

# ***Using iNSC patient-derived Oligodendrocytes to Characterize Small Molecules for Globoid-Cell Leukodystrophy***

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Abstract:

Globoid-cell leukodystrophy (GLD), known as Krabbe disease, is a classical lysosomal leukodystrophy caused by the deficiency of -galactocerebrosidase (GALC). This lysosomal hydrolase catalyzes the galactose removal of galactocerebroside and psychosine, which is physiologically present at low levels in myelin-forming cells. Prior work using cell-based, two-cell-based quantitative high-throughput screenings identified two classes of potential therapeutics: psychosine-reducing agents (inhibit the biosynthesis of psychosine), and GALC-assisting folding molecules (increase the stability of misfolded mutants). Using induced-neural stem cells (iNSC) established from GLD patient fibroblasts, we established GLD-patient-derived oligodendrocytes to validate further and characterize the GALC-folding assisting and psychosine-reducing molecules. The iNSC-derived oligodendrocytes from GLD patients carrying GALC misfolding mutants showed higher endogenous psychosine levels than respective controls. Using a throughput LC-MS/MS assay to quantify the intracellular psychosine levels, we determine the dose-response profiling of several analogs synthesized from both psychosine-reducing and GALC-folding assisting molecules. Currently, using the LC-MS/MS assays and determining the GALC activity, we are performing structure-activity-relationships (SARs) evaluations of these two classes of compounds. Specific GALC-folding assistant analogs produce sufficient enhancements of residual GALC activity to normalize the intracellular psychosine levels. The initial ADME characteristics indicate that some small molecules of both classes can be potential therapeutic agents for GLD caused by both misfolded and null GALC pathogenic variants.

# ***Monogenic Atopic Disorders: STAT5B mutations***

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## **Abstract:**

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways play a crucial role in mediating the signals of various cytokines, influencing diverse functions of leukocytes. Early-onset somatic STAT5B gain-of-function is a newly recognized monogenic atopic disorder that has been identified to involve in early-onset severe hypereosinophilia, along with symptoms such as urticaria, dermatitis, and diarrhea. We introduced the STAT5B mutations, identified in patients with atopic disorders, into plasmids. These plasmids were then transfected into primary human T cells and the STAT5 RFP reporter T28 cell line. After short- or long-term IL7 stimulation, STAT5b transcriptional activity and pSTAT5 transcription factor levels of T cells were measured by flow cytometry. The results showed that cells transfected with p.N642H and p.A716V plasmids exhibited higher STAT5 reporter activity, while cells transfected with p.Q177P had lower reporter activity compared to the wild-type (WT) after long term IL7 stimulation. However, human primary T cells transfected with p.Q177P plasmid expressed higher pSTAT5 compared to WT after short-term IL7 stimulation, supporting the previous findings that the dominant negative p.Q177P mutation did not impact increased STAT5 phosphorylation. No differences were observed for the rest of the mutations, including the p.R217H identified in patient with atopic dermatitis and reported as gain-of-function (GOF). We conclude that STAT5B variants associated with atopic symptoms in children exert different transcriptional effects through distinct pathomechanisms.

# ***Project Pick Up Sports and Health: A Service-Learning Model to Promote Health Literacy and Exposure to Health Careers amongst School-Aged Children in Washington Heights***

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Abstract:

**Objectives:** Pick Up Sports and Health (P.U.S.H.) is an initiative designed to improve health literacy and increase awareness of health careers amongst youth in Washington Heights.

**Methods:** P.U.S.H. utilizes a two-pronged approach for engaging school-aged children in physical activity and health lessons bimonthly. During each session, medical students and other healthcare affiliates (coaches) lead school-aged children in organized sports followed by informal mentorship and culturally sensitive workshops on diverse healthcare topics. To ensure the materials are accurate and up to date, they are reviewed and reinforced with source material from our partnership with the New York Department of Health (DOH) and Mental Hygiene.

**Results:** 75 medical students and other health professionals and institutions have served over 200 school-aged children with consistent and expandable educational programming. Through P.U.S.H.'s two-step model, coaches have built trust and rapport with youth, promoting deeper engagement during health lessons. The success of P.U.S.H. is measured by the high youth return rates and the positive feedback received from students, parents, and community partners. This community investment has led to partnerships with the DOH, Public School 128, Polo Grounds, and the Police Athletic League. These community partnerships along with P.U.S.H.'s status as a P&S Club allow for a continuous stream of coaches and youth participants, ensuring its longevity.

**Conclusion:** The success and sustainability of P.U.S.H. has demonstrated that this two-part model of pick-up sports/games accompanied by culturally sensitive health topics is a well-received, low-cost, and sustainable service-learning model for improving health literacy and exposing youth to health careers

# ***Assessment of the Healthy Monday Program: An Employee Wellness Initiative***

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Abstract:

**Background:** Burnout syndrome is common among healthcare professionals. Poor provider well-being and burnout are associated with poorer patient safety and increased medical errors. The Healthy Monday Program was developed for CUIMC faculty and staff to systematically explore the impact of weekly recommended self-care practice on attitude toward self-care, stress, and burnout.

**Objectives:** To determine if the Healthy Monday Program—a collaboration between CUIMC's integrative Therapies Program, Columbia's School-based Health Centers, and the Monday Campaigns—is able to improve self-reported measures of self-efficacy, stress, and burnout among participants at CUIMC.

**Methods:** The Healthy Monday 24-Week Program was an IRB-approved prospective cohort study that delivered wellness content via email every Monday. Content reflected evidence-based mind-body practices, including videos filmed by CUIMC experts. Participants received an anonymous survey at the end of the Program that asked them to evaluate, in a retrospective pre-post format, various elements of their well-being using both de novo as well as validated measures. Participant demographics were also collected.

**Results:** Eighty-five participants completed the end-of-Program survey (Table 1). Preliminary analysis suggests statistically significant self-reported benefit among participants for chief measures, including sense of burnout (Table 2). Additional analyses are ongoing, including McNemar testing to assess average individual-level change on these (and other) important measures. Further, subgroup analyses by demographic variables (including clinical role and years of experience) are planned.

**Conclusions:** The Healthy Monday Program seems to improve self-reported measures of well-being—including burnout—among CUIMC healthcare professionals.

# ***Piloting a Pediatric Health Equity and Quality Dashboard: Stakeholder perspectives on dashboard design and implementation strategies***

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**Abstract:**

**Objectives:** Dynamic data dashboards support hospital quality improvement (QI) by measuring and tracking institutional performance on quality metrics. How to adapt dashboards for equity-focused QI is still unknown. We aimed to identify stakeholder perspectives on design and implementation strategies for a health equity dashboard at our children's hospital.

