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Review Article

Murine Models of Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disorder. The study of diverse mouse models of lupus has provided clues to the etiology of SLE. Spontaneous mouse models of lupus have led to identification of numerous susceptibility loci from which several candidate genes have emerged. Meanwhile, induced models of lupus have provided insight into the role of environmental factors in lupus pathogenesis as well as provided a better understanding of cellular mechanisms involved in the onset and progression of disease. The SLE-like phenotypes present in these models have also served to screen numerous potential SLE therapies. Due to the complex nature of SLE, it is necessary to understand the effect specific targeted therapies have on immune homeostasis. Furthermore, knowledge gained from mouse models will provide novel therapy targets for the treatment of SLE.

1. Introduction

The etiology of the autoimmune disease systemic lupus erythematosus (SLE) is considered to be a combination of multiple genetic and environmental factors whose amalgamation breaches the threshold of immune tolerance. SLE is, therefore, a complex multigenic disorder. The causative genetic factors of such disorders are believed to be allelic variants with minor functional contributions to the disease state and, individually, are not sufficient to cause overt disease. However, the combination of several of these susceptibility loci can lead to epistatic interactions that greatly enhance the overall contribution by each locus, whereby protective mechanisms are overcome and pathogenesis ensues. Hence, the capacity to tailor SLE treatments could be greatly enhanced upon the identification of the genetic variants capable of inducing autoimmunity and how their involvement can magnify SLE. Indeed, concerted efforts in human studies and mouse models have been made in that direction. The recent annotation of millions of single nucleotide polymorphisms (SNPs) in the human genome and the inception of high-throughput genotyping technologies has enabled the use of genome-wide association studies (GWAS) for this purpose. To date, SLE susceptibility has been associated to dozens of genes by GWAS [1]. While these associations offer important new insights into SLE etiology, there are logistical limitations to GWAS. Extremely large sample sets are required to achieve significant associations and extrinsic factors such as ethnicity, clinical history, and lifestyle must be considered in choosing these sets. Further, GWAS are capable of identifying genomic associations but do not characterize the function that an allelic variation confers. For this, other methods are required.

There are numerous murine models that have long been employed in an effort to understand the cellular and genetic requirements for SLE induction. The classic models of spontaneous lupus include the F1 hybrid between the New Zealand Black (NZB) and New Zealand White (NZW) strains (NZB/W F1) and its derivatives, the MRL/*lpr*, and BXSB/*Yaa* strains whereas induced models include the pristane-induced model and the chronic graft-versus-host-disease models (cGVHD). All of these models portray their own iterations of lupus-like diseases with a subset of symptoms akin to those observed in human SLE, namely, autoantibody production, lymphoid activation and hyperplasia, and lupus nephritis. In addition to spontaneous and induced lupus models, there is a plethora of genetically modified mouse models that goes beyond the scope of this paper (reviewed in [2]). Undoubtedly, genetically modified models will be used in the characterization of genes identified by GWAS, and in fact, many of these models already exist [3]. Here, we focus on what has been learned from spontaneous and induced mouse

models of SLE and how they can be used to complement the recent advances in human studies. We also highlight how murine models have been used as tools to test therapies.

2. Classic Mouse Models of Spontaneous Lupus

2.1. NZB/W F1. The NZB/W F1 is the oldest classical model of lupus generated by the F1 hybrid between the NZB and NZW strains. Both NZB and NZW display limited autoimmunity, while NZB/W F1 hybrids develop severe lupus-like phenotypes comparable to that of lupus patients [4]. These lupus-like phenotypes include lymphadenopathy, splenomegaly, elevated serum antinuclear autoantibodies (ANA) including anti-dsDNA IgG, a majority of which are IgG2a and IgG3, and immune complex-mediated glomerulonephritis (GN) that becomes apparent at 5-6 months of age, leading to kidney failure and death at 10–12 months of age [4]. Unlike SLE patients and the MRL/*lpr* and BXSB/*Yaa* mouse models, NZB/W F1 mice lack autoantibodies against RNA-containing complexes. As for SLE patients, disease in the NZB/W F1 strain is strongly biased in favor of females, and this is at least in part due to estrogen levels. Indeed ovariectomy of NZB/W F1 mice not only delayed disease onset but also decreased autoantibody titer. Meanwhile, restoration of estradiol in ovariectomized NZB/W F1 mice reestablished high numbers of DNA-specific B cells, and thereby suggests a pathogenic role of estrogen in lupus [5]. The many contributions of the NZB/W F1 model to our understanding of lupus pathogenesis have been discussed in excellent reviews [2, 4] to which the reader is referred to.

2.1.1. NZM. An accidental backcross between NZB/W F1 and NZW followed by brother-sister matings generated 27 different recombinant inbred strains of New Zealand Mixed (NZM) mice among which NZM2328 and NZM2410 are now used as lupus models [6–8]. While both NZM2410 and NZM2328 strains exhibit a highly penetrant version of the NZB/W F1 disease with an earlier onset, NZM2410 differs from NZM2328 with a weaker gender bias [7]. The NZM2328 and 2410 strains share the same autoantibody specificities as NZB/W F1 mice. The homozygosity of the NZM strains and their potential enrichment for lupus susceptibility loci has facilitated genetic analyses, and arguably their greatest contribution has been to the understanding of the genetic basis of this disease.

2.1.2. Identification and Classification of Susceptibility Loci. In 1994, Morel et al. reported the first lupus linkage analysis which identified three NZM2410 susceptibility loci, *Sle1-3,* as being significantly correlated with GN development [7]. The analysis of these loci showed that disease was inherited as a threshold liability, that is, the probability of presenting disease by an individual increases with the number of susceptibility alleles it carries, a concept that has been confirmed in genetic analyses of the other lupus-prone strains. The NZM2410 model was also used to show the existence of NZW-derived suppressive loci, the strongest one, *Sles1*, being linked to the major histocompatibility complex (MHC) class II locus *H-2*^{z} [9]. These results showed that the disease outcome for a given genome represents the integration of susceptibility and resistance loci and that lupus susceptible strains carry genomes in which the susceptibility loci outweigh the resistance loci. Resistance (or transgressive) loci have subsequently been identified in other models, including lupus models (e.g., see below *Lmb3* in the MRL/lpr strain).

The phenotypes contributed by each NZM2410 susceptibility locus have been determined via detailed analysis of the immunological properties of congenic strains carrying the individual loci on a C57BL/6 (B6) genetic background in comparison to B6 mice [10–16]. Briefly, *Sle1* mediates the loss of tolerance to nuclear antigens leading to the production of autoreactive B and T cells culminating in the secretion of antinuclear autoantibodies. *Sle2* leads to B cell hyperactivity, elevated B-1 cell levels, and polyreactive IgM antibodies. *Sle*3 leads to decreased levels of activation-induced cell death in CD4^{+} T cells, with evidence that a non-T cell compartment is involved in the expression of this phenotype [15]. Interestingly, *Sle1* largely overlaps with NZM2328 *Cgnz1* and *Agnz1* on chromosome 1 and *Sle2* with NZM2328 *Adaz1* on chromosome 4 [17]. The NZM2328 loci were, however, evaluated in congenic strains in which the susceptibility intervals were replaced by nonautoimmune genomic segments, which makes impossible to directly compare the phenotypes of the respective susceptibility loci between the two strains.

