossman SF. Antibodies reactive with the B1 molecule inhibit cell cycle progression but not activation of human B lymphocytes. Eur J Immunol. 1986;16(8):881–887. doi:10.1002/eji.1830160802 [PubMed: 3091375]
91. Kanzaki M, Lindorfer MA, Garrison JC, Kojima I. Activation of the calcium-permeable cation channel CD20 by alpha subunits of the Gi protein. J Biol Chem. 1997;272(23):14733–14739. doi: 10.1074/jbc.272.23.14733 [PubMed: 9169438]
92. Bubien JK, Zhou LJ, Bell PD, Frizzell RA, Tedder TF. Transfection of the CD20 cell surface molecule into ectopic cell types generates a Ca2+ conductance found constitutively in B lymphocytes. J Cell Biol. 1993;121(5): 1121–1132. doi:10.1083/jcb.121.5.1121 [PubMed: 7684739]
93. Gürcan HM, Keskin DB, Stern JNH, Nitzberg MA, Shekhani H, Ahmed AR. A review of the current use of rituximab in autoimmune diseases. International Immunopharmacology. 2009;9(1):10–25. doi:10.1016/j.intimp.2008.10.004 [PubMed: 19000786]
94. US Food and Drug Administration. FDA approves first treatment for children with rare diseases that cause inflammation of small blood vessels. Press Release. Published March 24, 2020. Accessed March 27, 2020 http://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-children-rare-diseases-cause-inflammation-small-blood-vessels
95. Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: A phase I/II dose-escalation trial of rituximab. Arthritis & Rheumatism. 2004;50(8):2580–2589. doi:10.1002/art.20430 [PubMed: 15334472]
96. Gottenberg J-E, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Annals of the Rheumatic Diseases. 2005;64(6):913–920. doi:10.1136/ard.2004.029694 [PubMed: 15550531]
97. Marks SD, Patey S, Brogan PA, et al. B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus. Arthritis & Rheumatism. 2005;52(10):3168–3174. doi:10.1002/art.21351 [PubMed: 16200620]
98. Willems M, Haddad E, Niaudet P, et al. Rituximab therapy for childhood-onset systemic lupus erythematosus. The Journal of Pediatrics. 2006;148(5):623–627.e3. doi:10.1016/jjpeds.2006.01.041 [PubMed: 16737873]

99. Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopulos O, et al. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthritis Research & Therapy. 2006;8(3):R83. doi:10.1186/ar1954 [PubMed: 16677395]
100. Smith KGC, Jones RB, Burns SM, Jayne DRW. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. Arthritis & Rheumatism. 2006;54(9):2970–2982. doi:10.1002/art.22046 [PubMed: 16947528]
101. Tokunaga M, Saito K, Kawabata D, et al. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. Annals of the Rheumatic Diseases. 2007;66(4):470–475. doi:10.1136/ard.2006.057885 [PubMed: 17107983]
102. Tokunaga M, Fujii K, Saito K, et al. Down-regulation of CD40 and CD80 on B cells in patients with life-threatening systemic lupus erythematosus after successful treatment with rituximab. Rheumatology (Oxford). 2005;44(2):176–182. doi:10.1093/rheumatology/keh443 [PubMed: 15494350]
103. Gunnarsson I, Sundelin B, Jonsdottir T, Jacobson SH, Henriksson EW, Vollenhoven RF van. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. Arthritis & Rheumatism. 2007;56(4): 1263–1272. doi:10.1002/art.22505 [PubMed: 17393458]
104. Ng KP, Cambridge G, Leandro MJ, Edwards JCW, Ehrenstein M, Isenberg DA. B cell depletion therapy in systemic lupus erythematosus: long-term follow-up and predictors of response. Ann Rheum Dis. 2007;66(9):1259–1262. doi:10.1136/ard.2006.067124 [PubMed: 17412738]
105. Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology (Oxford). 2005;44(12):1542–1545. doi: 10.1093/rheumatology/kei080 [PubMed: 16188950]
106. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62(1):222–233. doi:10.1002/art.27233 [PubMed: 20039413]
107. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012;64(4):1215–1226. doi:10.1002/art.34359 [PubMed: 22231479]
108. Tew GW, Rabbee N, Wolslegel K, et al. Baseline autoantibody profiles predict normalization of complement and anti-dsDNA autoantibody levels following rituximab treatment in systemic lupus erythematosus. Lupus. 2010;19(2):146–157. doi: 10.1177/0961203309350752 [PubMed: 19946034]
109. Du FH, Mills EA, Mao-Draayer Y. Next-generation anti-CD20 monoclonal antibodies in autoimmune disease treatment. Auto Immun Highlights. 2017;8(1). doi:10.1007/s13317-017-0100-y
110. Schindler T, Rovin B, Furie R, et al. AB0423 Nobility, A Phase 2 Trial To Assess The Safety and Efficacy of Obinutuzumab, A Novel Type 2 Anti-CD20 Monoclonal Antibody (MAB), in Patients (PTS) with ISN/RPS Class III or IV Lupus Nephritis (LN). Annals of the Rheumatic Diseases. 2016;75(Suppl 2): 1051–1051. doi:10.1136/annrheumdis-2016-eular.2397 [PubMed: 26823530]
111. Campbell P Obinutuzumab for Treatment of Lupus Nephritis Shows Promise in Phase 2 Trial. HCPLive. Accessed March 28, 2020 https://www.mdmag.com/conference-coverage/acr-2019/obinutuzumab-for-lupus-nephritis-phase-2-trial
112. A Study to Evaluate the Safety and Efficacy of Obinutuzumab Compared With Placebo in Participants With Lupus Nephritis (LN) - Tabular View - ClinicalTrials.gov Accessed March 28, 2020 https://clinicaltrials.gov/ct2/show/record/NCT02550652
113. Masoud S, McAdoo SP, Bedi R, Cairns TD, Lightstone L. Ofatumumab for B cell depletion in patients with systemic lupus erythematosus who are allergic to rituximab. Rheumatology (Oxford). 2018;57(7): 1156–1161. doi:10.1093/rheumatology/key042 [PubMed: 29562252]
114. Vallerskog T, Gunnarsson I, Widhe M, et al. Treatment with rituximab affects both the cellular and the humoral arm of the immune system in patients with SLE. Clinical Immunology. 2007;122(1):62–74. doi:10.1016/j.clim.2006.08.016 [PubMed: 17046329]

