

OBJECTIVES/SPECIFIC AIMS: We investigated the association between relationship power imbalance (which can have a negative impact on HIV prevention) and male partner HIV testing, using baseline data from a HIV self-testing trial in 3 antenatal clinics in central Uganda. **METHODS/STUDY POPULATION:** Pregnant women with HIV-male partners were recruited and randomized by day into standard of care or intervention (HIV self-testing kits). Analyses were performed in SAS 9.4, with χ^2 tests and $p < 0.05$ for significance. **RESULTS/ANTICIPATED RESULTS:** In total, 1514 women were recruited (737 standard of care, 777 intervention). Overall, 39.6% of male partners had previously tested for HIV. Among women <26, contributions to expenses differed by partner testing (overall $p < 0.001$, 47.6% of women whose partners tested made no contribution vs. 63.2% of women whose partners did not test). Relationship status differed by partner testing (overall $p = 0.02$, 12.4% of women whose partners tested showed a sometimes difficult relationship vs. 5.7% of women whose partners did not test). Among women 26+, decision making for family visits differed by partner testing (overall $p = 0.005$, 52.9% of women made joint decisions with partners who tested vs. 36.5% whose partners did not test). **DISCUSSION/SIGNIFICANCE OF IMPACT:** Higher relationship power balance was associated with higher HIV testing among male partners when measured by contribution to expenses and decision making for family visits, but not relationship status. Relationship power balance should be considered when counseling women and men to increase HIV testing.

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Reward-based learning as a function of the severity of substance abuse risk in drug-naïve youth

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OBJECTIVES/SPECIFIC AIMS: Deficits in reward-based learning have been shown in youth at risk for developing substance use disorders (SUD). Here, we investigated whether computational models can be used to more precisely delineate the additive effects of such risk loading (i.e., the comparison between youth with ADHD, and those with ADHD and familial SUD) on reward-based learning in youth. **METHODS/STUDY POPULATION:** In total, 41 drug-naïve youth, stratified into 3 groups based on ADHD diagnosis and parental SUD: healthy controls (HC, $n = 13$; neither ADHD nor parental SUD), low risk (LR, $n = 13$; ADHD only), and high risk (HR, $n = 15$; both ADHD and parental SUD), performed a reward task. Learning rates, prediction and congruence t -scores were computed using a reinforcement learning model and analyzed via a multivariate ANOVA. **RESULTS/ANTICIPATED RESULTS:** The analyses showed a significant linear effect in task accuracy, which decreased with increasing risk profiles. Analyses of the model-derived variables also showed similar significant linear effects in learning rates and the congruence t -score, but not in the prediction t -score. These effects were primarily driven by significantly higher learning rate and congruence t -score in HC compared with HR youth. **DISCUSSION/SIGNIFICANCE OF IMPACT:** These results show most profound deficits in reward-learning in HR youth. These findings also show that computational analyses can offer added value over conventional behavioral analyses by more precisely evaluating group differences in relation to SUD risk.

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RNA-nanoparticles to enhance and track dendritic cell migration

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OBJECTIVES/SPECIFIC AIMS: Despite aggressive chemotherapy, surgical resection, and radiation therapy, glioblastoma remains almost universally fatal. In a pilot, randomized, and blinded clinical trial, we recently demonstrated that administration of RNA-loaded DC vaccines was associated with significantly improved progression-free and overall survival in patients with glioblastoma (Mitchell *et al.*, *Nature*, 2015). Furthermore, clinical outcomes correlated with DC migration to vaccine-site draining lymph nodes measured by Indium-111 labeling of RNA-loaded DCs and SPECT/CT imaging. Although these studies demonstrated that tracking DC migration may be an important clinical biomarker for response to DC vaccination, the