As predicted by the threshold liability findings from the linkage analysis, none of the NZM2410-derived *Sle* loci lead to full disease presentation. Instead, the stepwise combination of each congenic interval showed that the coexpression of these three major loci is necessary and sufficient for the development of fully penetrant disease [18]. The NZM2410 strain is to date the only autoimmune model in which the subset of loci that are necessary and sufficient for disease presentation has been identified. This achievement infused added significance to the identification of the genes corresponding to those three loci. A major obstacle towards the identification of these susceptibility genes has been revealed by the studies of the *Sle* congenic strains, which revealed that the original quantitative trait loci (QTLs) correspond to a cluster of susceptibility loci. This finding has been best demonstrated for *Sle1*, which is reviewed in detail in [3], corresponds to at least seven independent loci.

2.1.3. Identification of NZM2410 Susceptibility Genes. Progress towards the identification of lupus-susceptibility genes is ongoing in several models (see below), but it is by far the most advanced in NZM2410 as reviewed in [3]. Most of the genetic variants identified in these susceptibility genes are still in the process of formal validation, and the process by which they contribute to lupus pathogenesis is still largely unknown. However, variations in many of these genes has been directly associated with human lupus, which is by itself a strong validation of the mouse findings. The NZM2140 allele of *Fcgr2b*, which encodes for a negative regulator of B-cell signaling, contributes to an

autoimmune phenotype [19] and a large number of studies have established an association between *FCGR2B* variants and human SLE [20]. Consequently, the involvement of *Fcgr2b* in lupus pathogenesis has been validated in both mice and humans at the genetic and functional levels. Similarly, polymorphisms in *Cr2*, which encodes the complement receptor type 2 that acts as a B-cell coreceptor, contribute to the *Sle1c1* phenotypes [21, 22]. A common *CR2* haplotype is more frequent in SLE patients than in healthy controls, and novel CR2 splice variants are expressed on the follicular dendritic cells of SLE patients [23, 24]. *Sle1b* corresponds to polymorphisms in four signaling lymphocytic activation molecule (SLAM) family member genes [25], including *Ly108*, which was directly implicated in the regulation of B-cell tolerance [26]. Variants of *SLAMF3* (*LY9*) and *SLAMF4* (*CD244*) have been associated with human SLE [27, 28]. Finally for the *Sle1* subloci, *Sle1a1* corresponds to the expression of a novel splice isoform of the *Pbx1* gene that is associated with increased $CD4^+$ T cell activation in both mice and humans (Cuda et al., in revision). *Pbx1* function in T cells is unknown, and studies are ongoing to uncover the mechanisms linking *Pbx1* expression and T cell phenotypes. The *Sle3* locus induces a complex phenotype that includes myeloid cell-induced $CD4^+$ T-cell activation [29] and mild GN [12]. Polymorphisms in kallikrein (*Klk*) genes, which are located in the *Sle3* interval, have been associated with increased susceptibility to nephritis in the mouse and in SLE patients [30].

2.2. MRL/lpr

2.2.1. Derivation and Phenotype of the MRL/lpr Strain. The MRL strain was developed from several crosses of inbred strains. Specifically, most of the MRL genome was derived from the LG/J strain with minor contributions from C3H/Di, C57BL/6, and AKR/J [4]. Initial characterization of MRL substrains revealed one strain, termed MRL/*lpr*, which developed an SLE-like phenotype characterized by lymphadenopathy due to an accumulation of double negative ($CD4^-$ $CD8^-$) and $B220^+$ T-cells. These mice displayed an accelerated mortality rate, and unlike the NZB/W F1 mice, both males and females were significantly affected. In addition, the MRL/*lpr* substrain had high concentrations of circulating immunoglobulins, which included elevated levels of autoantibodies such as ANA, anti-ssDNA, anti-dsDNA, anti-Sm, and rheumatoid factors, resulting in large amounts of immune complexes [31]. This accelerated phenotype was attributed to a recessive autosomal mutation termed lymphoproliferation (*lpr*). The *lpr* mutation, located on chromosome 19, alters transcription of the Fas receptor [32].

2.2.2. Effect of Fas Signaling Deficiency in Disease Development. Fas is a surface-bound receptor belonging to the tumor necrosis factor receptor (TNF-R) family that induces apoptosis upon interacting with its ligand, FasL [33]. The defects in Fas transcription are caused by an insertion of the retrotransposon ETn which leads to aberrant, nonfunctional transcripts due to alternative splicing of the *Fas* gene [34]. Studies on B-cells and T-cells from MRL/*lpr* mice, which both express Fas, confirmed a defect in apoptosis due to the lack of functional Fas receptor [35]. Furthermore, a mutation on the FasL gene, termed generalized lymphoproliferative disease (*gld*), was shown to cause an autoimmune disorder similar to the *lpr* mutation [36, 37]. This recessive mutation, located on chromosome 1, caused a single amino acid change (Leu > Phe) which prevented FasL from binding to its receptor. Therefore, a deficiency in Fas signaling results in an SLE-like phenotype due to defective Fas-mediated apoptosis. In humans, defective Fas signaling can lead to the development of autoimmune lymphoproliferative syndrome (ALPS) which shares many symptoms with SLE although GN is uncommon in ALPS patients [38].

The SLE symptoms attributed to Fas deficiency in MRL/*lpr* mice are dependent on both $CD4^+$ T-cells and B-cells as their absence decreased autoimmunity [39, 40]. Further studies on Fas-deficient T-cells using the (C57BL/6 × MRL)F1 autoimmune strain resulted in lymphopenia as activated T-cells upregulated FasL, promoting the apoptosis of peripheral lymphocytes [41]. Meanwhile, in the presence of the *lpr* mutation, the nonautoimmune C3H/HeJ and C57BL/6J strains developed lymphoproliferation and had a reduced lifespan [42]. In addition, high levels of IgM and IgG antibodies, in particular autoantibodies against DNA and IgG, were detected in these strains. Conditional deletion of Fas in T-cells, B-cells, or both T-cells and B-cells in nonautoimmune C57BL/6 mice resulted in higher levels of autoantibodies but lymphoproliferation was not observed. To reconstitute the phenotype seen in *lpr* mice, Fas deletion had to be present in both lymphoid and nonlymphoid cells [41]. In particular, Fas deficiency in dendritic cells (DCs) led to systemic autoimmunity as it induced elevated ANA, splenomegaly, and accumulation of mature DCs [43].

