Conclusions Our study demonstrates that B cell-intrinsic IFN-γ receptor signals promote lupus pathogenesis via formation of spontaneous, autoimmune GCs. In addition, we have uncovered a novel cell-intrinsic program whereby IFN-γ, together with BCR-, TLR- and/or CD40 signals, orchestrates B cell expression of the GC master transcription regulator BCL-6. Our combined findings suggest that this IFN-γ signalling program may be a potential therapeutic target in SLE.

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AI-19 METABOLIC INHIBITION BY 2-DEOXYGLUCOSE PREVENTS AND REVERSES LUPUS IN MICE

[1]Thomas J Sproule, [1]John Wilson, [1]Elisabeth Adkins, [2]Byron P Crocker, [2]Laurence Morel, [1]**Derry C Roopenian***. *[1]The Jackson Laboratory, Bar Harbour, ME, USA; [2]Department of Pathology, University of Florida, Gainesville, FL, USA*

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Background Glucose is a primary substrate for cellular respiration. Glucose utilisation increases in highly metabolic cells including activated, proliferating T cells and B cells as well as cancers. Lupus is a disorder in which autoreactive CD4+ T cell and B cells that deviate from normal homeostasis by their uncontrolled proliferation and differentiation to effector cells. Therapeutic limitation of glycolysis is therefore an attractive approach for attenuating the highly energetic, pathogenic processes inherent to lupus. Here we investigate the potential of several metabolic inhibitors that target early and downstream aspects of cellular respiration to identify inhibitors that show potential in the prevention and treatment of lupus.

Materials and methods Metabolic inhibitors included: 1) a classic glycolysis inhibitor, 2 deoxyglucose (2 DG); 2) a mitochondrial complex I inhibitor/AMPK activator metformin (MET); 3) an mTOR inhibitor, rapamicin (RAPA); and 3) a pyruvate dehydrogenase kinase inhibitor, dichloroacetate (DCA). The drugs were provided in drinking water or mouse chow for 4–8 wks. NZB X NZW F1 (BWF1) and BXSB.*Yaa* mouse models of lupus were evaluated in prevention studies and in treatment of mice documented to be undergoing autoimmune disease. Longitudinal and terminal immunophenotyping was performed using flow cytometric, serological, histopathological analyses.

Results 2 DG, MET, DCA and RAPA, and combinations thereof were applied prior to the onset of autoimmune disease to BWF1 and BXSB. *Yaa* mice. MET and DCA showed minimal effects and RAPA resulted in partial attenuation. In contrast, 2 DG acted potently to abrogate multiple disease biomarkers while not causing immunodeficiency. Given the strong immunologically normalising effects of 2 DG in disease prevention, we performed therapeutic interventions in which 2 DG was supplied for 8 weeks to already diseased BWF1 and BXSB.*Yaa* mice. Within 4 weeks of treatment, 2 DG normalised all cellular, serological and pathological features characteristic of the BWF1 and BXSB. *Yaa* lupus like syndromes. Furthermore, the lifespans of BXSB. *Yaa* mice were extended after withdrawal of treatment (Figure 1).

Conclusions Overall, the results highlight the potent and remarkable normalising effect of 2 DG in the prevention and treatment lupus-like autoimmune disease in mouse models with differing genetic and mechanistic etiologies. Given findings, we propose that that therapeutic inhibition of early steps in glycolysis, as exemplified by 2 DG, has broad potential for the treatment of multiple autoimmune disorders. Our current efforts are focused on: 1) the potential of 2 DG in treatment of other autoimmune severe diseases; and 2) evaluation of potential downsides of metabolic inhibition by 2 DG and other inhibitors of glycolysis.

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AI-20 DEFECTIVE BCR INDUCED APOPTOSIS LINKED TO ELEVATED LEVELS OF 9-*O*-ACETYLATED SIALYL GANGLIOSIDES ON B CELLS IN LUPUS PROVIDES A POTENTIAL THERAPEUTIC TARGET FOR LUPUS

Xin Kai, Vinay S Mahajan, Kendra Taylor, **Shiv Pillai***. *Ragon Institute of MGH, MIT and Harvard, Cambridge Massachusetts, Massachusetts General Hospital, Harvard Medical School, Boston USA*

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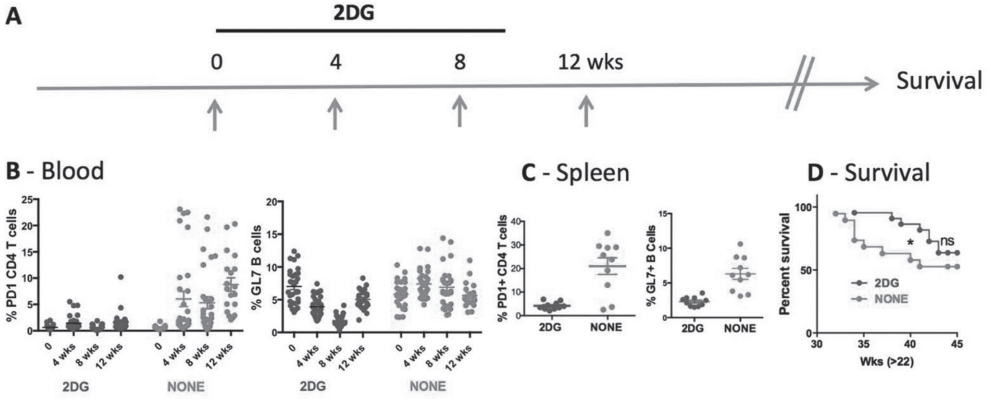

Abstract AI19 Figure 1 Exemplary data showing that treatment with 2DG reverses ongoing autoimmune disease of BXSB.*Yaa* mice. (**A**) Schematic of the therapeutic approach. (**B**) BXSB.*Yaa* mice were aged to 12 wks. FACS analysis of blood CD4+ T cells and B cells 0, 4, 8 of treatment and 12 wks (4 wks after treatment was withdrawn). (**C**) Analysis of CD4+ splenic CD4+ T cells and B cells 8 wks after treatment. (**D**) Survival of mice after withdrawal of treatment*. P ≤0.05.