**Methods:** Six stakeholders in clinical, quality, and administrative leadership were prioritized for interviews. The Consolidated Framework for Implementation Research (CFIR) guided development of interview questions and identification of relevant constructs. We conducted two rounds of semi-structured interviews. The first focused on dashboard design and a cognitive walkthrough exercise. The second focused on potential facilitators and barriers for implementation. We analyzed interviews using a modified rapid CFIR-based deductive analytic approach.

**Results:** Key themes were derived from the following parent codes: analytic interpretation; dashboard data & metrics; potential uses & benefits; interpreting inequities; metric selection; data digestion, access & reports; facilitators and barriers. While all participants felt that the dashboard would fill a key programmatic gap, barriers to implementation included feelings of helplessness, bandwidth constraints, and distrust of data. Suggested potential facilitators included ownership and accountability from a "point person" with "equity expertise"; integrating equity into existing initiatives, and selecting cross-cutting, evidence-based, discrete, actionable metrics, aligned with existing hospital initiatives.

**Conclusions:** While hospital leaders universally welcomed the health equity dashboard, they identified barriers such as insecurity interpreting and addressing disparities data. These may be addressed by validating REaL data capture, engaging with community stakeholders and using iterative processes for design improvement and identifying QI initiatives.

# ***Memory T cells formed in setting of dietary iron deficiency are impaired in anti-viral functionality***

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Abstract:

Protection from viral respiratory tract infections (VRTIs) is dependent on the establishment of memory T cell responses. Iron is an essential micronutrient for metabolic pathways of immunologic memory formation and iron deficiency is associated with increased morbidity and mortality to VRTIs. We established a murine model of influenza infection and dietary iron modulation to investigate the impact of iron on anti-viral memory T cell formation and functionality. Mice were placed on iron replete or deficient diets then infected with influenza after achieving target iron levels. We assessed the presence and functionality of memory T cells isolated from the lung and spleen during primary (X31) infection (days post infection (DPI) 5 and 7), recovery (DPI 28 and 35), and heterosubtypic/recall (PR8) infection (DPI 5) time points. We found no significant difference in the numbers or proportions of CD4<sup>+</sup> and CD8<sup>+</sup> influenza specific memory T-cells at any time point between the groups. Strikingly, the memory T cells generated by iron deficient mice displayed impaired production of key anti-viral cytokines, most notably IFN- $\gamma$ . Importantly, following recall challenge, iron deficient mice exhibited increased morbidity, as defined by increased weight loss. Functionality of memory T cells formed on iron deficient diets was not restored by in vitro co-culture with iron replete antigen presenting cells, suggesting an intrinsic defect in memory responses. This study reveals that memory T cells formed under iron deficient conditions are impaired in effector functionality suggesting a pathway by which immune responses in early life may be skewed by a common dietary problem.

# ***Treatment of Severe Metabolic Dysfunction-Associated Steatohepatitis In a 10-Year-Old Male with an MC4R Mutation with Semaglutide for One Year***

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## **Abstract:**

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in children. Clinical trials in adults show improvement in liver histology and liver enzymes in patients on GLP-1 agonists, but there are no ongoing clinical trials in children. Here we present the only case of an adolescent with an MC4R (melanocortin 4 receptor gene) obesity mutation with severe Type II MASH with bridging fibrosis treated for one year on a medium-acting GLP-1 agonist, semaglutide.

An 8-year-old male with a MC4R mutation presented with elevated ALT and BMI for 4 years. An ultrasound showed moderate to severe hepatic steatosis and lab tests excluded other etiologies of hepatic disease. Liver biopsy demonstrated Type 2 MASH, macrovesicular steatosis (75%) and early bridging fibrosis. Despite aggressive intervention through lifestyle changes and Vitamin E, his liver enzymes continued to trend upwards. One year after biopsy, weekly injections with semaglutide were started. One month later his ALT went from 134 U/L to 72 U/L. ALT normalized in 9 months after initiation of treatment (Figure 1). The patient had no side effects throughout treatment. About 1 year after starting semaglutide, due to insurance coverage lapses, the patient stopped receiving injections twice and his ALT increased rapidly both times.

This case presents the novel use of a medium-acting GLP-1 agonist in a pediatric patient with an MC4R mutation. There is limited published literature in this population. The data in our case support continued research on the use of GLP-1 agonists in children with MASH

# ***Ultra-low dose ketamine is safe and effective at reducing pain scores in pediatric patients***

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## **Abstract:**

**Introduction:** Ketamine is increasingly used in pediatrics as an adjuvant for pain control to treat pain, decrease opioid requirements, opioid related adverse effects and mitigate development of opioid tolerance. The reported effective dose range of ketamine is 0.05-1 milligrams (mg)/kilogram (kg)/hour (h) in children<sup>1,2</sup>. Our institution utilizes ketamine at doses far below these recommendations. We examined our use of ultra-low dose (ULD) ketamine over 6 months and report its safety and efficacy when used as an adjuvant to opioids.

**Methods:** This was a prospective study of 10 pain patients from August to December 2022. We examined patient characteristics, ketamine dose, adverse effect profile, as well as 24 hour pre- and post-ULD ketamine average total opioid dose, pain score, and sedation score.

**Results:** 10 patients received ULD ketamine concurrently with opioids during our study period. The age range was 2 to 22 years of age with the median being 16 years. The ULD ketamine dose range for pediatric pain patients was between 0.024 to 0.048mg/kg/h. The total opioid dose after 24 hours of ketamine administration was approximately the same as 24 hours prior to ketamine. Pain scores were significantly decreased 24 hours after ketamine initiation. Ketamine-related side effects were uncommon and there were no major adverse events (see Table 1).

**Conclusions:** The low doses of ketamine we describe, when used as an opioid adjuvant, appear to be safe and effective at reducing pain scores by almost 50%. Adverse effects related to ketamine at these doses were rare and very mild.



# ***Home Blood Pressure Monitoring in Adolescents and Young Adults, NHANES 2009-2014***

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## **Abstract:**

**Background:** Home blood pressure (BP) monitoring (HBPM) is a critical adjunct for diagnosis and management of hypertension (HTN), a major modifiable risk factor for cardiovascular disease. However, HBPM is an underutilized tool with only 38% of US adults with HTN performing HBPM monthly. Among adolescents and young adults, little is known about the prevalence and frequency of HBPM and what sociodemographic factors predict its use.

**Objectives:** Determine the prevalence and frequency of HBPM in US adolescents and young adults.

**Methods:** Using 2009-2014 National Health and Nutrition Examination Surveys (NHANES) data we examined HBPM use in those aged 16 to 25 years. Participants were asked “How often did you check your BP at home in the last 12 months?” Results were weighted by population sampling and stratified by age group.