2.2.3. Effect of the MRL Genetic Background in Disease Development. Expression of the *lpr* mutation in either the C3H/HeJ and C57BL/6J strains did not result in nephritis [44]. In contrast, Fas-sufficient, $MRL^{+/+}$ mice displayed the pathological effects of nephritis though onset of symptoms was significantly delayed when compared to MRL/*lpr* mice. Therefore, the MRL background genes play an important role in the development of disease. Characterization of (MRL-Fas^{lpr} × C57BL/6-Fas^{lpr})F2 mice revealed four susceptibility loci, *Lmb1–Lmb4*, that were linked to anti-dsDNA autoantibodies and glomerulonephritis [45]. In particular, studies on congenic mice showed that *Lmb3*, located on the telomeric region of chromosome 7, had a significant effect on lymphoproliferation and enhanced T-cell proliferation while T-cell apoptosis was reduced [46]. Recently, a single nonsense mutation (C > T) in the Coronin-1A gene, located within the *Lmb3* susceptibility locus, was identified in the Scripp substrain of C57BL/6 and it resulted in suppression of disease when crossed to MRL/*lpr* [47]. Coronin-1A binds F-actin and prevents its assembly and depolymerization. Nonfunctional Coronin-1A, from the mutant *Lmb3* locus, was associated with increased T-cell apoptosis and reduced T-cell activation and proliferation. Further characterization

of the MRL background should reveal additional candidate genes that promote autoimmunity in MRL/*lpr* mice.

2.3. BXSB/Yaa

2.3.1. Derivation and Phenotype of the BXSB/Yaa Strain. Lymphoproliferation was observed in males of an (C57BL6/J × SB/Le)F1 intercross and its backcross to SB/Le. A recombinant inbred strain, BXSB/Mp, was derived from this backcross, and nearly 100% of BXSB mice develop a lupus-like disease that was much more severe with earlier onset in males [48, 49]. The disease phenotypes include secondary lymphoid tissue hyperplasia, immune complex-mediated GN, monocytosis, hypergammaglobulinemia, antinuclear and antierythrocytic autoantibodies, and high-serum retroviral glycoprotein gp70 titers [48, 50]. Mean survival is roughly 5 months in males and 14 months in females, and the major cause of death is proliferative GN [48, 50].

2.3.2. Effect of the Y Chromosome in Disease Development. The fact that disease is greatly accelerated in BXSB males suggested the presence of a susceptibility element on the Y chromosome or that sex hormones play a role in this model. Orchiectomy did not delay onset or severity in BXSB males, while ovariectomy did not exacerbate disease in females, ruling out a hormonal effect [51]. Moreover, consomic studies showed that the BXSB-derived Y chromosome exacerbated disease when combined with either NZW or MRL genetic backgrounds [52, 53]. Thus, an element, termed Y-linked autoimmune accelerator (*Yaa*), was deemed to be responsible for the acute disease in BXSB males.

It is now known that *Yaa* is due to a translocation of the telomeric end of the X chromosome to the Y chromosome, resulting in the duplication of at least 16 genes and a ~2-fold expression in many of these genes [54, 55]. Among these is Toll-like Receptor 7 (*Tlr7*), which encodes an innate pattern recognition receptor found in B cells and antigen presenting cells (APCs). TLR7 is activated by viral ssRNA and signals through the myeloid differentiation primary response gene 88 (MyD88) adaptor resulting in nuclear factor NF-$\kappa\beta$ activation and expression of type I IFN (IFN I) and other proinflammatory cytokines [56]. Importantly, it has been shown that TLR signaling can act as signal 2 in B cell activation and that those interactions with endogenous RNA ligands are sufficient for autoreactive B cell activation [57, 58]. Additionally, disease activity is extremely sensitive to TLR7 expression. Where a 2-fold increase by the *Yaa* translocation only results in overt disease in the presences of other susceptibility alleles, greater increases in expression result in a *Tlr7* dose-responsive disease that does not require other lupus susceptibility loci [59]. Moreover, deletion of the endogenous copy of *Tlr7* from the X chromosome abrogates *Yaa*-induced monocytosis, lymphoid activation, splenomegaly, GN, and mortality [59–61]. Thus, *Tlr7* gene duplication has been deemed to be the major functional contributor to the *Yaa* phenotype. Shen et al. have recently reported a human allele of the *TLR7* gene with associated risk for SLE development in males [62]. This human susceptibility allele increased the expression of *TLR7* and of IFN I-regulated genes in blood monocytes. In this way, *TLR7* dose increases lupus susceptibility in both mice and humans.

It is also likely that there is a minor contribution from other genes in the translocated *Yaa* interval, since endogenous *Tlr7* deletion does not eliminate all *Yaa*-induced phenotypes. Lupus prone $Yaa^{+} \cdot Tlr7^{-}$ mice still display some humoral abnormalities, increased autoantibody production, and a decreased marginal zone (MZ) B cell compartment as compared to lupus prone $Yaa^{-} \cdot Tlr7^{+}$ mice [60, 61].

2.3.3. Effect of the BSXB Genetic Background in Disease Development. While the *Yaa* allele is certainly the most distinguishable feature of the BSXB model, it is not the whole story. In fact, the *Yaa* mutation alone is not sufficient to cause disease. This is clearly illustrated by the fact that nonlupus prone strains, such as B6 and CBA, that are consomic for the BSXB Y chromosome do not develop disease [52, 63]. The BXSB MHC ($H\text{-}2^{b/b}$) locus plays a dominant role in disease activity since congenic BSXB.H-$2^{d/d}$ mice have a less severe syndrome, while BSXB.H-$2^{b/d}$ and BSXB.H-$2^{b/b}$ mice have the full disease [64]. However, as stated above, B6·*Yaa* ($H\text{-}2^{b/b}$) mice have no malady. Therefore, there are non-MHC-linked autosomal elements in the BSXB genome that contribute to disease development.

Quantitative trait linkage analyses have identified BXSB susceptibility loci on chromosomes 1, 3, and 13 (*Bxs1-6*) [65, 66]. These loci are all derived from the parental SB/Le strain except for *Bxs5* on chromosome 3, which is a transgressive allele derived from B10 [49]. *Bxs1-4* are all located on chromosome 1 and studies using congenic mice confirmed that these loci confer lupus phenotypes [67]. Interestingly, *Bsx3* overlaps with *Sle1* and seems to have the most robust effect. This suggests that like *Sle1*, *Bsx3* may itself contain multiple susceptibility loci, some of which might be allelic. Of the four loci located on chromosome 1, only *Bsx2* has a proposed candidate gene. RNA and protein levels of the innate scavenger receptor *Marco* (macrophage receptor with collagenous structure) are reduced in the macrophages of *Bxs2*-containing congenic mice. This leads to a defect in clearance of apoptotic material, which is generally associated with the development of systemic autoimmunity [68].

Bxs6 on chromosome 13 is linked to increased serum gp70 and anti-gp70 autoantibody. The presence of *Yaa* greatly enhances *Bxs6* resulting in nephritis due to deposition of the associated gp70 immune complexes (gp70IC) in glomeruli. Gp70 is a glycoprotein subunit encoded by the viral envelope *env* gene of endogenous retroviruses that is produced by hepatocytes as an acute phase protein [69]. Though not proven conclusively, there is a good deal of evidence for a role of endogenous retroviruses in lupus pathogenesis (reviewed in [70]). *Bsx6* overlaps with two other loci, NZW-derived *Sgp3 [71]* and 129-derived *Gv1* [72], which are also involved in the regulation of serum gp70 levels. This positional and functional relationship between these three loci suggests that they may be caused by the same gene(s). Further, TLR7 activation causes *Sgp3*-mediated upregulation of serum gp70, in much the same way that *Yaa* enhances of *Bxs6*-mediated upregulation of serum gp70 [73]. *Sgp3* has been the most extensively analyzed and has

been recently narrowed down to a 5.42 Mb region in which 21 of the 30 genes encode Krüppel-associated box zinc-finger proteins (KRAB-ZFP) that are capable of suppressing proviral transcription through the heterochromatization viral integration sites [70]. KRAB-ZFPs are, therefore, the primary candidate genes for *Sgp3* and likely for *Bxs6*.