115. Wen J, Doerner J, Chalmers S, et al. B cell and/or autoantibody deficiency do not prevent neuropsychiatric disease in murine systemic lupus erythematosus. J Neuroinflammation. 2016;13(1):73. doi:10.1186/s12974-016-0537-3 [PubMed: 27055816]
116. Ahuja A, Shupe J, Dunn R, Kashgarian M, Kehry MR, Shlomchik MJ. Depletion of B Cells in Murine Lupus: Efficacy and Resistance. The Journal of Immunology. 2007;179(5):3351–3361. doi:10.4049/jimmunol.179.5.3351 [PubMed: 17709552]
117. Bekar KW, Owen T, Dunn R, et al. Prolonged effects of short-term anti-CD20 B cell depletion therapy in murine systemic lupus erythematosus. Arthritis Rheum. 2010;62(8):2443–2457. doi:10.1002/art.27515 [PubMed: 20506300]
118. Lin W, Seshasayee D, Lee WP, et al. Dual B Cell Immunotherapy Is Superior to Individual Anti-CD20 Depletion or BAFF Blockade in Murine Models of Spontaneous or Accelerated Lupus. Arthritis & Rheumatology. 2015;67(1):215–224. doi:10.1002/art.38907 [PubMed: 25303150]
119. Felten R, Scher F, Sagez F, Chasset F, Arnaud L. Spotlight on anifrolumab and its potential for the treatment of moderate-to-severe systemic lupus erythematosus: evidence to date. DrugDes Devel Ther. 2019;13:1535–1543. doi:10.2147/DDDT.S170969
120. Crow MK. Type I Interferon in the Pathogenesis of Lupus. The Journal of Immunology. 2014;192(12):5459–5468. doi:10.4049/jimmunol.1002795 [PubMed: 24907379]
121. Obermoser G, Pascual V. The interferon-alpha signature of systemic lupus erythematosus. Lupus. 2010;19(9):1012–1019. doi:10.1177/0961203310371161 [PubMed: 20693194]
122. Rönnblom L, Leonard D. Interferon pathway in SLE: one key to unlocking the mystery of the disease. Lupus Science & Medicine. 2019;6(1):e000270. doi:10.1136/lupus-2018-000270 [PubMed: 31497305]
123. Kim J-M, Park S-H, Kim H-Y, Kwok S-K. A Plasmacytoid Dendritic Cells-Type I Interferon Axis Is Critically Implicated in the Pathogenesis of Systemic Lupus Erythematosus. Int J Mol Sci. 2015;16(6): 14158–14170. doi:10.3390/ijms160614158 [PubMed: 26110387]
124. Rönnblom LE, Alm GV, Oberg KE. Possible induction of systemic lupus erythematosus by interferon-alpha treatment in a patient with a malignant carcinoid tumour. J Intern Med. 1990;227(3):207–210. doi:10.1111/j.1365-2796.1990.tb00144.x [PubMed: 1690258]
125. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis & Rheumatology (Hoboken, NJ). 2017;69(2):376–386. doi:10.1002/art.39962
126. Merrill JT, Furie R, Werth VP, et al. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. Lupus Sci Med. 2018;5(1):e000284. doi:10.1136/lupus-2018-000284 [PubMed: 30588322]
127. Furie RA, Morand EF, Bruce IN, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. The Lancet Rheumatology. 2019;1(4):e208–e219. doi:10.1016/S2665-9913(19)30076-1
128. Morand EF, Furie R, Tanaka Y, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. NEngl JMed. 2020;382(3):211–221. doi:10.1056/NEJMoa1912196
129. Khamashta M, Merrill JT, Werth VP, et al. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016;75(11):1909–1916. doi:10.1136/annrheumdis-2015-208562 [PubMed: 27009916]
130. Kalunian KC, Merrill JT, Maciuca R, et al. A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2016;75(1):196–202. doi:10.1136/annrheumdis-2014-206090 [PubMed: 26038091]
131. Boedigheimer MJ, Martin DA, Amoura Z, et al. Safety, pharmacokinetics and pharmacodynamics of AMG 811, an anti-interferon-γ monoclonal antibody, in SLE subjects without or with lupus nephritis. Lupus Sci Med. 2017;4(1):e000226. doi: 10.1136/lupus-2017-000226 [PubMed: 29018537]
132. Casey KA, Guo X, Smith MA, et al. Type I interferon receptor blockade with anifrolumab corrects innate and adaptive immune perturbations of SLE. Lupus Sci Med. 2018;5(1):e000286. doi:10.1136/lupus-2018-000286 [PubMed: 30538817]

