

**Background** Lupus is an autoimmune disease characterized by antibodies directed against nuclear components that induce immune complex-mediated injury to multiple organs. Underlying lupus is the induction of T-cell-dependent activation and clonal expansion of autoreactive B cells in germinal centers resulting in their differentiation into plasma cells that secrete pathogenic autoantibodies. Heightened glucose metabolism is inherent to immune/inflammatory disorders, but little is known of its role in lupus etiology. Present treatments for lupus rely heavily on broad-spectrum immunosuppressive agents, and there is a need for targeted therapies that effectively counteract this systemic autoimmune disorder.

**Methods** Here we examined the metabolic and gene expression profiles of key autoimmune populations in mouse models of spontaneous lupus and their responses to treatment with the glycolysis inhibitor 2-deoxyglucose (2DG) in drinking water. Therapeutic efficacy in terms of survival after long- vs. short-term 2DG-exposed times was assessed on BXS<sub>B</sub>.Yaa and NZBWF1 lupus-prone mice. Furthermore, a chimeric antigen receptor (CAR)-T immunotherapy was used to determine whether a targeted removal of an identified B cell subset can improve disease outcomes.

**Results** We found greater glucose uptake and glycolysis rate in spontaneous germinal center B cells (GCB) compared to that in follicular helper T cells (T<sub>fh</sub>). The differential dependency on glucose oxidation between GCB and T<sub>fh</sub> was determined, rendering GCB highly susceptible to oxidative stress-induced apoptosis triggered by glycolysis inhibition via 2DG. Short-term glycolytic inhibition selectively targeted GCB, sparing other autoreactive populations, including T<sub>fh</sub>. This reduction of GCB is, in turn, responsible for improving kidney function and lifespan of treated mice. Moreover, we identified a subset of GCB, which express TNFSF17 and exhibit a higher reliance on glucose metabolism than TNFSF17<sup>+</sup> GCB. Their depletion through its ligand TNFSF13-based CAR-T treatment significantly decreased mortality from lupus.

**Conclusions** Differential metabolic requirement for glucose between autoreactive GCB and T<sub>fh</sub> dictates different sensitivity to apoptosis via glycolytic inhibition, and this provides a metabolic niche for targeted lupus treatment. Combining therapies that selectively dampen GCB metabolism for survival with T cell-based immunotherapy could provide new effective treatments for lupus.

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#### THE EIF4 TRANSLATIONAL INHIBITOR PATEAMINE A IMPROVES IMMUNOLOGICAL AND NEUROLOGICAL FUNCTIONS IN BXS<sub>B</sub>.YAA LUPUS MICE

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**Background** Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by loss of tolerance and activation of the immune response. Clinical manifestations are heterogeneous and several organs can be affected including skin, joints, central nervous system and kidney. Traditional

treatments include the use of hydroxychloroquine, glucocorticosteroids, immunosuppressive and more recently, biological drugs such as belimumab or rituximab. In the last decade new alternatives have been proposed based on targeting interferon and cytokines. Mouse models have been extremely helpful to test the efficacy of new SLE therapies. In this work we analyze the therapeutic potential of a natural compound, Patemina A (PatA) to treat SLE. Pat A is an inhibitor of the translation initiation process with immunosuppressive properties that has been tested successfully in cancer mouse models.

**Methods** To test Pat A efficiency in SLE we used the BXS<sub>B</sub>.Yaa lupus model. Animals were treated for 8 weeks starting at the initial stages of disease (12 weeks). Sera was collected every three weeks and disease signs were followed. At the final point we performed serological analyses (cytokines and autoantibodies), flow cytometry on spleen to evaluate different cell populations, kidney histological and functional assays and behavioral tests to evaluate neuropsychiatric changes.

**Results** Our data shows that Pat A treatment increases the survival rate and is able to reduce circulating levels of proinflammatory cytokines and autoantibodies. We also observed improvement of cognitive functions (learning/memory, and depression behavioral tests) together with a reduction of proinflammatory cytokines locally in the hippocampus.

**Conclusion** These data suggests that translation inhibition improves lupus disease signs at the immunological and neurological levels opening a new line of research based on translation inhibition to treat lupus and possibly other autoimmune diseases with an inflammatory component, and may be a complement for present day treatments.

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#### A PEPTIDE MIMETIC OF THE KINASE INHIBITORY REGION OF SUPPRESSOR OF CYTOKINE SIGNALING-1 ATTENUATES LYMPHOCYTE ACTIVATION AND LUPUS PROGRESSION IN MRL/LPR LUPUS MODEL

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**Background** Lupus progression is driven by the aberrant activation of T and B lymphocytes which promote a dysregulated cytokine milieu and produce pathogenic antibodies. Many cytokines, including interferon gamma (IFN- $\gamma$ ), utilize the janus kinase/signal transduction and activation of transcription (JAK/STAT) pathway for signal propagation. Suppressor of Cytokine Signaling-1 (SOCS-1) is an inducible, intracellular protein which regulates the JAK/STAT pathway and IFN $\gamma$  signaling. We have previously shown that a peptide mimicking the kinase inhibitory region of SOCS1 (SOCS1-KIR) inhibited IFN- $\gamma$  signaling and inflammation-mediated disease progression.

Using MRL/lpr mice, which spontaneously develop SLE-like disease, we test the hypothesis that SOCS1-KIR administration inhibits T and B lymphocyte activation leading to an amelioration in lupus pathology.