3. Induced Models of Lupus

3.1. The Pristane-Induced Lupus Model. Unlike the mouse models mentioned above, in which genetic factors play the major role, induced mouse models develop lupus after exposure to certain environmental triggers. Intraperitoneal injections of pristane (2, 6, 10, and 14 tetramethylpentadecane, TMPD), an isoprenoid alkane found at high concentration in mineral oil, is a standard method to obtain ascitic fluid enriched in monoclonal antibodies. However, pristane administration in BALB/c mice induces autoantibodies characteristic of lupus, such as antiribonucleoprotein (RNP) antibodies (anti-Su, anti-Sm, and anti-U1RNP), anti-DNA, and anti-histone, to a level comparable to that found in MRL/*lpr* mice [74, 75]. Pristane-treated mice also have immune-complex deposition in the kidney leading to severe proteinuria and nephritis [75]. Besides the BALB/c strain, almost all mouse strains are susceptible, to a variable extent, to the pristane-induced production of antibody and lupus manifestations [76], confirming that environment has a considerable importance in lupus. Like human SLE patients and NZB/W F1 model, pristine-induced lupus is more severe in females than in males, at least in SJL/J strain [77].

3.1.1. Cytokines in Pristane-Induced Lupus. Inflammatory cytokines have critical effects in pristane-induced lupus. By using BALB/c IL-$6^{-/-}$ mice, it was found that anti-ssDNA, dsDNA, and chromatin antibodies are highly IL-6-dependent whereas anti-RNP/Sm and anti-Su antibodies have no obvious correlation with IL-6 levels [78]. Interestingly, anti-dsDNA antibodies generally develop after renal disease, which indicates that these autoantibodies do not participate in the development of nephritis in this model. When pristane was administered to lupus-prone NZB/W F1 mice, it greatly accelerated the disease and lead to large amounts of IL-12, anti-Sm, anti-Su, and anti-RNP autoantibody production, implying a link between IL-12 and these anti-RNP autoantibodies [79]. This was confirmed by the fact that IL-12 deficiency prevented pristane-treated mice from anti-RNP/Su IgG production and nephritis [80]. These studies revealed that the production of different autoantibodies may be induced by different cytokine pathways and contribute differently to end-organ disease. In another study, IFN-γ deficiency significantly protected pristane-treated BALB/c mice from autoantibody production and renal disease whereas IL-4 deficiency has no effect [81]. Thus, pristane-induced lupus may be attributable to a shift of the T-helper cell subsets, Th1-Th2, balance.

Overexpression of IFN-I and interferon-stimulated genes (ISGs, also called "interferon signature") has been closely associated with ANA production and disease severity in SLE patients [82]. Pristane-induced lupus is the only animal model that shows an interferon signature. Indeed, studies in pristane-induced lupus have revealed that IFN-I receptor deficiency (IFNAR$^{-/-}$ or IFNAR2$^{-/-}$) completely erased the interferon signature, eliminated anti-RNP, anti-Sm, and anti-dsDNA autoantibodies, reduced anti-ssDNA and anti-histone IgG, and significantly improved GN [83, 84]. IFN-I may contribute to autoantibody production by regulating TLR7/9 expression and activation in B cells [84]. IFN-I also seems to regulate another autoantibody mediator, IL-12, as IFNAR$^{-/-}$ mice fail to elevate IL-12 level following pristane treatment [83].

Instead of plasmacytoid dendritic cells (pDCs) which have been identified as the major producers of IFN-I in human lupus [85], an accumulation of peritoneal immature Ly6C^{high} monocytes is the major source of IFN-I in pristane-treated mice. Depletion of this cell population rapidly abolished the interferon signature and autoantibody production in pristane-treated mice [86]. IFN-I in turn mediates the recruitment of Ly6C^{high} immature monocytes to the peritoneum through the upregulation of chemokines such as CCL2, CCL7, and CCL12. IFN-1 also prevents the maturation of monocytes, with a twofold effect: firstly, immature monocytes are a major source of IFN-I. Therefore, blocking of monocyte maturation results in a vicious feedback loop of IFN-1 production, monocyte recruitment, and block in an immature state. Secondly, failure of monocyte maturation into phagocytic Ly6C^{low} monocytes/macrophages leads to an impaired clearance of cell debris, which is an important stimulus of inflammation and autoantibody production [87]. Thus, IFN-I production by Ly6C^{high} monocytes may be a major cause of chronic inflammation and SLE.

Pristane induces IFN-I production exclusively through the TLR7/MyD88 pathway [88]. TLR7 deficiency not only abolishes pristane-induced IFN-I production but also eliminates autoantibody production and renal disease, indicating a key role of TLR7/MyD88/IFN-I pathway in this model [88, 89]. FcγR recognizes the Fc portion of extracellular IgG and is proposed to mediate the intake of immune complex that subsequently activates endosomal TRLs, such as TLR7 [90]. However, IFN-I and autoantibody production are FcγR-independent in pristane-induced lupus [88]. Therefore, the modulation of TLR7 by pristane does not rely on immune complexes. The exact mechanism of pristane-mediated TLR7 activation remains to be identified.

3.1.2. Other Manifestations of Pristane-Induced Lupus. In addition to nephritis, hemorrhagic pulmonary capillaritis and arthritis have also been identified in pristane-treated mice [91]. 14 days after a single dose of pristane injection, bronchoalveolar lavage (BAL) fluid becomes hemorrhagic with elevated neutrophil counts and high levels of IL-6 and IL-10. Perivascular infiltrates of immune cells and endothelial injury are also found in the lung of pristine-treated mice [91]. Some SLE patients also develop pulmonary capillaritis [92], and whether pristane-induced hemorrhagic pulmonary capillaritis can serve as a valid model for human lupus lung disease remains to be verified. The arthritis symptoms in

pristane-induced lupus include synovial hyperplasia, periostitis, and progressive marginal erosions [93, 94]. Pristane-induced arthritis is tumor necrosis factor (TNF) α mediated, as treatment with neutralizing anti-TNF-α antibody ameliorates the arthritis symptoms [95]. The broader extension of end-organ targets as well as the preeminent role plays by IFN I make pristane-induced lupus arguably a model of choice for mechanistic studies of human lupus.

3.2. Induced Chronic Graft-versus-Host Disease

3.2.1. Highlights and Advantages of the Parent into F1 Method. Various models of induced graft-versus-host disease (GVHD) have been used as models of lupus. As with the pristane-induced model, these models require only a single injection of donor cells to induce a lupus-like syndrome. The disease process is reproducible, with severity correlating to the number of allografted cells. Because this method induces a rapid disease onset from a known starting point, the study of lupus induction is greatly facilitated as compared to the spontaneous models of lupus. As an example, autoantibodies are detectable as early as 10–14 days after induction in these models whereas it can be several weeks to months after birth for the same phenotype to develop in spontaneous lupus models. Further, since the donor T cells undergo activation and expansion, they are relatively easy to observe by flow cytometry, allowing the study of the effect of various modifications on the donor as well as the host cells.

