

# Mouse models of lupus: what they tell us and what they don't

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## ABSTRACT

Lupus is a complex heterogeneous disease characterised by autoantibody production and immune complex deposition followed by damage to target tissues. Animal models of human diseases are an invaluable tool for defining pathogenic mechanisms and testing of novel therapeutic agents. There are perhaps more applicable murine models of lupus than any other human disease. There are spontaneous models of lupus, inducible models of lupus, transgenic-induced lupus, gene knockout induced lupus and humanised mouse models of lupus. These mouse models of lupus have contributed significantly to our knowledge of the pathogenesis of lupus and served as valuable preclinical models for proof of concept for new therapies. Despite their utility, mouse models of lupus have their distinct limitations. Although similar, mouse and human immune systems are different and thus one cannot assume a mechanism for disease in one is translatable to the other. Efficacy and toxicity of compounds can vary significantly between humans and mice, also limiting direct translation. Finally, the heterogeneous aspects of human lupus, both in clinical presentation, underlying pathogenesis and genetics, are not completely represented in current mouse models. Thus, proving a therapy or mechanism of disease in one mouse model is similar to proving a mechanism/therapy in a limited subset of human lupus. These limitations, however, do not marginalise the importance of animal models nor the significant contributions they have made to our understanding of lupus.

## INTRODUCTION

Research into human diseases spans in vitro assessments to preclinical animal models of disease to in vivo human assessments and finally testing of therapeutics in humans. This step-by-step model has resulted in most of the major breakthroughs in new treatments for disease. Perhaps more so in lupus than any other human disease, mouse models have contributed significantly to our understanding of the disease and the development/testing of new treatments for the disease.<sup>1</sup> For the last four decades, we have characterised spontaneous murine models of lupus that were defined genetically and immunologically and served as the initial step in supporting or not the progress of new treatments to clinical trials for lupus.<sup>2,3</sup> As science and medicine progressed, transgenic techniques, gene

knockout techniques, inducible knockouts and humanised mouse models were developed that allowed further insight into the role of a single gene or molecule in lupus pathogenesis.<sup>4,5</sup> Most of the mouse models of lupus produce autoantibodies and develop immune complex glomerulonephritis and thus provide insight into the mechanisms of loss of tolerance and the development of glomerulonephritis.<sup>5</sup> No mouse model is completely representative of human lupus, perhaps due to the fact that human lupus is so heterogeneous that not one inbred mouse model can manifest the broad spectrum of disease present in human lupus.<sup>6,7</sup> Despite this shortcoming and the growing trend to move more into studying humans rather than mice, murine models of lupus have and continue to provide significant insight into disease pathogenesis and treatment. In this review, we cover selected mouse models of lupus; however, there are many others that are not included due to the expanding number of knockout models and transgenic models that develop a disease with similarities to human lupus.

## Spontaneous models of lupus

Spontaneous models of lupus were recognised four decades ago beginning with the New Zealand Black crossed with the New Zealand White mouse, the NZB/NZWF1 (BW) mouse.<sup>2</sup> BW mice produce autoantibodies (ANA and anti-dsDNA predominantly) and develop immune complex glomerulonephritis and mild vasculitis.<sup>3</sup> Similar to humans, lupus develops primarily in females with lesser percentage and severity in male mice. They do develop splenomegaly and hypergammaglobulinemia.<sup>3</sup> They do not manifest other clinical manifestations of lupus such as rash or arthritis. Disease develops slowly, primarily after 6 months of age, with 50% mortality in female mice at 9 months of age and in male mice at 15 months of age. BW mice were studied early on regarding mechanisms of loss of tolerance, autoantibody production, impact of sex/gender/sex hormones on disease and pathogenic factors in renal



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disease development.<sup>3</sup> They were used in the preclinical testing of many of the therapeutics taken to clinical trials in lupus.<sup>8,9</sup> One drawback for research of the BW mice is the long disease incubation time as well as the predominantly single-organ involvement. Investigators have used strategies to enhance disease expression including giving adenoviruses that express interferon (IFN) $\alpha$  leading to earlier disease expression or injecting toll-like receptor (TLR)7/9 agonists to accelerate disease development.<sup>10,11</sup> Another drawback is the need to breed the two strains together to get offspring for study. Nevertheless, they remain a useful staple for studies of lupus.