**Results:** 2,596 NHANES participants met inclusion criteria. 237 (9.1%) reported HBPM in the prior 12 months. Young adults performed HBPM more frequently than adolescents (Fig 1). Weekly HBPM was most prevalent in those with HTN (9.5%) or taking antihypertensive medication (25.5%). In adjusted models, HBPM performance was associated with having insurance [OR 1.64 (95% CI: 1.10 to 2.46)], higher education level [OR 12.99 (95% CI: 1.6 to 105.27), and obesity [OR 1.78 (95% CI: 1.03 to 3.07)].

**Conclusions:** HBPM is performed in a small proportion of adolescents and young adults between ages 16 to < 25. Factors associated with HBPM use were obesity, having insurance, and higher education level. Further studies should examine if digital innovations can increase the uptake of HBPM in these age groups.

# ***Discovery and validation of effective combination therapies targeting cell state-specific master regulator vulnerabilities by network-based protein activity inference in Diffuse Midline Glioma***

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**Abstract:**

**Objectives:** Diffuse Midline Glioma (DMG) are fatal pediatric brain tumors lacking effective systemic therapies. We leveraged systems biology algorithms and single-cell RNAseq (scRNAseq) to discover pharmacologically accessible Master Regulator (MR) vulnerabilities of heterogeneous DMG cell states to nominate novel combination therapies.

**Methods/Results:** We generated single-cell regulatory networks and protein activity (ARACNe/VIPER) from scRNAseq for 6 DMG patients. Clustering of cells by protein activity defined seven cell states with distinct MRs. We generated in vitro drug-induced differential protein activity for 372 drugs in two DMG cell lines to identify cell state MR-inverter drugs using OncoTarget/OncoTreat. Predicted drugs were distinct across cell states. We selected five drugs targeting OPC/cycling-like cells (Trametinib, Dinaciclib, Avapritinib, Mocetinostat, Etoposide), and four drugs targeting AC-like cells (Ruxolitinib, Venetoclax, Napabucasin, Larotrectonib) for validation. We generated scRNAseq for 95,687 cells after 5 days of treatment (vehicle or candidate drug) in subcutaneous SU-DIPG-17 mouse models, confirming reduction in tumor growth and significant depletion of either OPC/cycling-like or AC-like cells in line with our predictions for 8/9 drugs. We additionally treated a syngeneic orthotopic DMG model with each drug and found significant differences in survival with Avapritinib, Dinaciclib, and Trametinib. Further, the combination of drugs targeting OPC/cycling-like and AC-like cells (i.e. Trametinib+Ruxolitinib) showed significantly lower tumor volumes as compared to vehicles or each drug alone, with some combinations improving survival.

**Conclusions:** This work provides a precision medicine platform to identify drug combinations addressing DMG tumor heterogeneity for further clinical study to improve outcomes in this devastating disease.

# ***Multidisciplinary Care for People with Cerebral Palsy***

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Abstract:

Cerebral palsy (CP) is an injury to the developing brain that impairs movement. CP is the most common lifelong physical disability affecting approximately one million people in the US. CP care often includes multiple specialties to enhance physical function and support the social and emotional needs of patients and their families, but coordinating and navigating care for this complex condition can be a burden on patient families and providers alike.

At the Weinberg Family Cerebral Palsy Center, we have created a patient-centric lifespan multidisciplinary care model comprising six components:

**Diagnosis:** To determine whether a child has CP and the etiology.

**Care coordination:** A care coordinator integrates care across multiple medical specialties from Columbia/NYPH. Community education, programs and resources are offered for sustainable support.

**Co-location:** With multidisciplinary clinics, multiple medical needs can be addressed in a single visit.

**Mental health:** A holistic care approach with psychiatry, support groups and social work available for patients and their caregivers.

**Case conferences:** Monthly and annual conferences with ongoing professional education supports multidisciplinary care and providers.

**Primary care:** Collaboration with Columbia/NYPH to train primary care providers in CP to provide long term preventative care and monitoring.

Our presentation will outline the development of this multidisciplinary care model and highlight the challenges of a referral center and offer workarounds. We will also share future initiatives to improve care and access to care. We aim to present a model that can be replicated in other clinical settings which support providers and families with complex care needs.

# ***Maternal IL-10 restricts fetal emergency myelopoiesis***

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Abstract:

**Objectives:** Neonates, in contrast to adults, are highly susceptible to inflammation and infection. Here we investigate how late fetal liver (FL) mouse hematopoietic stem and progenitor cells (HSPC) respond to inflammation, testing the hypothesis that deficits in engagement of emergency myelopoiesis (EM) pathways limit neutrophil output and contribute to perinatal neutropenia.

**Methods:** in vivo mouse models of maternal inflammation

**Results:** We show that despite similar molecular wiring as adults, fetal HSPCs have limited production of myeloid cells at steady state and fail to activate a classical EM transcriptional program. Moreover, we find that fetal HSPCs are capable of responding to EM-inducing inflammatory stimuli in vitro, but are restricted by maternal anti-inflammatory factors, primarily interleukin-10 (IL-10), from activating EM pathways in utero. Accordingly, we demonstrate that loss of maternal IL-10 restores EM activation in fetal HSPCs but at the cost of fetal demise.

**Conclusions:** These results reveal the evolutionary trade-off inherent in maternal anti-inflammatory responses that maintain pregnancy but render the fetus unresponsive to EM activation signals and susceptible to infection.

# ***Development of PARDS during early life RSV infection is associated with distinct local immune responses but not increased viral load***

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Abstract:

Viral respiratory tract infections (VRTI) are among the first major pathogenic challenges to children. The development of pediatric acute respiratory distress syndrome (PARDS) is a rare but devastating complication of infection. We have previously identified the accumulation of cytotoxic T cell in the airway are associated with the development of PARDS. We performed longitudinal viral load quantification, high dimensional flow cytometry, and single cell RNA sequencing on airway and blood samples from healthy and infected infants to provide new insights into clinical disease severity during VRTI. RSV viral load (n =249 samples, n = 80 subjects, up to 14 days) was highest on first day of hospitalization with no difference in peak titer or rate of clearance based on presence of PARDS. Increased proportions of highly proliferative cytotoxic ab T cells with reduced proportions and diversity of gd T cells were observed in the airway during infection. Airway T cells upregulated CXCR6, a receptor necessary for migration into the airway. Interestingly, children with PARDS were found to have expanded populations of AREG expressing gd T cells which corresponded to higher levels of the protein amphiregulin, known to function in repair of tissue injury, in the airway. These results highlight unique immunologic features of the local environment during VRTI in infants with new insights into the relative contribution of pathogen and host factors to the development of PARDS. Additionally these results suggest possible mechanisms by which children mediate resolution of lung injury following severe disease.

