An efficacy model to test the ability of novel therapeutics to regulate development and progression of spontaneous systemic lupus erythematosus

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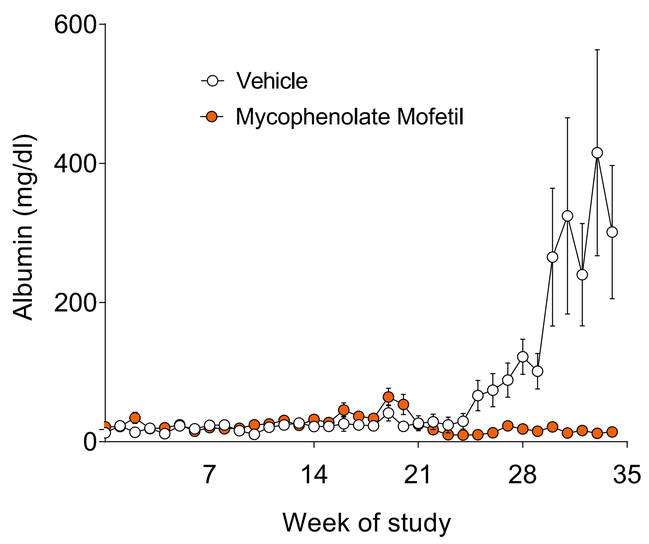
1 Systemic lupus erythematosus – Clinical features and the NZBW/F1 model

- Systemic Lupus Erythematosus (SLE) is an idiopathic autoimmune disease characterised by the generation of autoantibodies that deposit in end organs resulting in multi-system pathology.
- SLE etiology is multifactorial and not completely understood. Therapies for effective treatment of lupus are still lacking. Clinically, SLE has a heterogeneous presentation with a variety of manifestations including renal and neurological.
- At Charles River Laboratories, we utilise a clinically relevant model of SLE, the NZB/W F1 mouse. In this model, lupus develops spontaneously with an increase in autoantibodies at 5 months of age which peaks at 8-9 months and parallels with development of proteinuria, an indicator of kidney dysfunction (immune complex glomerulonephritis). This can be seen in-life by an increase in proteinuria levels, and at the *ex-vivo* analysis of lymph nodes, bone marrow and splenocytes.
- We show here that the NZB/W F1 spontaneous model of SLE is an effective translational tool to test efficacy of new therapies for treatment of lupus and use mycophenolate mofetil (MMF) as a benchmark to test novel therapies against.

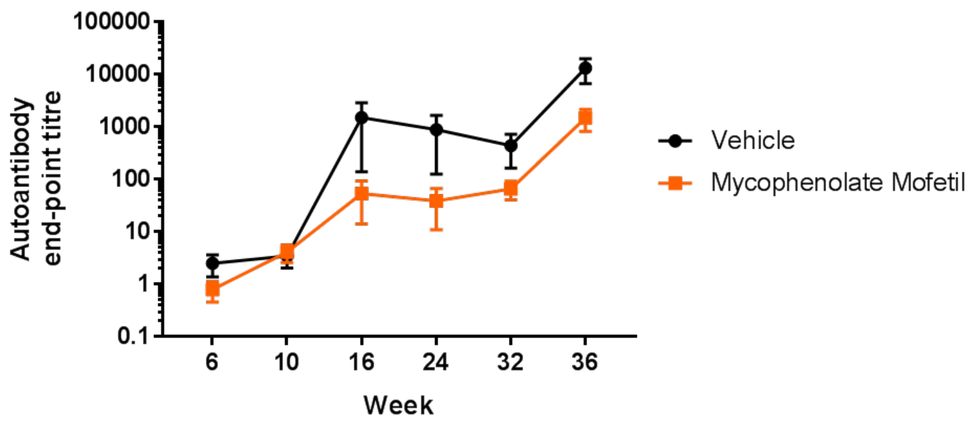
2 Evaluation of novel therapies on glomerulonephritis

The NZB/W F1 model displays an increase in proteinuria, as measured by albumin levels in blood serum, which is evident from week 21 to study end and can be reversed by MMF, an off-label therapy approved for treatment of lupus that inhibits inosine-5'-monophosphate dehydrogenase.



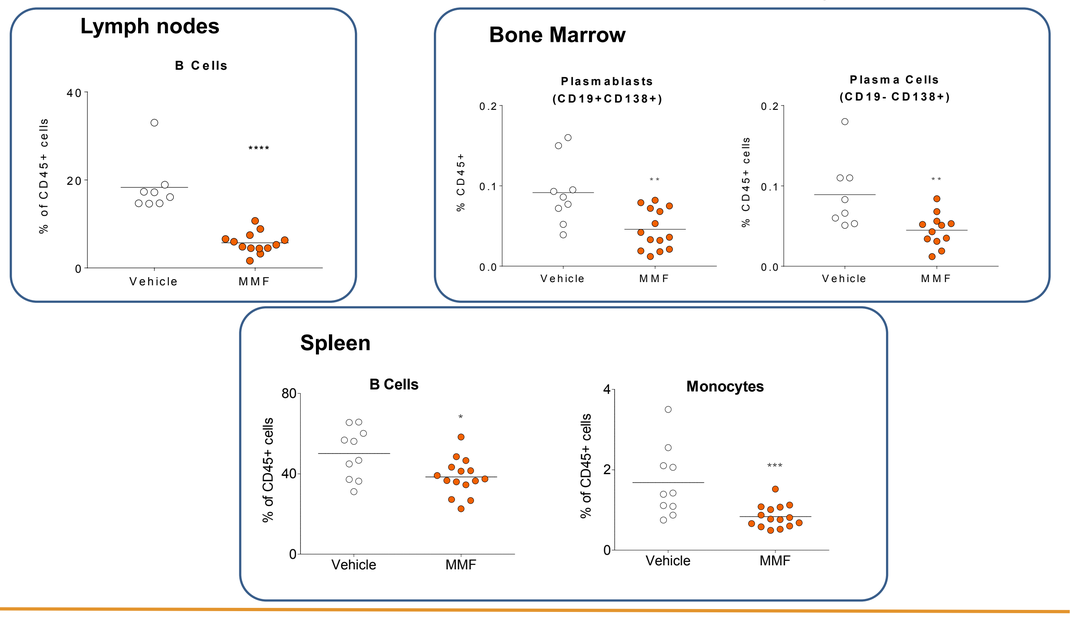
3 Autoantibody measurement to monitor the impact of a novel therapeutic on disease progression