Related strains to the NZB/NZWF1 mice are the NZM strains. These mice were generated by mating of pairs of NZB/NZWF1 mice for multiple generations. Over 20 NZM strains were generated and characterised for manifestations of lupus-like disease.<sup>12</sup> Two of them are used in lupus research laboratories today. One is the NZM2410 mouse. NZM2410 mice, like the parental NZB/NZWF1 mice, make autoantibodies and develop immune complex glomerulonephritis.<sup>13–16</sup> They do not develop vasculitis. Different from B/W mice, the development of lupus occurs more or less at the same time and similar severity in males and females, though there are differences. The NZM2410 mouse strain was used extensively for defining the genetics of lupus. By backcrossing to C57BL6 mice, Mohan, Wakeland and Morel generated a series of congenic mice that contained the susceptibility loci for lupus (sle1,2,3) mice.<sup>13,17,18</sup> They further characterised the phenotype of immune abnormalities and disease expression for each of the three loci and fine mapped the genes involved, primarily focusing on the sle1 locus.<sup>16</sup> There are a number of genes in this locus that they further characterised, including identifying complement receptor 2 as one of the candidate genes.<sup>19</sup> NZM2410 mice have the advantage over B/W mice in that they are a single strain that can be expanded by breeding to each other. They, like BW mice, are primarily a model of immune complex glomerulonephritis without skin disease or arthritis.<sup>14</sup> Disease develops faster in NZM2410 mice than in B/W mice with a 6-month 50% mortality rate. They are being used currently in preclinical trials of candidate drugs.<sup>20</sup> They have significantly contributed to our understanding of multi-genic interactions in the pathogenesis of lupus. The congenic sle1,2,3 mice, which express the susceptibility loci of NZM2410 mice on the C57BL6 background, are also used extensively.<sup>21</sup> Different transgenes and gene knockouts can be more rapidly bred onto the sle1,2,3 background as most transgenes and knockouts are on the B6 genetic background. Thus, one can backcross a gene knockout or transgenic much more quickly onto the sle1,2,3 compared with the time-intensive process of crossing to Murphy Roths Large (MRL)/lymphoproliferation (lpr) or NZM2410 mice, allowing quicker assessment of the impact of the knockout or transgene on disease.<sup>22,23</sup> One can derive congenic mice to study on the sle1,2,3 strain after only 3–4 generations,

while it takes 10–12 generations of backcrosses to fully backcross to NZM2410 or other lupus strains.

The other NZM strain being studied is the NZM2328.<sup>12,24</sup> They also develop renal disease, produce anti-dsDNA antibodies, but slower onset of disease with 50% mortality occurring at 9 months of age. This strain has the advantage that disease is much more prevalent in females than males similar to BW mice and human disease.<sup>12,25,26</sup> The other interesting feature of this strain is that they have two-stage renal disease, acute glomerulonephritis followed by a more chronic nephritis.<sup>25,26</sup> These mice were also used to show that autoantibodies, especially anti-dsDNA antibodies, are not required for development of renal disease.<sup>27,28</sup>