# ***Use of Quality Improvement Methodology to Improve Completion of EPA-Focused WBAs in the Pediatrics Clerkship***

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**Abstract:**

**Background:** Implementation of Entrustable Professional Activity (EPA)-focused workplace-based assessments (WBAs) remains a challenge. A growing body of literature describes the application of quality improvement (QI) methodology to initiatives within medical education. To our knowledge, no studies have used QI methodology to improve completion of EPA-focused WBAs in a core medical student clerkship.

**Objective:** The specific aim of this project was to increase the number of WBAs completed from a baseline of 1 WBA per student to 6 WBAs per student per pediatric clerkship half-block (3 weeks).

**Design/Methods:** Pediatric clerkship students at Columbia University Vagelos College of Physicians and Surgeons (10-19 per block, 126 per year) rotate through multiple clinical settings at one of two clinical sites over 6 weeks. An EPA-focused WBA was created to provide targeted, just in time feedback. A key driver diagram was constructed to identify primary factors affecting WBA completion and inform plans for interventions based on faculty and student feedback and review of course evaluations focused on barriers and facilitators of WBA completion (Figure 1). The outcome measure was the number of WBAs completed for each student per clerkship half-block. Serial Plan, Do, Study, Act (PDSA) cycles were used to test interventions predicted to improve WBA completion. Number of WBAs completed were tracked in a time series model to evaluate the effectiveness of individual PDSA cycles and inform plans for subsequent interventions.

**Results:** The number of WBAs per student increased from a baseline of 1 to a sustained mean of 6.6 (Figure 2). Based on the rules of special cause variation, two shifts were seen in the median line on the u-chart (1.1 to 4 to 6.6). Substantial and sustained increases in completion of WBAs were associated with faculty and resident development and implementation of additional EPA-focused WBAs, such as EPA 9, to create more opportunities for feedback and direct observation.

**Conclusions:** While barriers to WBA completion are well understood, information is limited on successful strategies to increase the number of WBAs completed. Institutions who are looking to integrate more opportunities for feedback can apply lessons learned to increase utilization of WBAs in their clerkships. Next steps will include exploring the effectiveness of interventions to increase the quality of WBAs completed, particularly the narrative comments, and assessing whether increases in the number of WBAs completed for an individual student correlate with changes in skill progression and development.

# ***Integration of Health-related social needs screening and referrals in pediatric clinical care: A qualitative study***

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## **Abstract:**

**Background:** Health-related social needs (HRSN) are risk factors for the development of chronic diseases, including childhood obesity. Parental perceptions of the role of HRSN interventions on childhood obesity have not been explored.

**Objective:** To examine parental perceptions, facilitators, and barriers related to HRSN screening, community service referrals, and their perceived impact on infant nutrition.

**Methods:** We conducted in-depth interviews with parents of infants < 2 years old who completed HRSN screening at urban, hospital-affiliated primary care practices. A modified Chronic Care Model for Childhood Obesity served as the framework for the interview guide. Using principles of immersion-crystallization during study team discussions, a code book was created and used to guide a thematic analysis of the interview content.

**Results:** Among the 20 interviewed parents, mean age was 31 years, 100% reported female gender, and 70% identified as Hispanic/Latino. Parents perceived HRSN screening as vital to care delivery. Facilitators to completing screening were integration into well-child visits and providing explanations for the screening. Lengthy questionnaires and lack of choice in response modality were barriers. For community service referrals, geographic proximity and use of patient navigators were facilitators while barriers included burdensome enrollment documentation and strict program eligibility. Parents perceived that improved food quality and consistent availability would promote healthy infant weight.

**Conclusion:** Parents valued HRSN screening and community service referrals. Parental choice, providing the rationale for screening, active assistance, and alignment with referral organizations for consistent, healthy food options should be incorporated into HRSN interventions to reduce risk factors for childhood obesity.

# ***Therapeutic targeting of ferroptosis by selective Inhibitors of the 15LOX/PEBP1 Complex***

**Author: Tuana Demir<sup>1</sup> MD**

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**Abstract:**

Ferroptosis, a non-apoptotic cell death mechanism driven by robust oxidation of polyunsaturated fatty acid-containing phospholipids, is implicated in neuronal death and functional deficits after TBI. A required step in TBI-induced ferroptosis is peroxidation of arachidonoyl-phosphatidyl-ethanolamine (A-PE) catalyzed by the complex of 15-lipoxygenase (15LOX) with PE-binding protein (PEBP1). We hypothesized that inhibitors targeting 15-LOX/PEBP1 complexes will specifically inhibit ferroptosis and improve outcome after TBI while a pan-LOX inhibitor can affect synthesis of lipid mediators such as resolvins that are key in resolution of inflammation post-TBI. To test this hypothesis we designed, synthesized and tested a library of 26 compounds using biochemical, molecular and cell biology models along with redox lipidomic and computational analyses. We identified two lead compounds NCATS1 and NCATS2 which effectively suppressed ferroptosis in vitro assessed by PI positivity using flow cytometry. Both compounds attenuated pro-ferroptotic A-PE oxidation but did not affect biosynthesis of pro-/anti-inflammatory lipid mediators in vitro and in vivo. NCATS1-2 showed weak radical scavenging activity assessed by their interaction with 2,2-diphenyl-1-picrylhydrazyl radical. Computationally, NCATS1-2 affected proper A-PE positioning at the catalytic site or blocked oxygen delivery to the catalytic iron of 15LOX/PEBP1 complex. NCATS1-2 improved survival in a model of oxidant injury and NCAT1 improved spatial memory acquisition assessed by Morris Water Maze task after controlled cortical impact (5.0 m/s, 1.2 mm depth, n=10/group) in 8-10 w/o C57BL/6J mice. Our successful strategy may be applied to screening additional chemical libraries to reveal new ferroptosis-targeting therapies for TBI. Support: NS061817, NS076511, AI156923, AI156924.