Elevated autoantibody levels (anti-dsDNA) are seen on week 16, peaking at week 36. The aim of many novel therapies is to prevent or decrease autoantibody production with the aim of reducing severity of disease. The control drug MMF decreased the levels of autoantibodies from week 16 to week 36. This provides a control against which novel therapies can be benchmarked.



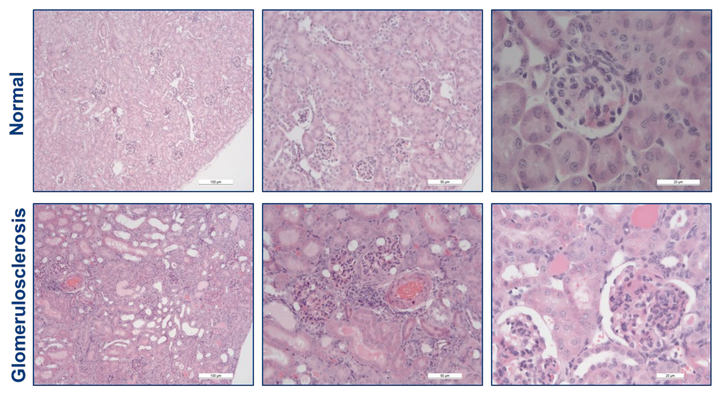
4 Efficacy of novel therapies on B cell function by flow cytometry

Auto-antibodies produced by adherent B cell responses have been associated with SLE pathology. The ability of novel therapies to target B cell function and phenotype can be assessed by flow cytometry. MMF decreased the frequency of B cells in the lymph node and the number of plasmablasts and plasma cells in bone marrow on week 36. MMF also decreased B cells and monocytes in spleen.



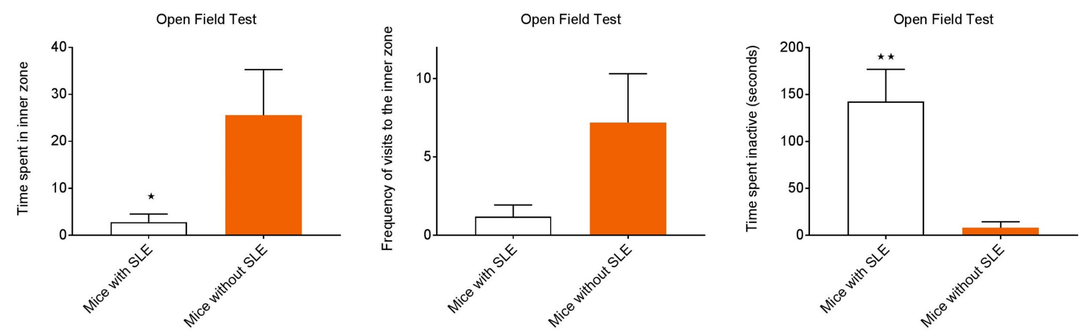
5 Efficacy of novel therapies on glomerulonephritis

We have characterised the NZB/W F1 model using histopathological analysis to study glomerulonephritis compared to naïve controls. NZB/W F1 mice can be used to assess the efficacy of novel therapies on mesangial proliferation and mononuclear cell infilitration within the glomeruli and sclerosis affecting the glomeruli.



6 Option to test novel therapies on SLE-related anxiety and depression behaviours

We have assessed depression- and anxiety-related behaviours in the NZB/W F1 mouse model using the open maze test. We found changes in the time spent in the inner zone of the open maze, frequency of visits to the inner zone and time spent inactive compared to naïve controls. The neurological deficits can be correlated with autoantibody production and autoreactive B cell depletion.



7 Conclusions

- The NZB/W F1 model provides a good efficacy model for testing novel therapies aimed at modulating and controlling SLE.
- The model has high translational relevance because it recapitulates the following characteristics of human disease which are proteinuria, formation of autoantibodies, glomerulonephritis and clinical signs of depression- and anxiety-related behaviours.
- The main markers for tracking SLE progression in this model are proteinuria (nephritis) and anti-dsDNA antibodies (autoimmunity), B cell phenotype and expansion and histology. Together, these cover many of the targets of novel therapies within the SLE field.
- At Charles River, we have shown efficacy of clinically relevant standard of care drugs on nephritis, autoantibody production and autoreactive B cell depletion. However given the heterogeneity of disease, complex pathological mechanism and absence of a complete cure, novel therapies are still needed.

References

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