complexity and regulatory requirements associated with nuclear labelling to track DC migration limits widespread application of this technique. We have therefore developed RNA-loaded magnetic nanoparticles (RNA-NPs) to enhance DC migration to LNs and track that migration with a widely available imaging modality (i.e., MRI). **METHODS/STUDY POPULATION:** Cationic liposomes were loaded with iron oxide nanoparticles with or without cholesterol. The resulting nanoparticles were complexed with RNA and used to transfect DCs *ex vivo*. RNA-NP-loaded DsRed+ DCs were then injected intradermally into mice and tracked noninvasively with T2-weighted IIT MRI before excision and quantification with flow cytometry. **RESULTS/ANTICIPATED RESULTS:** In vitro experiments demonstrate that iron oxide loading does not reduce RNA-NP-mediated transfection of DCs. Additionally, replacement of cationic lipids with cholesterol increased RNA-NP transfection of the DC2.4 cell line and enhanced the T cell stimulatory capacity of treated bone marrow-derived dendritic cells (BMDCs). Compared to electroporation, RNA-NPs enhanced DC migration to lymph nodes and reduced T2 MRI intensity in DC-bearing lymph nodes. **DISCUSSION/SIGNIFICANCE OF IMPACT:** This data suggests that iron oxide-loaded RNA-NPs enable noninvasive cell tracking with MRI and enhance DC migration to lymph nodes. We have further shown that inclusion of cholesterol in RNA-NPs augments the stimulatory capacity of transfected DCs. Future work will consider effects of RNA-NPs on antitumor immune responses and the utility of MRI-detected DC migration as a biomarker of vaccine efficacy.

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Role of the antioxidant enzyme catalase in respiratory syncytial virus infection

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OBJECTIVES/SPECIFIC AIMS: The goal of this study is to further evaluate underlying disease parameters in respiratory syncytial virus (RSV) infection, that is reduction in antioxidant potential, and determining if supplementation of the antioxidant enzyme catalase could be employed as a potential therapeutic. **METHODS/STUDY POPULATION:** Nasopharyngeal secretions were obtained from patients (<2 years old) verified for RSV infection, and assessed for catalase activity and correlated with disease parameters. In addition, the BALB/c animal model of RSV infection was utilized to directly study the effect of supplemental catalase on RSV-related disease parameters *in vivo*. The catalase formulation used in these studies is pegylated, and has been tested to provide long-term increased catalase activity *in vivo*. We are also currently working on designing an *in vitro* model of catalase supplementation in A549 bronchial epithelial cells. **RESULTS/ANTICIPATED RESULTS:** Our preliminary data shows that patients with more severe disease (based on hospitalization, oxygen supplementation) have significantly lower levels of catalase activity ($p < 0.02$). Additionally, when pegylated-Catalase (PG-CAT) treatment is utilized in RSV infection of mice, there is significant improvement in several disease parameters. PG-CAT-treated mice show an attenuated body weight loss ($p < 0.001$) and clinical disease ($p < 0.02$), and also have lower levels of key pro-inflammatory cytokines including CXCL1 and TNF- α . PG-CAT treatment also resulted in a minor decrease in viral titer, which is being further evaluated. In addition, PG-CAT treatment resulted in an improvement in airway hyperresponsiveness observed at baseline, we are further characterizing this improvement and also conducting methacholine challenges. Currently, we are working to determine the underlying mechanism through which PG-CAT results in these improvements, and whether it is through changes in immune cell populations, cellular signaling or apoptosis signaling pathways (i.e., caspases). **DISCUSSION/SIGNIFICANCE OF IMPACT:** RSV is the leading cause of viral pneumonia and bronchiolitis in infants, with no vaccines or effective therapeutics available currently. Our study indicates that catalase activity could be used as a potential correlate for disease severity and be used as an indicator of disease during patient treatment. Additionally, and more importantly supplementation of catalase could be used as a potential therapeutic for treatment of RSV.

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Role of tissue non-specific alkaline phosphatase (TNAP) in promoting the survival of acute myeloid leukemia (AML) cells within the bone marrow microenvironment