133. Riggs JM, Hanna RN, Rajan B, et al. Characterisation of anifrolumab, a fully human anti-interferon receptor antagonist antibody for the treatment of systemic lupus erythematosus. Lupus Science & Medicine. 2018;5(1):e000261. doi:10.1136/lupus-2018-000261 [PubMed: 29644082]
134. Santiago-Raber M-L, Baccala R, Haraldsson KM, et al. Type-I Interferon Receptor Deficiency Reduces Lupus-like Disease in NZB Mice. J Exp Med. 2003;197(6):777–788. doi:10.1084/jem.20021996 [PubMed: 12642605]
135. Agrawal H, Jacob N, Carreras E, et al. Deficiency of Type I IFN Receptor in Lupus-Prone New Zealand Mixed 2328 Mice Decreases Dendritic Cell Numbers and Activation and Protects from Disease. The Journal of Immunology. 2009;183(9):6021–6029. doi:10.4049/jimmunol.0803872 [PubMed: 19812195]
136. Braun D, Geraldes P, Demengeot J. Type I Interferon controls the onset and severity of autoimmune manifestations in lpr mice. Journal of Autoimmunity. 2003;20(1):15–25. doi:10.1016/S0896-8411(02)00109-9 [PubMed: 12604309]
137. Baccala R, Gonzalez-Quintial R, Schreiber RD, Lawson BR, Kono DH, Theofilopoulos AN. Anti-IFNAR Antibody Treatment Ameliorates Disease in Lupus-Predisposed Mice. J Immunol. 2012;189(12):5976–5984. doi:10.4049/jimmunol.1201477 [PubMed: 23175700]
138. Hron JD, Peng SL. Type I IFN protects against murine lupus. J Immunol. 2004;173(3):2134–2142. doi:10.4049/jimmunol.173.3.2134 [PubMed: 15265950]
139. Zhuang H, Szeto C, Han S, Yang L, Reeves WH. Animal Models of Interferon Signature Positive Lupus. Front Immunol. 2015;6. doi:10.3389/fimmu.2015.00291 [PubMed: 25688242]
140. Der E, Ranabothu S, Suryawanshi H, et al. Single cell RNA sequencing to dissect the molecular heterogeneity in lupus nephritis. JCIInsight. 2017;2(9). doi: 10.1172/jci.insight.93009
141. Der E, Suryawanshi H, Morozov P, et al. Tubular cell and keratinocyte single-cell transcriptomics applied to lupus nephritis reveal type I IFN and fibrosis relevant pathways. Nat Immunol. 2019;20(7):915–927. doi:10.1038/s41590-019-0386-1 [PubMed: 31110316]
142. Arazi A, Rao DA, Berthier CC, et al. The immune cell landscape in kidneys of patients with lupus nephritis. Nat Immunol. 2019;20(7):902–914. doi:10.1038/s41590-019-0398-x [PubMed: 31209404]
143. Smith CD, Cyr M. The history of lupus erythematosus. From Hippocrates to Osler. Rheum Dis Clin North Am. 1988; 14(1): 1–14.
144. Dubois EL, Horowitz RE, Demopoulos HB, Teplitz R. NZB/NZW mice as a model of systemic lupus erythematosus. JAMA. 1966;195(4):285–289. [PubMed: 4159181]
145. Murphy E, Roths J. A Single gene model for massive lymphoproliferation with immune complex disease in new mouse strain MRL. Proceedings of the 16th International Congress in Hematology Published online January 1, 1978:69–72.
146. Andrews BS, Eisenberg RA, Theofilopoulos AN, et al. Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. J Exp Med. 1978; 148(5): 1198–1215. doi:10.1084/jem.148.5.1198 [PubMed: 309911]
147. Satoh M, Reeves WH. Induction of lupus-associated autoantibodies in BALB/c mice by intraperitoneal injection of pristane. J Exp Med. 1994;180(6):2341–2346. doi:10.1084/jem.180.6.2341 [PubMed: 7964507]
148. Celhar T, Fairhurst A-M. Modelling clinical systemic lupus erythematosus: similarities, differences and success stories. Rheumatology (Oxford). 2017;56(suppl_1):i88–i99. doi:10.1093/rheumatology/kew400 [PubMed: 28013204]
149. Perry D, Sang A, Yin Y, Zheng Y-Y, Morel L. Murine models of systemic lupus erythematosus. JBiomedBiotechnol. 2011;2011:271694. doi:10.1155/2011/271694
150. Reeves WH, Lee PY, Weinstein JS, Satoh M, Lu L. Induction of autoimmunity by pristane and other naturally-occurring hydrocarbons. Trends Immunol. 2009;30(9):455–464. doi:10.1016/j.it.2009.06.003 [PubMed: 19699150]
151. IFNα Inducible Models of Murine SLE. Accessed May 13, 2020 https://www-ncbi-nlm-nih-gov.elibrary.einstein.yu.edu/pmc/articles/PMC3788378/
152. Morel L Genetics of SLE: evidence from mouse models. Nat Rev Rheumatol. 2010;6(6) :348–357. doi:10.1038/nrrheum.2010.63 [PubMed: 20440287]