A third strain of mice, the MRL/lpr mouse was generated by intercrossing four different strains of mice (LG, B6, AKR and C3H).<sup>29,30</sup> MRL/lpr mice are unique among lupus strains in that they develop a full panel of lupus autoantibodies (ANA, anti-dsDNA, anti-Sm, anti-Ro and anti-La) and have additional lupus manifestations including arthritis, cerebritis, skin rash and vasculitis.<sup>31–33</sup> The disease, however, is more prevalent and accelerated in females, but not as prominent as in B/W or NZM2328 mice, with 50% mortality at 6 months. The background genetics of the MRL/lpr mouse is complex, but the lpr gene is a single-gene mutation in the Fas receptor gene.<sup>34,35</sup> This gene is important in apoptosis of B cells and T cells.<sup>36</sup> The defect in Fas thus leads to marked splenomegaly and lymphadenopathy, primarily made up of an unusual set of 'double-negative T cells' (CD3+CD4–CD8–).<sup>37,38</sup> The role of these double-negative T cells remains unclear, but the lpr gene significantly accelerates development of disease compared with MRL/+ mice that lack the Fas mutation.<sup>39,40</sup> A deficiency of Fas ligand (called gld) has a similar accelerating effect on lupus-like disease as the Fas receptor on the MRL background.<sup>41</sup> It is of interest that although Fas-deficient humans have lymphadenopathy and other immune abnormalities they do not develop a lupus-like syndrome, perhaps due to their not having an otherwise susceptible genetic background.<sup>42</sup> Similarly, B6, BALB/c, C3H and AKR mice, onto which the lpr gene was bred, develop splenomegaly, autoantibodies and lymphadenopathy, but have very mild autoimmune disease.<sup>43,44</sup> The MRL+ mouse lacks the lpr mutation. These mice develop a more benign lupus phenotype at a much later age (18 months) and are used primarily to study accelerants of disease.<sup>30,45</sup> The MRL/lpr mouse is used extensively for assessments of candidate treatments for lupus due to the more rapid onset of disease and the multiple manifestations of disease.<sup>46–48</sup> The mouse is not a perfect model for human lupus as, unlike in the majority of human lupus, disease is not primarily driven by IFN $\alpha$ , but more IFN $\gamma$ , and the dominance of the lpr mutation in accelerating disease also differs from human lupus.<sup>10,49</sup>

Another spontaneous murine model of lupus is the BXS mouse. This mouse model is different from all others as disease only occurs in male mice. The genetic risk for disease was mapped to a locus on the Y chromosome

referred to as Yaa.<sup>50 51</sup> Two groups near simultaneously identified yaa as a translocation of a region of the X chromosome onto the Y chromosome.<sup>52–54</sup> This region was shown to contain the TLR7 gene and subsequent eloquent studies confirmed it is the duplication and resultant over-expression of TLR7 that is required for lupus-like disease expression.<sup>53</sup> The Yaa genetic locus was then bred onto other lupus-prone backgrounds and shown to accelerate and enhance disease expression.<sup>55 56</sup> This discovery was critical in demonstrating the important role of TLR7-inducing increased type I IFNs as a causative pathway for lupus.<sup>53</sup> Disease in the BXSb mouse is limited, similar to most other models, to glomerulonephritis. There are other spontaneous lupus mouse models, including SNF1 mice, whose disease expression is similar to that of BW mice.<sup>56</sup> Use of SNF1 mice and other models is limited compared with the above-listed strains.

Most of these strains have served as preclinical models for the testing of potential new lupus therapies. Therapies directed at the BAFF/BLyS axis, IFN, interleukin (IL)17, B cells, plasmablasts, T cells, dendritic cells and TLRs, among many others, were given to at least one of the murine lupus models.<sup>57–60</sup> Unfortunately, efficacy in a mouse model of lupus does not always translate to efficacy in human lupus, as the therapies that failed in human trials, all had efficacy in preclinical mouse models.<sup>61</sup> Given that the mouse strains are genetically alike and experimental conditions and concomitant meds are easily controlled, compared with the heterogeneity of human lupus and confounders present in any human experiment, success in mouse studies can only be considered a first necessary step in drug development.