# ***Yes-associated Protein Mediates Acute Lung Injury in Adult but not Juvenile Mice***

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## Abstract:

Adults with The Acute Respiratory Distress Syndrome (ARDS) have worse outcomes than children with Pediatric ARDS. This finding is reproduced in animal models, suggesting a difference in Acute Lung Injury (ALI) mechanisms. Understanding these differences could inform age-specific treatment. Since Yes-associated protein (YAP) is important for lung repair, we hypothesized that YAP underlies ALI mechanisms. To induce ALI, we intranasally instilled mice with *Pseudomonas aeruginosa* strain K ( $2.5 \times 10^5$  colony forming units) in juvenile (3-week-old) and adult (10-week-old) C57BL/6J mice. 24h later, we collected bronchoalveolar lavage (BAL) fluid and measured protein and cell count. To knockdown YAP expression, we injected siRNA 24h before *P. aeruginosa* instillation. Mouse lungs were enriched for nuclear and cytosolic fractions for immunoblot analysis. For immunoprecipitation, cytosolic fraction was added to anti-YAP antibody-coated beads. Bound proteins were identified by mass spectrometry. Adult mice had significantly increased BAL cell counts and protein 24h after *P. aeruginosa* instillation as compared to juveniles. In adult mice, *P. aeruginosa* instillation increased whole lung YAP expression in both cytosolic and nuclear fractions by >3-fold; YAP expression was not increased in juvenile mice. Knockdown of YAP expression in adult mice blocked *P. aeruginosa*-induced BAL cell count increases. Proteomics analysis revealed 62 proteins that had altered YAP binding upon *P. aeruginosa* treatment. The complement factors H and I had >23-fold and >4-fold increases in YAP binding. We conclude, adult mice exhibited YAP-dependent ALI; juveniles did not. YAP-dependent mechanisms may be secondary to YAP binding to the complement inhibitory proteins H and I.

# ***The role of CXCR4-CXCL12 in the development and migration of human natural killer cells***

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Abstract:

Natural killer (NK) cells play a critical role in controlling viral infection and malignancy. As they mature, NK cells interact with various microenvironments; however, much about their development and interactions with these microenvironments are still unknown. We have identified the chemokine receptor CXCR4 and its ligand CXCL12 as potentially playing a role in the specific cellular interactions between NK cells and their environments. First, using in-vitro NK cell differentiation protocols, we found that treatment of CD34<sup>+</sup> precursor cells with CXCR4 antagonist AMD3100 leads to a lower efficiency of NK cell generation. Since previous work demonstrates the necessity for cell migration for development, we interrogated the effect of AMD3100 on NK cell migration. We analyzed live cell imaging data and found that AMD3100 treatment of NK cells or progenitor cells on developmentally supportive CXCL12<sup>+</sup> stromal cells results in altered migratory properties, including less arrest on the stromal cells and increased length of migration. Additionally, high resolution microscopy suggests that integrins could be interacting with CXCR4 in NK cells. Our data suggests that abrogating the interaction between CXCR4 and CXCL12 decreases the efficiency of NK cell differentiation and alters their migratory properties. Future studies will focus on the necessity for CXCR4-CXCL12 in specific key transitions in development and interrogate the role of integrins in this process. Defining the role of CXCR4 in NK biology is critical in developing better treatment options for patients with NK cell primary immunodeficiencies as well as expanding NK cells ex-vivo for immunotherapeutic applications.

# ***Effects of inhibiting N-glycan processing on antibody-mediated cellular cytotoxicity in human natural killer cells***

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Abstract:

Adults with The Acute Respiratory Distress Syndrome (ARDS) have worse outcomes than children with Pediatric ARDS. This finding is reproduced in animal models, suggesting a difference in Acute Lung Injury (ALI) mechanisms. Understanding these differences could inform age-specific treatment. Since Yes-associated protein (YAP) is important for lung repair, we hypothesized that YAP underlies ALI mechanisms. To induce ALI, we intranasally instilled mice with *Pseudomonas aeruginosa* strain K (2.5 x 10<sup>5</sup> colony forming units) in juvenile (3-week-old) and adult (10-week-old) C57BL/6J mice. 24h later, we collected bronchoalveolar lavage (BAL) fluid and measured protein and cell count. To knockdown YAP expression, we injected siRNA 24h before *P. aeruginosa* instillation. Mouse lungs were enriched for nuclear and cytosolic fractions for immunoblot analysis. For immunoprecipitation, cytosolic fraction was added to anti-YAP antibody-coated beads. Bound proteins were identified by mass spectrometry. Adult mice had significantly increased BAL cell counts and protein 24h after *P. aeruginosa* instillation as compared to juveniles. In adult mice, *P. aeruginosa* instillation increased whole lung YAP expression in both cytosolic and nuclear fractions by >3-fold; YAP expression was not increased in juvenile mice. Knockdown of YAP expression in adult mice blocked *P. aeruginosa*-induced BAL cell count increases. Proteomics analysis revealed 62 proteins that had altered YAP binding upon *P. aeruginosa* treatment. The complement factors H and I had >23-fold and >4-fold increases in YAP binding. We conclude, adult mice exhibited YAP-dependent ALI; juveniles did not. YAP-dependent mechanisms may be secondary to YAP binding to the complement inhibitory proteins H and I.

# ***Nkx2.7 is a Novel Regulator of Craniofacial Development***

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## **Abstract:**

Craniofacial malformations account for one third of congenital defects at birth. Clinical phenotypes such as DiGeorge Syndrome illustrate a developmental link between cardiovascular and craniofacial morphogenesis. Recent fate mapping studies in mice and zebrafish identify a cardiopharyngeal multipotent progenitor that gives rise to the heart, branchiomeric muscles, and pharyngeal arch (PA) arteries. NKX2-5 is a key cardiac transcription factor associated with human congenital heart disease and mouse models of Nkx2-5 deficiency emphasize critical roles in cardiac development. The function of Nkx factors in craniofacial patterning has not been elucidated. In zebrafish, nkx2.5 and nkx2.7 are paralogous genes of the NK4 family expressed in cardiomyocytes and PAs. Here, we show that Nkx2.7 serves as a previously unappreciated regulator of craniofacial muscle and cartilage formation. Our novel studies reveal a requirement for nkx2.7 in PA1- and PA2-derived branchiomeric muscle and cartilage elements for which nkx2.5 cannot compensate. Corroborating this finding is our molecular evolution analysis of NK4 genes which demonstrate that nkx2.5 and nkx2.7 are ohnologs resulting from two rounds of vertebrate whole genome duplications. The mechanistic function of nkx2.7 is illuminated by cell counting experiments uncovering a requirement for nkx2.7 in specification of PA1 and PA2 branchiomeric muscle progenitors. Furthermore, single cell RNA-sequencing from wild-type and nkx2.7<sup>-/-</sup> embryos identifies decreased expression of ventral neural crest targets downstream of nkx2.7 in cartilage morphogenesis. Our studies shed light on an evolutionarily conserved, unique function of Nkx2.7 in vertebrate craniofacial development and have potential to improve therapeutic interventions for patients with congenital deformities of the head and neck.

