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.

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 S1PR1 signaling that its large size prevents it from entering secondary lymphoid organs and acting as a functional antagonist to down-regulate 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.

Supported by NIH grants R35HL135821 and R01EY031715.

**Abstracts**

**Lupus Clinical Trials**

<table>
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<tr>
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<th>UPDATE ON PROGRESS OF THE MESENCHYMAL STROMAL CELL TRIAL IN REFRACTORY LUPUS</th>
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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 and more than 5 ongoing medications. There are not any participating centers across the US. The trial will have two cohorts, one receiving low dose MSCs and a high dose cohort of five million cells per kg, given as 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...
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 signifi-
cant 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 manage-
ment 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

Background Lupus is an autoimmune disease characterized by 
bacteria directed against nuclear components that induce 
imune complex-mediated injury to multiple organs. Underly-
ing 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 counter-
act this systemic autoimmune disorder.

Methods Here we examined the metabolic and gene expres-
son 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 autoim-
une-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 tar-
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 deter-
mined, 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 met-
abolic 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 mor-
tality 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.

Acknowledgments We thank the funding resources from JAX
Director Initiative Fund, the RILITE Foundation, and the
John and Marcia Goldman Foundation.

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 extend-
ing 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
therapies for lupus via targeted removal of autoreactive B
cells.

1301 LACTOBACILLUS SPP. ACT IN SYNERGY TO ATTENUATE
SPLENOMEGALY AND LYMPHADENOPATHY IN LUPUS-
PRONE MRL/1PR MICE

Commensal bacteria and the immune system have a close and
strong relationship that maintains a balance to control inflam-
mation. 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 previ-
ously 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