### Induced/accelerated models of lupus

The spontaneous models of lupus provided important insight into the complex genetics of lupus, as well as the potential for a single-gene mutation to markedly accelerate/enhance disease expression. Lupus in humans, however, is believed to be the result of an environmental factor triggering disease in a genetically prone individual. Identifying the environmental trigger has been as elusive or more so than defining the susceptibility genes. Perhaps the most widely used murine model of induced disease is the pristane-induced model.<sup>62</sup> Pristane is a mineral oil that was given intraperitoneally in BALB/c mice to induce peritoneal irritation and enhance the yield of monoclonal antibodies from ascites when hybridomas were subsequently injected. Satoh *et al* noted that pristane-injected mice, after a number of months, developed a lupus-like disease with immune complex glomerulonephritis, mild erosive arthritis and many lupus-associated autoantibodies.<sup>63</sup> A number of strains of mice develop a lupus-like disease following pristane injection. B6 mice, when injected with pristane, develop low-grade autoimmunity, but also develop pulmonary vasculitis and pulmonary haemorrhage, yielding a valuable animal model for studying this rare, but devastating complication of lupus.<sup>64–66</sup> A number of studies have identified key pathways involved

in development of disease that are relevant to human lupus. Among other key findings, studies demonstrated that pristane-induced lupus is highly dependent on over-production of type I IFNs, similar to over half of patients with lupus.<sup>67 68</sup> This overproduction of type I IFNs requires expression of TLR7.<sup>67–70</sup> Pristane-induced lupus is the best example of an environmental factor inducing lupus-like disease in a strain that otherwise is not autoimmune.

A more recently developed mouse model for lupus used resiquimod cream administered to the ears of specific strains of mice.<sup>71 72</sup> This cream, containing a TLR7 ligand, is in human use in management of pre-cancerous skin lesions. When repeatedly rubbed onto the ears of BALB/c mice and limited other strains, a lupus-like disease develops in 2–4 weeks with autoantibody production, splenomegaly and immune complex glomerulonephritis. The mice exhibit, as expected, heightened levels of type I IFN activity.<sup>71 72</sup> Unfortunately, induction of disease in B6 mice is less predictable, thus limiting, to some extent, the ability to use this model to discern disease mechanisms and key pathways using transgenic or genetic knockout mice. The rapidity of disease onset is, however, attractive compared with the incubation time of other induced or spontaneous models.

Solvent exposure is thought to be a possible occupational risk factor for developing lupus. In particular, the degreasing solvent, trichloroethylene (TCE), has been most frequently implicated and most widely studied. TCE has been identified as a possible factor in studies of geographic lupus clusters in Arizona and North Carolina near military bases where high levels of TCE were found in drinking water.<sup>73–75</sup> Other potential environmental exposures tested for their role in lupus include silica, persistent organic pollutants and heavy metals, most commonly mercury.<sup>76–79</sup> Different gulf war environmental exposures were also used to assess their impact on autoimmunity.<sup>80</sup> In most of these cases, exposure of non-autoimmune-prone mice with these agents did not induce autoimmunity or lupus, though specific effects on immune cell subsets could be defined. Alternatively, most were found to accelerate development of lupus in lupus-prone mice such as MRL/+ mice.<sup>74</sup> Defining the relevance of these studies to induction of human lupus via environmental exposure remains to be determined.

Another studied induced murine model of lupus is graft-versus-host (GVH) disease, induced by performing bone marrow transplant experiments into F1 crosses, using as the donor one of the parental strains.<sup>81</sup> Depending on the strains used in these experiments, one can induce acute GVH disease with autoantibodies and immune complex nephritis. Other combinations lead to development of chronic GVH disease. Given that GVH is primarily a T-cell-driven disease, these models were informative in defining the role of T cell alloreactivity/autoreactivity in driving B cell autoantibody production and tissue damage.<sup>82 83</sup>