# ***Optimizing the Synergistic Action of Medium-chain Triglycerides and Omega-3 Fatty Acids for Preserving Cellular Metabolic Homeostasis and Inhibiting LPS-induced Pro-inflammatory Responses***

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## **Abstract:**

Adults with The Acute Respiratory Distress Syndrome (ARDS) have worse outcomes than children with Pediatric ARDS. This finding is reproduced in animal models, suggesting a difference in Acute Lung Injury (ALI) mechanisms. Understanding these differences could inform age-specific treatment. Since Yes-associated protein (YAP) is important for lung repair, we hypothesized that YAP underlies ALI mechanisms. To induce ALI, we intranasally instilled mice with *Pseudomonas aeruginosa* strain K ( $2.5 \times 10^5$  colony forming units) in juvenile (3-week-old) and adult (10-week-old) C57BL/6J mice. 24h later, we collected bronchoalveolar lavage (BAL) fluid and measured protein and cell count. To knockdown YAP expression, we injected siRNA 24h before *P. aeruginosa* instillation. Mouse lungs were enriched for nuclear and cytosolic fractions for immunoblot analysis. For immunoprecipitation, cytosolic fraction was added to anti-YAP antibody-coated beads. Bound proteins were identified by mass spectrometry. Adult mice had significantly increased BAL cell counts and protein 24h after *P. aeruginosa* instillation as compared to juveniles. In adult mice, *P. aeruginosa* instillation increased whole lung YAP expression in both cytosolic and nuclear fractions by >3-fold; YAP expression was not increased in juvenile mice. Knockdown of YAP expression in adult mice blocked *P. aeruginosa*-induced BAL cell count increases. Proteomics analysis revealed 62 proteins that had altered YAP binding upon *P. aeruginosa* treatment. The complement factors H and I had >23-fold and >4-fold increases in YAP binding. We conclude, adult mice exhibited YAP-dependent ALI; juveniles did not. YAP-dependent mechanisms may be secondary to YAP binding to the complement inhibitory proteins H and I.

# ***Postnatal Treatment with a Neurosteroid Mitigates Autistic-like Behaviors in a Preclinical Model of Placental Hormone Loss***

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Abstract:

Placental pathology or premature placental loss due to preterm delivery is linked to a higher risk of neurodevelopmental disorders, such as autism spectrum disorder (ASD). Allopregnanolone (ALLO), a neurosteroid that enhances GABAA receptor activity, plays a key role in brain development. Using conditional KO mice in which the synthesis of ALLO is reduced specifically in the placenta (pIKO model), we found that placental ALLO insufficiency results in ASD-like features in male offspring only. Interestingly, treating pIKO fetuses with ALLO (through the dam) completely prevented these behavioral differences.

We now aim to test whether postnatal treatment with ALLO has the potential to rescue ASD-like behaviors in pIKO mice. We administered ALLO (10 mg/kg; SC) or vehicle to pups at birth (P0), in the pIKO mouse model, where the *akr1c14* gene encoding the ALLO synthesis enzyme is deleted in Cyp19-cre expressing trophoblasts but not in the pups. We assessed ASD-like behaviors by measuring isolation calling responses from P4 to P8, evaluating early sensorimotor development at P5, and calculating autism severity scores at P30 based on stereotypies and sociability assessments.

Injecting ALLO at birth completely prevented communication and sensorimotor deficits in male pIKO pups. However, unlike prenatal ALLO treatment, postnatal treatment only reduced, rather than normalized, autism severity scores in adult pIKO males in whom specific stereotypical behaviors were increased.

Our data suggests that ALLO replacement could be a potential therapy for ASD-like behaviors in individuals with disrupted placental endocrine support. However, the timing of ALLO administration needs to be carefully considered

# ***The Child Opportunity Index in Gastroesophageal Reflux Disease Management: Analysis of socioeconomic status in anti-reflux surgical procedure in a multi-center review***

**Author: Tania Gennell**

Additional Authors: Peter Calvaresi, Samantha Rosen, Myron Allukian MD, Shaun Kunisaki MD, Matthew Clifton, Cornelia Griggs MD, Leslie Knod MD, Robert Russell, Shawn Rangel MD MSCE, Elisabeth Tracy, Robin Petroze MD MPH, Afif Kulaylat MD, Jennifer R. DeFazio MD

Abstract:

**Purpose:** The child opportunity index (COI) provides neighborhood information with resultant quintiles to indicate quality of resources and conditions. COI stratifies into very low  $\leq 20$ ,  $20 < \text{low} \leq 40$ ,  $40 < \text{high} \leq 80$ , and  $80 < \text{very high} \leq 100$  with higher scores reflecting better surgical outcomes. Children that undergo surgical management of gastroesophageal reflux disease (GERD) may have residual symptoms that require unanticipated hospital visits, which poses a challenge in low COI patients. The purpose of this study was to analyze COI and how it may affect choice of anti-reflux surgery.

**Methods:** Multi-institution, IRB-approved retrospective review of patients less than 3 years old who underwent Nissen fundoplication (n=1104) and post-pyloric feeding tube procedures (n=97), including surgical jejunostomy (SJ) or gastrojejunostomy (GJ) between 2010-2020 was performed. Kruskal-Wallis Test was performed to compare COI between patients in the Nissen group and post-pyloric tube placement patients.

**Results:** The median COI amongst patients that underwent Nissen was 37, indicating a low COI. In comparison, the post-pyloric enteric tube group had a significantly higher COI (median= 57,  $p=0.0002$ ). More patients in the Nissen group (60.6%) had public insurance than patients in the post-pyloric tube group (40.1%). ( $p=0.0005$ ).

**Conclusion:** Children with a significantly lower COI tend to undergo Nissen fundoplication. Previous data within our group has shown increased unanticipated hospitalizations in GJ patients versus Nissen patients one year after surgery. This unanticipated healthcare burden may be even more impactful in patients with lower COI. Consideration to Nissen over post-pyloric enteric tube should be given in this vulnerable population.

# ***Cerebral Autoregulation In The Post-operative Period In Neonates With Critical Congenital Heart Disease***

**Author: Eliza Gentzler MD**

Additional Authors: Joseph Isler Ph.D, Eleanor Estebanez, NP, Ganga Krishnamurthy, MD, Angelica Vasquez, MD, Diana Vargas, MD, Nimrod Goldshtrom, MD

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Abstract:

**Objectives:** Neonates with congenital heart disease requiring neonatal surgery are at risk for neurodevelopmental impairment. Impaired cerebral autoregulation (CA) has been associated with poor outcomes in prematurity and hypoxic-ischemic encephalopathy. We aimed to describe the evolution of CA in the post-operative period.