In the parent into F1 (P → F1) model, lymphocytes are transferred into a semiallogenic recipient such that the donor cells react to the host, and the host is tolerant to the donor allograft. (reviewed in [96]). Depending on the model used, an acute or a chronic GVHD (aGVHD or cGVHD) ensues. In most models of P → F1, such as B6 into (B6 × DBA)F1, aGVHD is induced by donor $CD8^+$ T cells, which manifests as severe lymphopenia of host cells as well as strain-specific connective tissue diseases. Host B cells are most sensitive to this CTL killing and may be almost completely ablated after 2 weeks, followed by host APCs, then $CD4^+$ T cells, and finally host $CD8^+$ T cells. Conversely, DBA into (B6 × DBA)F1 (DBA → BDF1) results in cGVHD, a donor $CD4^+$-mediated response resulting in massive host polyclonal B cell activation, expansion, and immunoglobulin production. This chronic condition exhibits several similarities to SLE, including ANA, lupus-specific autoantibodies, and immune complex-mediated GN. Another feature of DBA → BDF1 is that the lupus pathogenesis in this model is more severe in females than males allowing the study of gender-biased lupus etiology [97, 98]. Additionally, DBA → BDF1 allows for identification of CTL-promoting treatments *in vivo*, such as with agonist anti-CD40 antibody, IL12, and antagonist anti-CD80 antibody [99–101].

The induction of a cGVHD instead of aGVDH response is caused by a diminished capacity for DBA $CD8^+$ T cells to produce a CTL response to the F1 host. Correspondingly, B6 into (B6 × DBA)F1 will result in cGVHD if the donor cells are depleted of $CD8^+$ T cells. The ensuing lupus phenotypes include ANA, anti-dsDNA and anti-RBC autoantibodies, and GN. The major advantage of B6(-CD8) → F1 over the DBA → BDF1 model is that genetic modification of the donor cells can be examined due to the plethora of knockout and transgenic B6 mice. To this extent, this model has demonstrated that partial CTL deficiency due to the lack of perforin (B6·$Pfp^{-/-}$ → F1) or Fas/FasL (B6·*gld* → F1) was sufficient to induce a $CD4^+$-mediated cGVHD phenotype.

B6(-CD8) → F1 was also used as a complement of B6 → F1 (not depleted of $CD8^+$ T cells) to study *in vivo* mechanisms that mediate the overall donor $CD8^+$ T cell versus $CD4^+$ T cell response, and thus result in aGVHD versus cGVHD. One such study demonstrated that TNFα blockade inhibited the early induction of CTLs and skewed T cell cytokine profile to antibody promoting IL-4, IL-6, and IL-10, resulting in an antibody mediated cGVHD response [102]. This novel finding revealed the potential of TNFα-blocking treatments to instigate humoral autoimmunity. Another study described a positive role in B6(-CD8) → F1 cGVHD and a negative role in B6 → F1 aGVHD for the TNF family member, TRAIL, highlighting its role in the promotion of lupus [103].

3.2.2. B6·H-2^{bm12} ← → B6 cGVHD. When B6·H-2^{bm12} lymphocytes, whose MHC II locus confers a 3 amino acid substitution in H-2^b, are transferred into B6 hosts with the wild-type H-2^b locus, cGVHD develops. The lupus-like phenotypes in this model include ANA, anti-dsDNA, antichromatin, and anti-Sm autoantibodies, and GN [104]. Since the MHC disparity between donor and host is limited to class II in this model, $CD8^+$ T cell depletion of donor lymphocytes is not required. Also, since this model works equally well with B6·H-2^{bm12} → B6 and B6 → B6·H-2^{bm12}, donor and host gene modifications can be examined by the use of knockout and transgenic mice.

Although cGVHD has been shown to be mediated through donor $CD4^+$ T cells and host B cells, an interesting facet of cGVHD was revealed using this model. The observation that a response did not occur in $CD4^{-/-}$ hosts indicated a role for endogenous $CD4^+$ T cells [189]. Further, B cells raised in such an environment had intrinsic defects in their ability to produce an alloresponse [190]. It has been recently reported that B cells require "nurturing" during early ontogeny in the form of IL-4 [191]. In lieu of endogenous $CD4^+$ T cell nurturing, large doses of rIL-4 or agonist anti-CD40 antibody in $CD4^{-/-}$ hosts during this critical developmental period were also sufficient for B cells to develop with alloreactive potential.

4. Therapeutic Studies for SLE on Mouse Models

Mouse models of SLE have been used not only to dissect disease mechanisms but also to test potential therapies. In addition to validating targets, testing drugs on mouse models of SLE has proved indispensable before they go to clinical trials. We have summarized the major therapeutic studies that have been conducted on mice models of SLE in Table 1. Several components of the immune system, such as cytokines, B-cells, T-cells, and hormones have been identified as potential targets for therapy, which have been

Table 1: Summary of treatments tested in mouse models of lupus, their targets, proposed mechanisms, outcomes in the mouse, and follow up in clinical trials.

Targets	Treatment	Mouse model	Mechanisms	Main outcomes	Ref	Clinical trial
			Targeting cytokines			
IL-6	IL-6R mAb	MRL/lpr		Nephritis↓, anti-dsDNA Ab↓	[105]	*Tocilizumab**
	IL-6R mAb	NZB/W F1	Inhibits IgG class switch	Survival↑, IgG ANA↓, proteinuria↓	[107]	A Phase I trial showed both decreased disease activity and side effects [106]
	IL-6 mAb	NZB/W F1	Suppresses autoreactive B cell and T cell	Nephritis↓, anti-dsDNA Ab↓	[108]	
IL-10	IL-10 inhibitor (AS101)	NZB/W F1	Decreases IL-10, increases TNF-α	Delayed onset, anti-DNA Ab↓, proteinuria↓, glomerular deposition↓	[109]	Antagonizing anti- IL-10 mAb A small-scale trial showed efficacy. [110]
	IL-10 mAb	NZB/W F1	Neutralizes IL-10, increases TNF-α	Delayed onset, survival↑, ANA↓	[111]	
	rIL-10	MRL/lpr	Suppresses Th1 response	IgG2a anti-dsDNA↓	[112]	
	AAV-IL-10 (low exp.)	B6·Sle1·Sle2·Sle3	Suppresses Th1 response	ANA↓, GN↓, T cell activation↓	[113]	
TNF-α	rTNF-α	NZB/W F1	Decreases cellular response	Delayed onset, survival↑	[114]	*Infliximab* A small-scale trial showed both efficacy and side effects [115] *Etanercept* Phase II trial for discoid lupus in progress
IFN-α	IFN-α kinoid vaccination	NZB/W F1	Induces anti IFN-α neutralizing Ab	Delayed onset, survival↑, proteinuria↓	[116]	*MEDI-545 (sifalimumab)* Phase I trial showed positive result [117] *rhuMab IFN-α (Rontalizumab)* Phase I trial showed positive result [118]
IFN-β	IFN-β	MRL/lpr	Reduces both cellular and humoral responses and cytokine production	Survival↑, proteinuria↓, skin lesions↓, ANA↓, splenomegaly↓	[119]	
IFN-γ	IFN-γ cDNA vaccination	MRL/lpr	Induces anti IFN-γ neutralizing Ab	Survival↑, lymphoid hyperplasia↓, ANA↓, GN↓	[120]	*AMG 811* Phase I trial in progress
	IFN-γ mAb	NZB/W F1		Survival↑, proteinuria↓, anti-DNA Ab↓	[121]	
IL-17	Rock2 inhibitor (Fasudil)	MRL/lpr	Inhibits IRF4 phosphorylation and reduces IL-17 and IL-21 production	Anti-dsDNA Ab↓, glomerular deposition↓, proteinuria↓	[122]	
IL-21	IL-21R·Fc	MRL/lpr	Decreases T cell numbers and alters B cell functions	Total Ig ↓, anti-dsDNA Ab↓, proteinuria↓ skin lesions↓, lymphadenopathy↓	[123]	
IL-18	IL-18 cDNA vaccination	MRL/lpr	Induces anti-IL-18 neutralizing Ab	Survival↑, GN↓, IFN- γ↓	[124]	