A specific, but rapid model of immune complex glomerulonephritis, developed by the Lefkowitz group, can be generated by injecting anti-glomerular basement

membrane (GBM) antibodies into mice.<sup>84–85</sup> These antibodies are usually generated by injecting rabbits with mouse glomerular extracts and deriving their serum containing anti-mouse GBM antibodies. An even more robust disease, developed by Mohan and colleagues, can be induced by pre-immunising the mice with rabbit IgG subcutaneously inducing an anti-rabbit IgG response prior to then injecting the rabbit anti-GBM antibodies.<sup>86–87</sup> These induced models of glomerulonephritis are helpful for discerning the pathogenic factors in renal inflammation and damage that occur downstream of immune complex deposition.

### Transgenic models of lupus

The advent of transgenic techniques allowed researchers to express or overexpress a gene product or protein to discern their role in lupus and immunity in general. One of the earliest uses of transgenic technology was to introduce immunoglobulin heavy and light chain genes that code for autoantibodies (ie, rheumatoid factor or anti-dsDNA antibodies).<sup>88–89</sup> Since these antibodies were against self-antigens, insight was gained as to how tolerance is maintained by studying how an autoantibody-producing B cell is handled in a lupus-prone mouse versus a normal mouse. The concept of receptor editing was defined using transgenic mice expressing autoreactive antibodies. In normal immunity, a B cell expressing a heavy chain that is autoreactive when paired with a specific light chain will receptor edit, dropping the autoreactive light chain and replacing it with a different light chain that is not autoreactive.<sup>88–89</sup> Lupus-prone mice were subsequently shown to not be as effective in receptor editing. Overexpression of the Ets factor Fli-1 gene led to a lupus-like disease among other models where overexpression of a gene can lead to disease (ie, TLR7 as in BXS mice).<sup>90–91</sup> Overexpression of genes that are immune modulatory (transforming growth factor (TGF) $\beta$ , IL10, Bcl2) provided insight into the role of these factors in immune tolerance.<sup>20</sup> Knock-in technology was developed that allowed putting a gene specifically into the genetic locus of the native gene. This technique is used to further define defects in immune function and autoimmune development in lupus.<sup>92–94</sup>

### Knockout models of lupus

The technique of gene knockout has been used extensively to study pathogenetic mechanisms in lupus. A large number of such knockout studies were performed on the MRL/lpr background and provided important understanding of the effects of certain genes and certain cells on disease. An example of new insight derived from MRL/lpr knockout studies were the experiments by the Shlomchik group on B cells. Total knockout of B cells ameliorated disease. Mice that have B cells, but cannot produce antibodies, had less disease, but not a complete lack of disease.<sup>95–98</sup> These findings support that B cells play an important role in lupus independent of autoantibody production, including production of key cytokines, serving as antigen-presenting cells and being necessary

for formation of lymphoid-like organs in target tissues such as the kidney and synovium.<sup>95–98</sup> Another example is when the TLR7 and TLR9 knockouts were bred onto the MRL/lpr background. TLR7-deficient mice have significantly less disease, do not produce anti-Sm or anti-RNP and have prolonged survival. TLR9-deficient mice, surprisingly, have accelerated disease despite lacking anti-dsDNA antibodies. TLR7/TLR9 double knockouts were protected, suggesting the TLR9-accelerant effect is dependent on TLR7.<sup>99–101</sup> Using Cre recombinase and Floxed technology allowed specific deletion of a gene in a cell of choice, while allowing expression in all other cell types, thus allowing definition of the role of a specific gene in a specific cell type.<sup>102</sup> Conditional knockout technology allowed one to induce the knockout at a specific time point in the mouse, thus allowing the immune system to develop and mature prior to knocking out the specific gene of choice. . Dozens of genes were knocked out, leading to autoimmunity including C1q, C4, DNaseIL3 and TGF $\beta$ .<sup>103–104</sup> Studies knocking out specific FcRs, apoptosis genes and cellular debris clearance genes have provided important insight into the role these different factors play in immunity and autoimmunity. Knockout of genes other than TLR7 (ie, factor B, Fli-1, IFN $\alpha$ , among others) resulted in decreased disease expression, implying a key role of these factors in disease development.<sup>4103</sup>