Highlights

- Similar therapeutic and immunological effects are observed in human and murine SLE studies
- Studies with belimumab and rituximab treatment reveal resistant B cell populations, present in both human and murine SLE
- CyTOF immunophenotyping can identify potential SLE patient clusters more likely to respond to specific therapies
- Testing in lupus animal models remains an important avenue in SLE drug development

Table 1:

Comparison of Human and Mouse SLE Manifestations *

	Human	Mouse Models			
		NZB/WF1	**MRL/lpr**	**BXSB**	**Pristane-Induced**
Year of first description/discovery	1833[143]	1966[144]	1976[145]	1978[146]	1994[147]
Female (F)/Male (M) ratio	F>>M	F>>M	F>M	M>>F	F>M
Age of onset[4–6,148–150]	15–44 years	25 weeks	8 weeks	9 weeks	4 weeks
Mean Survival[4–6,148–150]		45 weeks	17 weeks	30 weeks	25 weeks
IFN signature[5,151]	Strong	Weak	Weak	Unclear	Strong
Clinical Manifestations[5]					
ANA/ anti-dsDNA	+	+	+	+	+
Low complement	+	+	+	+	+
Nephritis	+	+	+	+	+
Neurological involvement	+	+	+	–	–
Skin manifestations	+	–	+	–	–
Arthritis	+ <	–	+	–	–
Relative popularity **		5	26	4	3

* Adapted in part from References 5 and 148.