Table 1: Continued.

Targets	Treatment	Mouse model	Mechanisms	Main outcomes	Ref	Clinical trial
BAFF	Adenovirus-BAFF-R-Ig	NZM2410	Depletes B cell, decreases T cell activation and myeloproliferation	Survival↑, proteinuria↓, splenomegaly↓, reverses disease	[125]	*Belimumab*
	Anti-BAFF-Ig	B6·lyn$^{-/-}$		Nephritis↓,	[129]	Phase III met primary complex end point. [126, 127].
BAFF and April	Human TACI-Ig	NZB/WF1	Blocks BAFF and April signaling	Survival↑, proteinuria↓, no significant change in anti-dsDNA Ab level	[130]	*Atacicept* Phase II terminated [128]
	Adenovirus-TACI-Ig (w/ or w/o CTLA4-Ig co-administration)	NZB/W F1	Blocks BAFF and April signaling splenic B cell depletion	Survival↑, delayed onset,, ANA↓, proteinuria↓, nephritis↓, reverses disease only when CTLA4-Ig coadministered	[131]	
	Adenovirus-TACI-Fc	MRL/lpr, NZB/W F1,	Blocks BAFF and April signaling	In MRL/lpr: survival↑, GN↓, proteinuria↓,In NZB/W F1: anti-TACI antibodies neutralized TACI-Fc	[132]	
	Adenovirus-TACI-Ig	NZM2410	Blocks on BAFF and April signaling;	Survival↑, proteinuria↓, splenomegaly↓, reverses disease	[125]	
B cell depletion						
CD20	Anti-CD20 mAb	MRL/lpr	ADCC, CDC	Serum Ab and ANA↓, nephritis↓, proteinuria↓, dermatitis↓	[133]	*Rituximab* Failed to reach primary end point [134, 135]
	Anti-CD20 mAb	NZB/W F1	ADCC, CDC	Treatment on 12–28-wk-old mice ameliorates disease, while treatment on 4-wk old mice hastens disease	[137]	*Ocrelizumab* Phase III terminated [136]
CD22	Anti-CD22 mAb	NZB/W F1	ADCC, targets inhibitory receptor	Able to deplete several B cell subsets. No significant effect on improving survival	[137]	*Epratuzumab* Phase IIb trial showed positive result [138, 139]
CD79	Anti-CD79 α and Anti-CD79 β mAb	MRL/lpr		Survival↑, IgG antichromatin↓, skin lesions↓ Inflammatory infiltrates↓	[140]	
Proteasome	Proteasome inhibitor bortezomib	NZB/W F1 and MRL/lpr	Eliminates both short-lived and long-lived plasma cells	Survival↑, ANA↓, GN↓	[141]	
Targeting T cell-APC interactions						
	CTLA4-Ig	NZB/W F1	Inhibits B7-CD28 interaction	Survival↑, ANA↓	[142, 143]	*Abatacept* The ACCESS trial is in progress [144]

Table 1: Continued.

Targets	Treatment	Mouse model	Mechanisms	Main outcomes	Ref	Clinical trial
	Adenovirus-CTLA4-Ig	NZB/W F1	Inhibits B7-CD28 interaction	Survival↑, ANA↓, GN↓	[145]	
CD28-B7	CTLA4-Ig transgene	B6 lyn$^{-/-}$	Inhibits B7-CD28 interaction	Myeloid hyperplasia↓, splenomegaly↓ IgG ANA↓, renal disease unaffected	[146]	
	CTLA4-Ig and anti-gp39	NZB/W F1	Simultaneously inhibits B7-CD28 and CD40/gp39 interaction	Survival↑, ANA↓, GN↓, effects are more significant than CTLA4-Ig alone	[143]	
			Targeting T follicular helper cells			
CD3	Nasal anti-CD3 Ab	NZB/W F1	Downregulates the expression of IL17 and IL21 by Tfh cells	ANA↓, GN↓	[147]	
ICOS-B7RP-1	anti-B7RP-1 Ab	NZB/W F1	Downregulates ICOS and reduces Tfh cell number	Survival↓, anti-dsDNA Ab↓, proteinuria↓	[148]	
			Targeting other receptors			
FcgRIIB	FcgRIIB expressing retrovirus	NZM2410, BXSB, B6Fcgr2b$^{-/-}$	Restores FcgRIIB level	ANA↓, immune complex deposition↓, proteinuria↓, GN↓, lung pathology↓	[149]	
TLR7/TLR9	Immunoregulatory sequence (IRS) 954	NZB/W F1	Reduces the production of IFN-α	Survival↑, ANA↓, proteinuria↓, GN↓,	[150]	
Programmed death-1 (PD-1)	Neutralizing PD-1Ab	NZB/W F1	Promotes suppressive CD8$^+$ T cells	Survival↑, delayed nephritis, IgG↓, anti-dsDNA IgG↓	[151]	
			Targeting cell signaling			
Syk	Syk inhibitor R788	NZB/W F1	Blocks B cell receptor (BCR) and FcR signaling	Survival↑, proteinuria↓, renal disease↓	[152]	
	Syk inhibitor R788	MRL/lpr or BAK/BAX$^{-/-}$	Blocks BCR and FcR signaling	Skin lesions↓ lymphadenopathy and splenomegaly↓, renal disease↓	[153]	
PI3K γ	AS605240 compound	MRL/lpr	Reduces T and B cell activation	Survival↑, renal infiltrates↓, GN↓	[154]	
mTOR	Rapamycin	NZB/W F1	Immunosuppression	Survival↑, anti-dsDNA Ab↓, splenomegaly↓, albuminuria↓	[155]	*Rapamycin* A small scale trial showed efficacy [156]
			Cellular therapies			
Regulatory B cells (Breg)	Anti-CD40 injection	MRL/lpr	Agonistic anti-CD40 expands Breg	Survival↑, anti-dsDNA Ab↓, proteinuria↓, skin lesions↓	[157]	
Regulatory T cells (Treg)	Adoptive transfer of ex vivo expanded Treg	NZB/W F1	T cell suppression	Survival↑, renal IC deposition↓, proteinuria↓, GN↓	[158, 159]	
Umbilical cord mesenchymal stem cells (MSC)		MRL/lpr	immunosuppressive and anti-inflammatory properties	anti-dsDNA Ab↓, Proteinuria↓, renal disease↓	[160]	A small-scale trial showed positive result [161]
Umbilical cord mesenchymal stem cells (MSC)		NZB/W F1	immunosuppressive and anti-inflammatory properties	Survival↑, anti-dsDNA Ab↓, proteinuria↓, renal disease↓	[162]	

Table 1: Continued.

