half-life, thereby allowing sCAR T cell killing only when the antiCD19 switch is present. Treatment of BXSB males with sCAR T plus continuous antiCD19 switch reduced B cell numbers, circulating immunoglobulins, autoantibodies, and nephritis. To document the efficacy of a shorter course of treatment, B6 mice were given three every other day doses of antiCD19 switch. There was depletion of virtually all $CD19^+$ B cells and plasma cells from the bone marrow, spleen, and peritoneum, as well as most $CD19^-$ plasma cells in the bone marrow and spleen. When BXSB males with active disease were similarly treated, there was a transient elimination of B cells and disease remission associated with about a 2-month prolonged survival. To address whether recurrence could be prevented by repeated sCAR T +antiCD19 treatment, BXSB males with active lupus were given an additional two cycles of antiCD19 switch at 60 and 138 days. Circulating B cells, IgM and IgG, and anti-chromatin levels were reduced after each switch cycle and increased in the intervening periods. Notably, proteinuria did not recur, and there were no deaths beyond day 8 after the start of treatment compared with 100% mortality in the sCAR T +PBS controls. These studies inform on the potential effectiveness and limitations of therapeutic depletion of B cells in SLE and suggest a possible strategy for employing CAR T cells to minimize immunosuppression.

### 1206 SPHINGOSINE 1-PHOSPHATE (S1P) REGULATION OF VASCULAR AND IMMUNE SYSTEMS: MECHANISMS AND THERAPEUTIC APPROACHES

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Metabolism of cellular membranes forms lipid mediators that activate their cognate G protein- coupled receptors (GPCR) to regulate cellular responses. Our laboratory has contributed to this area by cloning of the human cyclooxygenase-2 (COX-2) that produces prostanoids as well as cloning and deorphaning of the first S1P receptor (S1PR1). This GPCR is now the target of small molecule drugs that are approved to treat many autoimmune diseases, including multiple sclerosis and ulcerative colitis. Recent clinical trials are testing if S1PR-targeted compounds are beneficial for systemic lupus erythematosus (SLE). Our recent studies on S1P have focused on S1P chaperones, which are defined as proteins that bind and present S1P to its GPCRs to direct specific signaling modes. Specifically, HDL-bound apolipoprotein M (ApoM) binds to S1P and regulates specific biological processes, such as maintenance of vascular endothelial cell (EC) barrier function, suppression of cytokine-induced inflammatory gene expression, EC survival and regulation of lymphopoiesis. HDL-bound S1P levels are decreased in SLE, sepsis, diabetes, aging and cardiovascular disease, and contributes to pathological processes by suppressing EC S1PR1 signaling. To develop a therapeutic strategy to enhance HDL-S1P/EC S1PR1 signaling axis that supports EC resilience, we engineered two recombinant fusion proteins – a soluble form (ApoM-Fc) and ApoA1-ApoM (A1M) that forms HDL-like nanoparticles. Recent work shows that A1M chaperones S1P as well as prostacyclin (PGI2), enhances EC barrier function and suppress inflammatory processes *in vitro* and *in vivo*. ApoM-bound S1P does not suppress lymphocyte egress suggesting that its large size prevents it from entering secondary lymphoid organs and acting as a functional antagonist to downregulate lymphocyte S1PR1. Studies on chaperone bound S1P action on ECs during pathological changes will be presented. These mechanistic studies have deepened our understanding of S1P biology thus allows rational design of new therapeutic approaches to not only tame the immune system but also enhance vascular endothelial functions.

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## Lupus Clinical Trials

### 1207 UPDATE ON PROGRESS OF THE MESENCHYMAL STROMAL CELL TRIAL IN REFRACTORY LUPUS

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**Body** There is a growing interest and use of cellular therapies in almost all fields of medicine. Mesenchymal stromal cells (MSCs) are pluripotent in their ability to differentiate in chondrocytes, adipocytes and osteoblasts. They more recently were reported to have significant immune activity, primarily by producing anti-inflammatory molecules. They can be derived from umbilical cords, adipose tissue and bone marrow primarily. Recent studies have tested their safety and efficacy in immune mediated diseases including graft versus host disease, inflammatory bowel disease and Type I diabetes among others. Reports of uncontrolled trials of MSCs in China suggest safety and efficacy of MSCs as treatment for refractory lupus. Based on encouraging results of a Phase I trial of 6 patients with lupus treated with MSCs, we initiated the first placebo- controlled trial of MSCs to treat lupus patients refractory to standard of care medications. There are nine participating centers across the US. The trial has two cohorts, one receiving low dose MSCs (one million cells/kg) and a high dose cohort of five million cells per kg, given as a one- time infusion. Patients then attend 10 follow-up visits over a year. Primary outcome is a decrease in the SRI of 4 at week 24. Inclusion criteria are patients with confirmed lupus refractory to 6 months of standard of care therapy defined by a SLEDAI of 6 or greater at screening. Exclusions were ongoing use of biologics, pregnancy, active infections, cancer, active CNS lupus or advanced renal disease. The first patient was screened in November of 2018. Patients are randomized with a 2/1 ratio of MSCs/placebo. Cohort 1 consisting of 41 patients was completed in May of 2021. We have infused 10 out of 40 patients in Cohort 2 to this point. Extensive studies of B cell, T cell, monocyte, dendritic cell and PMN number, function and phenotype are being performed. To this point there are no safety signals or concerns with DSMB reviews quarterly. There have been no SAEs