**Methods:** This is a retrospective study of neonates undergoing cardiac surgery in a Level IV NICU (2019-2020). Vital signs and near-infrared spectroscopy (NIRS) data were collected from bedside monitors for 72 hours following surgery. CA was computed by time domain methods using mean arterial pressure (MAP) and cerebral NIRS to produce a CA score using Pearson correlation (COx).

**Results:** 68 neonates (25 single ventricle) (SV) were included with mean ( $\pm$ sd) gestational age of 38.9 ( $\pm$  1) weeks and median (IQR) age at surgery of 7 (5-13) days. Time spent with impaired CA (COx > 0.3) in the first 12 postoperative hours was 29.3% ( $\pm$  13.1%) and between 60-72 hours was 24.9% ( $\pm$  10%). ANOVA with Tukey correction comparing each 12-hour block of CA in the 72 hours post op showed statistically significant reduction of impaired CA time from the immediate post-op period to the end of 72 hours ( $p < 0.001$ ). CA was optimized at MAP values between 55-70 mmHg.

**Conclusions:** CA is most impaired in the immediate post-op period and its quantification allows us to identify an optimal MAP which may allow for neuroprotective strategies in post-op care.

Further work is necessary to characterize how this disturbance contributes to neurodevelopmental impairment if impairments could be mitigated by medical management



# ***Engaging Youth in Pollution and Lung Health Monitoring in Washington Heights, New York City: A Pilot Study***

**Author: Meghana Giri<sup>1</sup>**

Additional Authors: Adina Cazacu-De Luca<sup>2</sup>, Rachel Youngwood<sup>3</sup>, Kyung Hwa Jung<sup>4</sup> PhD; Génesis Abreu<sup>5</sup> BS, MS, Thalía Flores Perez<sup>5</sup>, Diane Arevalo<sup>5</sup>, Jared Fox<sup>6</sup> PhD, Steven Chillrud<sup>7</sup> PhD, Stephanie Lovinsky-Desir, MD<sup>4</sup>;

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**Abstract:**

**Objectives:** Children in Washington Heights are exposed to high particulate matter (PM<sub>2.5</sub>) pollution from vehicles on the world's busiest motor vehicle bridge, George Washington Bridge, leading to asthma rates that exceed city-wide rates. We launched a pilot study with local students and a community-based organization to assess feasibility of deploying personal air monitors to teenagers in Washington Heights and explore associations between pollution and airway inflammation.

**Methods:** Students wore an ultrasonic personal air pollution sampler, global positioning tracker, and accelerometer watch for 72-hours. Fractional exhaled nitric oxide (FeNO), a marker of airway inflammation, was measured daily. Adherence to wearing monitors was calculated. Transportation details were collected by daily questionnaires and post-study feedback by focus group.

**Results:** 10 students (ages 16-21) participated. FeNO was stratified at 26ppb: n=5 had "higher FeNO" (mean±SD: 43.2±21.53ppb) and n=5 had "lower FeNO" (11.7±3.54ppb). Those with higher vs. lower FeNO experienced greater PM<sub>2.5</sub> exposure while commuting (24.72±29.36µg/m<sup>3</sup> vs. 16.98±16.95µg/m<sup>3</sup>) (Figure1), were more likely to commute by subway and/or bus (80% vs. 60%), and spent more time above Environmental Protection Agency's daily PM<sub>2.5</sub> threshold of 35µg/m<sup>3</sup> while commuting (226/1123.5mins[20.12%] vs. 182/1375.2mins[13.23%]). All met adherence criteria, 80% were enthusiastic about wearing monitors again, and 70% would potentially change their commute based on personal pollution data.

**Conclusions:** In this small pilot study, elevated airway inflammation was associated with higher PM<sub>2.5</sub> exposure, particularly while commuting by public transportation. Engaging community partners and teenagers in personal air monitoring is feasible, allowing for future studies to enhance student-led advocacy for greener environments.

# ***Implementation of Rapid Genome Sequencing for Critically Ill Infants With Complex Congenital Heart Disease***

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## **Abstract:**

**Objectives:** Rapid genome sequencing (rGS) has been shown to improve care of critically ill infants. Congenital heart disease (CHD) is a leading cause of infant mortality and is often caused by genetic disorders, yet the utility of rGS has not been prospectively studied in this population.

**Methods:** We conducted a prospective evaluation of rGS to improve the care of infants with complex CHD in our cardiac neonatal intensive care unit.

**Results:** In a cohort of 48 infants with complex CHD, rGS diagnosed 14 genetic disorders in 13 (27%) individuals and led to changes in clinical management in 8 (62%) cases with diagnostic results. These included 2 cases in whom genetic diagnoses helped avert intensive, futile interventions before cardiac neonatal intensive care unit discharge, and 3 cases in whom eye disease was diagnosed and treated in early childhood.

**Conclusions:** Our study provides the first prospective evaluation of rGS for infants with complex CHD to our knowledge. We found that rGS diagnosed genetic disorders in 27% of cases and led to changes in management in 62% of cases with diagnostic results. Our model of care depended on coordination between neonatologists, cardiologists, surgeons, geneticists, and genetic counselors. These findings highlight the important role of rGS in CHD and demonstrate the need for expanded study of how to implement this resource to a broader population of infants with CHD.

# ***A multifaceted deep dive into the NK cell developmental niche within human secondary lymphoid tissue***

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## **Abstract:**

Human NK cell maturation from CD34<sup>+</sup> progenitors can be promoted in vitro by cytokines including IL-15, SCF, Flt3L and IL-7, and contact-dependent signals from stromal cells. However, a full characterization of the cells that provide these signals in sites of NK cell development, and how progenitors are trafficked to microenvironments that support their differentiation, has not been fully defined. Using a novel 45-marker cyclic immunofluorescence panel and complementary flow cytometric analysis we have identified stromal and cytokine niches in pediatric tonsil that we propose support discrete stages of NK cell maturation and homeostasis. We observed a relationship between the spatial distribution of chemokine ligands and NK cell populations. Non-cytotoxic NK cell subsets were found adjacent to CCL19-expressing cells in subepithelial and interfollicular regions. CD34<sup>+</sup> NK cell progenitors were in proximity to CXCL12<sup>+</sup> stromal cells within the interfollicular and parafollicular space in tonsil. Tonsillar stromal cells include gp38<sup>+</sup>CD31<sup>+</sup>CD34<sup>+</sup> lymphatic endothelial cells and a gp38<sup>+</sup>CD31<sup>–</sup>CD34<sup>–</sup> fibroblast reticular cell (FRC) population with a mesenchymal phenotype similar to bone marrow stromal cells. Characterization of FRCs in tonsil revealed that they express cytokines known to promote NK cell development including SCF, IL-7, and IL-15. Tonsillar FRCs can also express Flt3L but are not the only source of Flt3L in tonsil. Together this data provides in-depth characterization of the stromal cells providing a developmental niche for NK cell progenitors in secondary lymphoid tissue.