Targets	Treatment	Mouse model	Mechanisms	Main outcomes	Ref	Clinical trial
Bone marrow derived mesenchymal stem cell (BM-MSC)		NZB/W F1	Inhibition of B cell proliferation and differentiation dependent on IFN-γ	Glomerular IC deposition↓, lymphocytic infiltration↓, glomerular proliferation↓, anti-dsDNA Ab and proteinuria unaffected	[163]	
			Sex hormone modulation			
Estrogen	Nafoxidine	NZB/W F1		Delayed onset, survival↑, ANA↓, proteinuria↓	[164]	*Tamoxifen* A small-scale trial showed no effect [165]
Estrogen	Tamoxifen	NZB/W F1	Reduces IgG3 ANA production	Survival↑, IgG3 ANA↓, proteinuria↓, thrombocytopenia↓, glomerular deposits↓	[166, 167]	*Fulvestrant* (estrogen receptor downregulator) A small-scale trial showed some efficacy [168]
Estrogen	Raloxifene	NZB/W F1	Inhibits B cell function	Anti-DNA Ab↓, kidney damage↓	[169]	
Estrogen	Indole-3-carbinol	NZB/W F1	Blocks B cell and T cell differentiation	Survival↑, ANA↓, nephritis↓	[170]	
Androgen	Androgen treatment on castrated female	NZB/W F1	Unspecified	Survival↑, IgG ANA↓	[171]	*Dehydroepiandrosterone* Little clinical effect [172]
Androgen	Androgen treatment	NZB/W F1, MRL/lpr	Unspecified	Survival↑, anti-DNA Ab↓	[173]	
			Peptide-based immunotherapy			
Laminin	Laminin derived peptides	MRL/lpr	Laminin derived peptides competitively bind with ANA and prevent their deposition in the kidney	Survival↑, proteinuria↓, GN↓	[174]	
HSC chaperone protein	U1-70K snRNP derived peptide administered in saline (P140)	MRL/lpr	Impairs autoimmune T cell response	Survival↑, proteinuria↓, anti-dsDNA Ab↓	[175, 176]	*P140* A phase IIa study showed positive result [177]
Autoreactive B and T cells	Histone peptide $H2B_{10-33}$, $H4_{16-39}$, $H4_{71-94}$	(SWR/ NZB)F1	Impairs autoimmune B and T cell	Survival↑, proteinuria↓, ANA↓	[178]	
Suppressive $CD8^+$ T cells	pCONS	NZB/W F1	Promotes suppressive $CD8^+$ T cells by regulating Foxp3 and PD-1	Survival↑, nephritis↓, ANA↓	[179–181]	
Unclear	CDR1 of human anti-DNA Ab (hCDR1)	NZB/W F1	Modulation of cytokines, regulatory T cells and T cell apoptosis	ANA↓, nephritis↓, CNS symptoms↓	[182]	*hCDR1* A small-scale trial showed positive result [182]
			Other therapies			
Histone deacetylase	Histone deacetylase inhibitors TSA and SAHA	MRL/lpr	Decreases transcription of key cytokines involved in SLE	Splenomegaly↓, proteinuria↓, renal disease↓	[183]	

Table 1: Continued.

Targets	Treatment	Mouse model	Mechanisms	Main outcomes	Ref	Clinical trial
Topoisomerase I	Topoisomerase I Inhibitor irinotecan	NZB/W F1	Prevents anti-dsDNA Ab from binding to dsDNA	Survival↑, proteinuria↓ subendothelial immune deposit↓	[184]	
ACE	ACE inhibitor Captopril	NZB/W F1 and MRL/lpr	Reduces TGF- β, IL-4 and IL-10 production	Delayed onset, proteinuria↓, renal lesion↓	[185]	
HMG-CoA reductase	HMG-CoA reductase inhibitor Statin	NZB/W F1	Immunomodulatory effects on B and T cells and APCs	ANA↓, serum urea↓, proteinuria↓, nephritis↓	[186]	
ACE and HMG-CoA reductase	Coadministration of Statin and ACE inhibitor Imidapril	MRL/lpr	Synergistic effect	Survival↑, ANA↓, proteinuria↓, glomerular deposits↓, renal monocyte attractant CCL2/MCP-1↓	[187]	
CCL2/MCP-1	Spiegelmer mNOX-E36	MRL/lpr	mNOX-E36 blocks CCL2 without induction of IFN-α production	Survival↑, nephritis↓, skin lesion↓, peribronchial inflammation↓	[188]	

* Drug names are shown in *italic* font.

tested in mouse models of lupus, most often in a preventive rather than therapeutic mode. Some of the most successful therapeutic approaches have lead to clinical trials, several of which are currently in progress. Among them, Belimumab, a humanized monoclonal antibody directed against B-cell activating factor (BAFF), is the first biologic treatment that has met clinical trial end points and has been recommended for SLE treatment. BAFF regulates the survival of B-cells. It was determined that lupus-prone mice and SLE patients have elevated levels of BAFF. Additionally, nonautoimmune transgenic mice overexpressing BAFF showed lupus-like symptoms [130]. Targeting BAFF receptors (BAFF-R, TACI, or BCMA) in the NZM2410 and MRL/lpr lupus mouse models was effective in reducing disease symptoms [125, 132]. Murine studies targeting the BAFF pathway were followed by clinical trials targeting BAFF in SLE patients. The success of Belimumab in clinical trials is considered a breakthrough in the search for new therapies for SLE [126, 127]. This example serves to illustrate the important role mouse models play in the development of effective treatments for this complex human disease.

A major limitation for drug trials in humans is that although physiological parameters are collected, it is difficult to determine changes in internal organs, such as the lymphoid organs and the kidneys. For example, the anti-CD20 antibody (Rituximab) is able to deplete B cells in humans through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [192]. However, this data was mainly obtained from human peripheral blood B cells, which represents only 2% of the total B cells in the body [193]. Studies in mice have shown that unlike the blood, the spleen, bone marrow, and peritoneal cavity provide a reservoir for B cells in which they are more resistant to drug depletion [133, 194, 195]. Therefore, depletion efficacy seen in human blood does not necessarily reflect a global depletion. This may be one of the reasons why two randomized, double-blind, phase II/III trials failed to show an effect of Rituximab over placebo in SLE patients [134, 135]. Moreover, drug efficacy may be different between lupus-prone and lupus-resistant mice. Anti-CD20 depletion of B cells has been shown to be much more efficient in BALB/c than in MRL/lpr mice [133]. Therefore, it is crucial to test potential SLE therapies and drugs directly in lupus-prone mice.