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attributed to the investigational product. Given the blind of the study, we cannot report on efficacy, though there are a number of participants who met the primary outcome of an SRI of 4 at 24 weeks. COVID had a profound impact on the study due to halting of enrollment for 5 months and a need for video visits due to institutional policies. A significant issue was protocol changes regarding disease activity measures in video visits. Other delays included a designed 12-week safety assessment upon completion of Cohort 1 prior to enrollment in Cohort 2 as well as a staggered start for the first six patients in Cohort 2 requiring a safety assessment by the DSMB chair at week 1 post infusion prior to the screening of the next patient.

**Conclusions** There is no safety signal between the active treatment and placebo group in either Cohort to this date. Efficacy assessments await completion of the study as the two cohorts are combined for determination of efficacy. COVID has a profound impact on enrollment and management of the study. Results of the validity of assessment of different disease measures via video appointments is being assessed to inform future trials. We believe we will reach our enrollment goal and the study will answer the primary aim of whether MSCs are a potential therapeutic for patients with refractory lupus.

## 1208 DIFFERENTIAL RELIANCE ON GLUCOSE OXIDATION BY ACTIVATED AUTOREACTIVE B CELLS PROVIDES A NOVEL TARGET OF THERAPEUTIC INTERVENTION

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**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 pathogenesis. 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 spontaneous murine models of lupus and their responses to treatment with the glycolysis inhibitor 2- deoxyglucose (2DG) in drinking water. Therapeutic efficacy in terms of primary autoimmune-cell population sensitivity and survival after 2DG administration was assessed on BXSB.*Yaa* and NZBWF1 lupus-prone mice. Furthermore, a chimeric antigen receptor (CAR)-T cell approach 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 rates in spontaneous activated autoreactive B cells (AABC) closely resembling germinal center B (GCB) cells compared to those in follicular helper T (Tfh) cells. The differential dependency on glucose oxidation between GCB and Tfh cells was determined, rendering GCB cells highly susceptible to oxidative stress-induced apoptosis triggered by short-term glycolysis inhibition via 2DG. The treatment selectively targeted AABC/GCB cells with high glycolytic dependence, sparing other autoreactive populations, including Tfh cells with greater metabolic flexibility. This reduction of AABC/GCB cells is, in turn, linked with significantly reducing proteinuria and improving lifespan of treated mice. Moreover, we identified a subset of AABC/GCB cells, which express TNFSF17 and exhibit a higher reliance on glucose metabolism than TNFSF17$^-$ B cells. Their depletion through its ligand TNFSF13-based CAR-T treatment significantly decreased mortality in lupus-prone mice.

**Conclusions** Differential metabolic requirement for glucose between autoreactive AABC/GCB cells and Tfh cells dictates different sensitivity to apoptosis via glycolytic inhibition, and our data provide a metabolic niche for novel targeted lupus treatment. Combining therapies that selectively dampen AABC/GCB-cell metabolism with T cell-based immunotherapy could provide new effective treatments for lupus.

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**Lay summary** The primary metabolic adaptation of activating T and B cells is an increase in glucose metabolism. We found that autoreactive B cells have elevated consumption of glucose over other T or B cell types. Using murine models of lupus, we uncovered that treatment of lupus-prone mice with 2-deoxy- glucose, an inhibitor of glucose utilization, resulted in the preferential reduction of these pathogenic B cells. This reduction resulted in improving kidney function, and extending lifespan. We also used a T cell- based immunotherapy approach targeting a subset of these B cells and successfully reduce the mortality of lupus-prone mice. Overall, these results indicate the promise of two new and highly effective treatments for lupus via targeted removal of autoreactive B cells.

## 1301 *LACTOBACILLUS* SPP. ACT IN SYNERGY TO ATTENUATE SPLENOMEGALY AND LYMPHADENOPATHY IN LUPUS-PRONE MRL/*LPR* MICE

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Commensal bacteria and the immune system have a close and strong relationship that maintains a balance to control inflammation. Alterations of the microbiota, known as dysbiosis, can direct reactivity to self-antigens not only in the intestinal mucosa but also at the systemic level. Our laboratory previously reported gut dysbiosis, particularly lower abundance of bacteria in the family *Lactobacillaceae*, in lupus-prone MRL/*lpr* mice, a model of systemic autoimmunity. Restoring the microbiota with a mix of 5 different *Lactobacillus* species

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