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OBJECTIVES/SPECIFIC AIMS: Treatment of acute myeloid leukemia (AML) is challenging, as apoptosis-resistant AML cells often persist within the bone marrow microenvironment despite chemotherapy. The overall goal of our laboratory is to identify and ultimately target the bone marrow factors that protect AML cells. **METHODS/STUDY POPULATION:** Using cell cultures, we previously reported that SDF-1 (CXCL12), an abundant bone marrow chemokine, induces apoptosis of isolated CXCR4+ AML cells, including freshly isolated bone marrow-derived AML cells from approximately one-third of AML patients. However, co-culture of AML cells with differentiating osteoblasts protected AML cells from apoptosis. **RESULTS/ANTICIPATED RESULTS:** Histone deacetylase inhibitors (HDACi) abrogated the ability of osteoblasts to protect AML cells and altered expression of matrix mineralization genes including tissue nonspecific alkaline phosphatase (TNAP). A different drug, cyclosporine A (CSA), similarly inhibited osteoblast-mediated protection of AML cells and reduced TNAP expression. Specifically targeting osteoblast TNAP via siRNA was sufficient to prevent osteoblasts from protecting AML cells in co-cultures. In addition, we are targeting TNAP enzymatically. **DISCUSSION/SIGNIFICANCE OF IMPACT:** Our results indicate that targeting TNAP may be useful in AML treatment to render the bone marrow microenvironment more hostile to leukemic cell survival.

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Severity of childhood-onset systemic lupus erythematosus: Impact of preceding and co-existing autoimmune cytopenias (protocol)

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OBJECTIVES/SPECIFIC AIMS: The goals of our study are: (1) To test the hypothesis that the presence of any autoimmune cytopenia (ITP, AIHA, or ES) at time of cSLE diagnosis is associated with decreased risk of developing LN. (1b) To test the hypothesis that there is a lower risk of LN in patients with cSLE and any co-existing autoimmune cytopenia (ITP, AIHA, or ES) who had treatment with immunomodulatory or immunosuppressive therapy (intravenous immunoglobulin, corticosteroids, rituximab, or cyclophosphamide) before diagnosis of cSLE. (2) To test the hypothesis that in patients with cSLE who develop LN, the presence of any co-existing autoimmune cytopenia (ITP, AIHA, or ES) at time of cSLE diagnosis is associated with less severe LN. (3) To test the hypothesis that at the time of cSLE diagnosis, there is a lower incidence of double-stranded DNA (dsDNA) and a higher incidence of ribonucleoprotein autoantibodies in those with co-existing autoimmune cytopenias (ITP, AIHA, or ES). **METHODS/STUDY POPULATION:** This is a retrospective study of a large cohort of patients from the Emory Children's Center, Children's Healthcare of Atlanta (CHOA) satellite clinics and pediatric rheumatology inpatient services at any of the 3 CHOA hospitals (Egleston, Scottish Rite, and Hughes Spalding) with ICD 9 or ICD 10 codes corresponding to a diagnosis of SLE between January 1, 2000 and January 31, 2015. We will include patients diagnosed at age 2–16 years who meet at least 4 of the 11 American College of Rheumatology (ACR) classification criteria for SLE. We will consider these patients as having cSLE. We will exclude patients with less than 2 years of follow-up data and patients with a pre-existing diagnosis of cSLE who transferred care to our Emory/CHOA center. We will define time of diagnosis as time from initial evaluation for cSLE by a pediatric rheumatologist up to 28 days post cSLE diagnosis. We will define co-existing autoimmune cytopenia as preceding diagnosis of a primary autoimmune cytopenia or the presence of an autoimmune cytopenia at the time of initial evaluation for cSLE and up to 28 days post cSLE diagnosis. We will define AIHA as hemoglobin ≤ 10 g/dL with positive direct Coombs and/or reticulocytosis. We will define ITP as thrombocytopenia $<100,000/\text{mm}^3$ and Evans syndrome as concurrent or sequential AIHA and ITP. We will define lupus nephritis (LN) as the presence of urine protein to creatinine ratio >0.5 in a patient with cSLE and/or biopsy demonstrating LN. IRB approval of the study protocol with waiver of informed consent has been obtained from the CHOA IRB. **RESULTS/ANTICIPATED RESULTS:** We have approximately 40 newly diagnosed cSLE patients annually; therefore, a study population of 400 patients with cSLE is possible. Therefore, assuming 50% of cSLE patients without autoimmune cytopenias have LN and 22% of cSLE patients with autoimmune cytopenias have LN, at an alpha of 0.05,