The latest technology and perhaps most useful for studies of gene function is the CRISPR/Cas9 technique.<sup>104</sup> This incredible gene editing technology allows one to specifically introduce point mutations into genes of choice that can either knockout gene function or alter gene function/expression.<sup>105</sup> Thus, a specific lupus susceptibility single-nucleotide polymorphism can be introduced through this technique, allowing one to study the effect of that specific nucleotide change. An advantage to this technology is that it can be applied to any strain of mice, whereas prior knockout work was very difficult unless done in the B6/129 strain. CRISPR/Cas9 can be done in any strain, including MRL/lpr or NZM2410 mice, allowing rapid assessment of the impact of the genetic change without having to perform multiple genetic backcrosses. To study the dozens of identified and verified lupus susceptibility loci, a number of laboratories are using the CRISPR/Cas9 system to introduce the identified nucleotide change and study the effects in specific immune cells and systemic disease.

### HUMANISED MICE

A common concern and criticism of studies done in mice is that mice are not humans and the mouse and human immune systems differ in a number of different areas including TLR expression, complement protein and inhibitor differences, Ig differences and FcR differences, among others. Using immune-deficient mice, techniques are available for establishing a humanised mouse immune system, including a lupus humanised mouse immune system.<sup>106–107</sup> Once fully developed, these mice

**Table 1** Summary of spontaneous and induced mouse models of lupus

Strain	Glomerulonephritis	Arthritis	Cerebritis	Skin	Anti-dsDNA	Anti-ENA	M/F prevalence
MRL/lpr	Active proliferative 3–4 months	Microscopic synovitis	Cognitive dysfunction	Rash on face and back	+++	++	F=M
MRL/+	Very late in life	Mild microscopic synovitis	Late cognitive dysfunction	Mild	++	+	F>M
NZN/NZW	Active proliferative 4–5 months	Absent	Absent	Absent	+++	–	F>>M
NZM2410	Active proliferative 3–4 months	Absent	Absent	Absent	+++	–	F=M
NZM2383	Active proliferative followed by chronic scarring	Absent	Absent	Absent	+++	–	F>>>M
BXSB	Proliferative at 4–5 months	Absent	Absent	Absent	+++	–	M>>>>F
SNF1	Mild proliferative at 6 months	Absent	Absent	Absent	+++	–	F>>M
Pristane induced	Active proliferative at 8–10 months	Absent	Absent	Absent	+++	++	?
Resiquimod induced	Proliferative at 4 weeks of exposure	Absent	Absent	Absent	+	–	?
Anti-GBM induced	Active proliferative at 2–3 weeks post injection	Absent	Absent	Absent	–	–	F=M
Graft versus host disease	Acute and chronic depending on model	Absent	Absent	Present	+	–	F=M

F, female; GBM, glomerular basement membrane; lpr, lymphoproliferation; M, male; MRL, Murphy Roths Large; NZ, New Zealand.

will be useful in specific gene editing experiments and in preclinical testing of new therapeutics as the response to treatment in these mice will be more like the human response than the mouse response.

## SUMMARY

Lupus mouse models have proven an invaluable resource to study lupus over the last 40 years. Findings in these models have provided novel insight into the pathogenesis of lupus at the cellular and molecular level. They are valuable as preclinical models in discerning the possible therapeutic value of a pharmacological intervention. Newer technologies, specifically CRISPr/Cas9 and humanised mice, will provide even more valuable as tools for dissecting lupus pathogenesis. Although mouse and human immune systems are different and efficacy of a treatment in mice is not always translatable to human lupus, studies of lupus in mice remain, and will continue to be, extremely valuable for understanding lupus pathogenesis and treatment (table 1).

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