** Relative popularity depicts the number of Pubmed research articles (rounded, × 100) containing the respective strain/model names

Table 2:

Key features of SLE Animal Models *

Category	Mouse Model Family	Associated strains/models	Genetic Loci[9–11,152]	Implicated Pathways	Organ Manifestations Usually Studied	Advantages	Disadvantages
Spontaneous	NZB/WF1	NZM2328, NZM2410, SLE1-3	Spg3, Nba2, SLE1-3	Genetic susceptibility	nephritis, vasculitis	Multigenic disease; Can be accelerated by interferon	Slow development of disease; Requires cross of two strains to generate lupus prone mice
	MRL/lpr	MRL/+, B6. lpr	Lmb3, Fas	Fas-mediated apoptosis	Nephritis; neuropsychiatric manifestations, skin, vasculitis, arthritis, salivary gland infiltration modeling Sjogren's	Recapitulates many of the clinical manifestations observed in human SLE; Early disease onset; Severe disease	Fas mutations do not drive human SLE; Lympadenopathy, splenomegaly, and double negative T cells are absent or much less common in human lupus
	BXSB	TLR7-tg	Bxs1-6	TLR7-induced production of IFN	nephritis	Evaluation of TLR7-driven mechanisms	Male predominance does not reflect human SLE
Induced	Pristane		---		nephritis, arthritis, pulmonary vasculitis	Inducible in non-autoimmune strains; Model of environmentally-driven disease	Strains are differentially susceptible; Significant early (non-lupus related) mortality; Slow onset; Clinical manifestations are mild
	Resiquimod/ Imiquimod		---	TLR7-mediated inflammation	nephritis, splenomegaly	Induces systemic autoimmunity in both male and female	Limited organ manifestations
	Nephrotoxic serum nephritis (NTN)	Anti-GBM	---		nephritis	Inducible in non-autoimmune strains; Rapid onset; Predictable timing	Strains are differentially susceptible; Limited to nephritis;
Other	Chronic graft versus host disease		---	graft-vs-host reactions; T cell-mediated	nephritis	Inducible in B6; Useful for evaluation of T cell driven mechanisms	Slow onset; Mild disease, limited to nephritis

* Adapted in part from References 5 and 148.

Table 3:

Summary of Drug Development Findings in Human and Mouse SLE

	Human SLE		Mouse SLE	
	TheraDeutic	**Immunolosical**	**Therapeutic**	**Immunoloeical**
Belimumab	↓ : disease activity, organ system manifestations, incidence and severity of disease flares, steroid-sparing effects ↓ : anti-dsDNA titers	↓ : naïve, activated, plasmacytoid B cells - : plasma cells, class-switched memory B cells, T cells	↓ : disease activity, autoantibody production	↓ : T2, marginal zone, follicular B cells, plasma cells - : T cells
MMF	↓ : disease activity, organ system manifestations, incidence of flares	↓ : almost all B cell subsets, Th17 and Tres cells ↓ : VEGF, PDGF-BB, CXCL12, CXCL9, B cell and STAT3 pathways - : double-nesative memory B cells	↓ : disease activity, organ infiltrates and manifestations, Anti-dsDNA levels	Mixed results ↓ : podocyte urokine receptor expression, PKC/fibronectin deposition in glomeruli/ interstititium
Abatacept	↓ : anti-dsDNA, complement levels - : efficacy	↓ : disease activity in patients with high plasma, dendritic, neutrophil, and natural killer cells	↓ : disease activity, organ manifestations, decreased autoantibody production	↓ : T and B cell activation/ proliferation ↓ : serum IFNg, IL-4, CD11b, CD11c, Gr1, CD21, CD86, MHCII in splenic B cells
Rituximab	- : efficacy ↓ : anti-dsDNA, anti-cardiolipin ↓ : complement, BAFF levels	- : double negative and CD5+ memory B cells ↓ : CD40, CD80 expression on B cells ↓ : activated CD4, CD8, Treg cells	↓ : disease activity, autoantibody production	↓ : B cell subsets, T cell activation - : splenic MZ and T2 B cells
Anti-IFN	↓ : disease activity, organ system manifestations, incidence and severity of disease flares, steroid-sparing effects	↑ : class-switched memory B cells, CD4, CD8, CXCR5 +/- memory cells ↓ : CXCL13, BAFF, CCL19, endothelial cell markers	↓ : disease activity, organ manifestation, autoantibody production	↓ : activated T, activated B cells, macrophages, $CD40^{hi}$ pDC

Symbols: ↓ indicate a decrease or improvement; ↑ indicate an increase; - indicate no change