we will have $> 80\%$ power to detect significant differences. We expect to show phenotypic differences in patients with co-existing autoimmune cytopenia and cSLE from other newly diagnosed cSLE patients. We expect that the presence of a co-existing autoimmune cytopenia and cSLE is associated with decreased risk of developing LN. We expect that there will be a decreased prevalence of LN in cSLE patients pretreated with immunosuppression further highlighting that earlier indicators of LN risk and early interventions are necessary. We expect to find decreased severity of LN in patients with a co-existing autoimmune cytopenia at time of cSLE diagnosis. **DISCUSSION/SIGNIFICANCE OF IMPACT:** Our study will be conducted on one of the largest single-center cohorts of cSLE patients. We will determine whether pediatric patients with SLE and autoimmune cytopenias have a distinct clinical or serological phenotype and less severe disease. Our results will be significant in developing hypothesis for further retrospective or prospective multi-center or large database and immunological studies to understand the relationship of each individual autoimmune cytopenia to cSLE. It will provide the necessary background for further clinical and immunological studies to identify predictive biomarkers of cSLE severity.

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Sexual dimorphism in a mouse model of syndromic thoracic aortic aneurysm

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OBJECTIVES/SPECIFIC AIMS: Pre-clinical and clinical observations have noted that increased aortic dilation is associated with male sex. Using an experimental model of severe, syndromic thoracic aortic aneurysms, we quantify aortic dilation and elastin stability in male Versus female mice. **METHODS/STUDY POPULATION:** Ascending aortas from male and female FBN1mgR/mgR mice and their wild type littermates were assessed every 4 weeks from 6 to 18 weeks of age by ultrasound. Measurements were taken luminal edge to luminal edge in diastole. At termination, aortas were harvested for RT-PCR analysis of extracellular matrix genes. Aortas were serially sectioned and elastin fragmentation was imaged by auto-fluorescence. **RESULTS/ANTICIPATED RESULTS:** At 12 weeks of age, differences of aortic diameters between male and female FBN1mgR/mgR mice were significantly different (2.24 ± 0.43 vs. 1.57 ± 0.22 mm; $p=0.002$), while there were no significant differences between sexes of wild type littermates (1.29 ± 0.13 vs. 1.23 ± 0.08 mm; $p=0.71$). Male sex was associated with increased elastin but not fibrillin-1 mRNA expression. Ascending aortas from male and female FBN1mgR/mgR mice significantly differed in the degree of elastin fragmentation (2.76 vs. 1.85 breaks/ $100 \mu\text{m}$ aorta; $p=0.03$). **DISCUSSION/SIGNIFICANCE OF IMPACT:** Sexual dimorphism of thoracic aortic dilation observed in human TAA patients was recapitulated in the fibrillin-1 hypomorphic mouse model of syndromic thoracic aortic aneurysms. Differences in this mouse model could be explained by the differential expression of extracellular matrix genes.

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Sodium-glucose transporter 2 is a novel diagnostic and therapeutic target for early-stage lung adenocarcinoma

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OBJECTIVES/SPECIFIC AIMS: Lung cancer claims 160,000 lives in the United States every year, and lung adenocarcinoma (LADC) is the most frequent type. Early diagnosis is crucial. Computed tomography (CT) is very sensitive in identifying early-stage lung nodules, but has low specificity. Increased glucose uptake is a hallmark of cancer measurable in vivo by fluorodeoxyglucose (FDG) positron-emission tomography (PET). FDG PET is widely used for cancer staging but has low sensitivity in the diagnosis of solitary lung nodules. We have previously identified an alternative glucose transporter, SGLT2, expressed in different types of cancer but not detected by FDG PET. SGLT2 activity can be measured in vivo with the PET tracer methyl-4-fluorodeoxyglucose (Me4FDG). The objective of this study was to test the hypothesis that SGLT2 is a novel diagnostic and therapeutic target in FDG-negative, early stage LADC. **METHODS/STUDY POPULATION:** To study glucose transporter expression in LADC, we performed immunohistochemistry with SGLT2- and GLUT1-specific antibodies in human lung pre-malignant lesions and LADC samples. To verify the possibility of detecting SGLT2 activity in vivo, we performed microPET imaging with the SGLT-specific tracer Me4FDG in a Kras-driven, p53-null genetically engineered mouse model and in patient-derived xenografts