There are obvious limitations in evaluating lupus therapies in mouse models. SLE targets the skin, joints, kidneys, and many other organs in humans whereas mouse models of SLE are characterized mainly by the development of nephritis. This is probably due to the fact that the genetic background is far more complicated in lupus patients than in mouse models. Some lupus mice may develop lupus-like symptoms other than renal disease, such as joint swelling and skin rash in a portion of MRL/lpr mice, and pulmonary symptoms in pristane-induced mice (see above). However, no mouse model can mimic the complexity of human lupus. Thus, drugs validated in mouse models may only be effective for a subset of symptoms or patients. To mimic the genetic and pathological heterogeneity in humans, it is crucial to use various mouse models in therapeutic studies. It has been shown that same treatment can have variable effects on different mouse models. For example, treatment with a soluble form of the BAFF receptor (BAFF-R-Ig) induces complete and enduring remission of established nephritis in NZM2410 mice [125], while it is unable to reverse nephritis in NZB/W F1 model unless a soluble form of cytotoxic T-lymphocyte antigen 4 (CTLA4-Ig) is coadministered to block T cell coactivation [131]. This difference is probably due to the fact that nephritic NZB/W F1 mice produce more inflammatory mediators in the kidney than do nephritic NZM2410 mice [125]. Thus, the genetic background should be taken into account when testing therapies on mouse models, and multiple models should be used to ensure

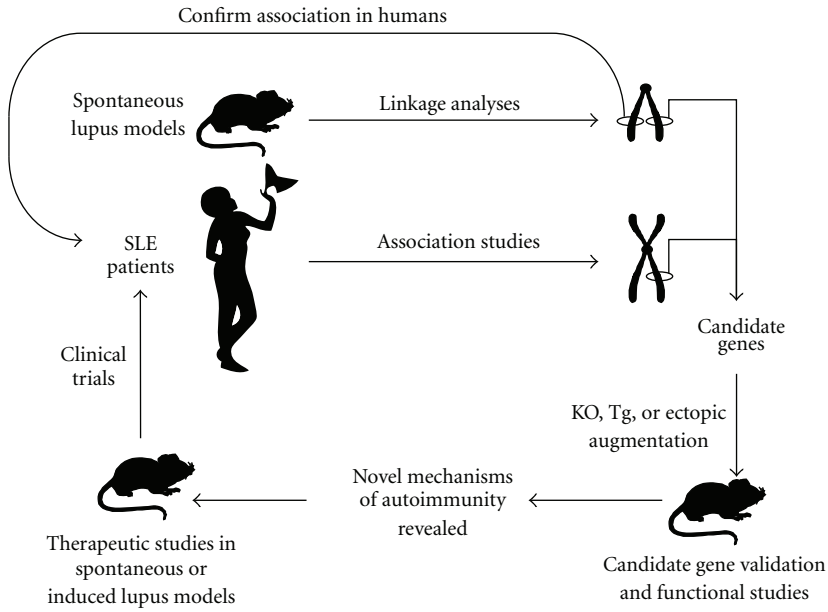

Figure 1: Integration of human and murine studies for new SLE drug discovery. Study of human SLE patients and mouse models of lupus has led to the identification of potential therapeutic targets. In-depth studies in murine models are undertaken to validate the association of the potential targets with disease symptoms. The efficacy of targeted treatments are first tested on murine models of lupus prior to the initiation of human clinical trials.

the applicability of drugs on the more complicated human genetic background.

5. Summary

Murine models are useful tools for the study of the etiology of lupus. A multitude of models exist, each sharing a subset of attributes with SLE observed in humans. In addition, each model affords the study of different aspects of lupus pathogenesis. For example, the cGVHD and pristane-induced models allow for the study of the mechanisms involved at the onset of the disease, while the spontaneous models allow for probing of the genetic causes of disease. NZB/W F1 and DBA → DBF1 can be used to study phenotypes in a gender-biased context similar to that seen in humans. All models are valid candidates for the study of therapeutic interventions.

To date, the use of murine models has identified several novel candidate genes, and some of them have been associated to SLE in humans. Further value in these models is demonstrated by that fact that these genes were not initially identified in human SLE studies. On the other hand, recent genome-wide human studies have identified an array of genes, many of which have no currently described role in lupus. To this effect, murine models allow for forward genetics to identify novel genes that can then be probed using a candidate gene approach to discover their human susceptibility allele counterparts (Figure 1). Conversely, genes identified by human studies can be translated to genetically modified murine models where their roles in lupus pathogenesis can be followed in a forward genetics manner. Both methodologies have proven their usefulness and have the shared goal of identifying novel pathways and targets for disease intervention.

Abbreviations

ADCC:	Antibody dependent cell-mediated cytotoxicity
aGVHD:	Acute graft-versus-host-disease
ALPS:	Autoimmune lymphoproliferative syndrome
ANA:	Antinuclear antibody
APC:	Antigen presenting cells
anti-RNP antibodies:	Anti-ribonucleoprotein antibodies: anti-Su, anti-Sm, and anti-U1RNP
BAFF-R-Ig:	B-cell-activating factor receptor immunoglobulin
CCL:	Chemokine C-C motif ligand
CDC:	Complement-dependent cytotoxicity
cGVHD:	Chronic graft-versus-host-disease
Cr2:	Complement receptor type 2 CR2 (humans)
CTLA-4-Ig:	Cytotoxic T-lymphocyte antigen 4 immunoglobulin
CTL:	Cytotoxic T cell
DC:	Dendritic cell
Fcgr2b:	Fc receptor for IgG2b FCGR2B (humans)
gld:	Generalized lymphoproliferative disease
GN:	Glomerulonephritis
gp70:	Glycoprotein 70
GWAS:	Genome wide association studies

H-2: Murine MHC II
IFNAR: Interferon alpha receptor
IFN I: Type I interferon
IL: Interleukin
ISG: Interferon-stimulated gene
Klk: Kallikrein
KRAB-ZFP: Krüppel-associated box zinc-finger proteins
Marco: Macrophage receptor with collagenous structure
MHC: Major histocompatibility complex
MyD88: Myeloid differentiation primary response gene 88
MZ: Marginal zone
NF-$\kappa\beta$: Nuclear factor kappa-light-chain-enhancer of activated B cells
NZB/W F1: First generation offspring from cross between NZB and NZW
NZB: New Zealand black
NZM: New Zealand mixed
NZW: New Zealand white
Pbx1: Pre-B-cell leukemia transcription factor 1
pDCs: Plasmacytoid dendritic cells
QTL: Quantitative trait loci
SLAM: Signaling lymphocytic activation molecule
SLE: Systemic lupus erythematosus
SNP: Single nucleotide polymorphism
Th1: T helper 1
Th2: T helper 2
tlr7: Toll-like receptor 7
TMPD: Pristane (2, 6, 10, 14 tetramethylpentadecane)
TNF: Tumor necrosis factor
TNF-R: Tumor necrosis factor receptor
TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand
RBC: Red blood cell
Yaa: Y-linked autoimmune acceleration.

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