# ***Exploring Catchment Area Methodologies to Assess the Inclusivity of a Large Academic Pediatric Emergency Department***

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Abstract:

**Objectives:** Hospital “inclusivity” is a new quality measure concept assessing concordance between the demographics of a hospital’s patient population and that of its catchment area. How to best define catchment area for the purpose of measuring inclusivity is undetermined. Our overall goal is to examine variation in hospital inclusivity by catchment area definition. In this preliminary work we developed and described four definitions of catchment area for the MSCH emergency department (ED).

**Methods:** We conducted a cross-sectional study of all MSCH ED visits (2021-2022). We geocoded visits to census tracts by patient address. Census tracts were ordered by the number of unique patients to determine the last census tract that added significant patients to the cumulative patient count. We measured distance from the hospital to the geographic centroid of the last census tract as either (a) straight-line distance or (b) shortest drive-time. We varied distance by (i) 100% or (ii) 50% of the total. Catchment area was defined as the smallest convex polygon enclosing all selected tracts (convex hull).

**Results:** We defined and mapped four catchment areas (Fig. 1) Catchment areas varied by number of unique patients (27,382-29,929), census tracts (1,776-4406) and percentage of tracts with patients (48-66%) (Table 1). Census tracts with high patient density in Rockland County expanded our catchment areas.

**Conclusions:** Even minor variations in parameters modify catchment area geography. Policies assessing hospital inclusivity must carefully consider catchment area definitions in their implementation as well as the impact of factors unique to local geography and markets.

# ***The interface of mTOR and STAT3 signaling in the Th2 diathesis***

**Author: Haley Lei Huang, PhD**

Pathobiology and Molecular Medicine program of CUIMC

Abstract:

The escalating prevalence of allergic diseases globally represents a significant public health concern, with some conditions like anaphylaxis being potentially fatal. While the etiology of common allergic diseases is predominantly polygenic and multifaceted, Primary Atopic Disorders (PADs) present a unique subset as monogenic diseases, often manifesting in more severe phenotypes and increased comorbidity. Since only a limited number of patients are affected by PADs, their study and relevance to common allergic disease have been more limited. In this study, we utilize PADs as a disease model to study the immune pathways and pathomechanisms implicated in allergic diseases.

We examine two PADs associated with dysfunctions in the IL6-STAT3 pathway and the CARD11-BCL10-MALT1 complex, which display overlapping clinical features such as elevated serum IgE levels, enhanced Th2 cytokine production, atopic dermatitis, and increased susceptibility to bacterial respiratory infections. Our research investigates the mechanistic link between the STAT3 and mTORC1 pathways by using STAT3 and CARD11 mutant patients and mouse models. Our results reveal that impaired STAT3 signaling or mTORC1 activity favors Th2 cell differentiation and leads to a compromised regulatory T cell phenotype and function. Furthermore, we demonstrate that mTOR regulates STAT activity via CISH/SOCS signaling. Intriguingly, the reversal of Th2 phenotypes using an mTORC1 agonist, such as exogenous glutamine, suggests mTOR as a central pathomechanism in Th2 diathesis. This finding highlights mTOR as a novel therapeutic target in allergic disease treatment, offering potential for innovative intervention strategies

# ***The interface of mTOR and STAT3 signaling in the Th2 diathesis***

**Author: Grazia Iannello<sup>1</sup> PhD**

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<sup>2</sup>Division of Molecular Genetics, Department of Pediatrics, Columbia University Irving Medical Center, New York, NY, USA.

Abstract:

**Objective:** OCRL is an X-linked gene encoding for an Inositol Polyphosphate-5-Phosphatase involved in cell migration, membranes trafficking, and actin polymerization. Truncating mutations in exons 1-7 lead to Dent-2 disease while mutations in exons 8-24 cause Lowe syndrome (LS). Two isoforms are seen in humans, with the long isoform A exclusively expressed in the brain. The isoform-specific function is unknown.

**Methods:** Whole-exome sequencing was used to screen a 5-year-old male with extreme obesity and short stature with brain-specific LS clinical manifestations without kidney or eye phenotype. We generated PBMC-derived iPSC and used CRISPR-Cas9 to generate the isogenic control. iPSCs were differentiated into neurons. qPCR and RNA sequencing were used to investigate differential OCRL expression.

**Results:** We identified for the first time a mutation in exon 19 of OCRL (p. L713Rfs\*28) which leads to the lack of expression of the brain isoform A in patient-derived iPSC and iPSC-derived neurons vs. controls, which was restored in the CRISPR-corrected line. RNA seq on iPSC-derived neurons showed downregulation (AP2A1, AP2B1, CLTB) and upregulation (TFRC, RAB1B, CLTA, CLINT1, APPL1) of genes involved in clathrin-mediated trafficking compared to controls. The expression of these genes was rescued in the isogenic control neurons, suggesting a key role for OCRL in endocytic trafficking.

**Conclusion:** We have identified a new OCRL brain-specific pathogenic variant in an obese patient which impairs cellular trafficking and is potentially associated with the patient obesity phenotype. The unique location of the identified pathogenic variant may help elucidating the role of OCRL in the brain.

# ***Systemic Vein Stenting in a Pediatric Patient After Total Artificial Heart Implantation***

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**Abstract:**

**Objectives/Background:** The Total Artificial Heart (TAH) (Syncardia, Tucson, AZ) is used as a bridge to transplant (BTT) for patients with biventricular heart failure and use in pediatrics is limited. A known complication after TAH is compression of the left sided pulmonary veins, inferior vena cava, and the left bronchus. We describe the use of TAH in a pediatric patient as a successful BTT. The post-TAH course included obstruction of both cavae with poor device filling and decreased TAH output that was successfully treated with bi-caval stent placement - a novel intervention never previously described.

**Case description/Methods:** A 15-year-old female with dilated cardiomyopathy status-post orthotopic heart transplant (OHT) seven years prior, presented with acute on chronic heart failure. She had a history of allograft rejection with persistent biventricular systolic dysfunction. With the intention of bridging her to re-transplantation, she underwent placement of a 70-cc TAH, after sizing per manufacturer guidelines. Her chest was closed after partial sternal resection and decoupling of TAH pumps; however, the device had poor filling and low flow. Echocardiography demonstrated severe gradients across the systemic veins and decision was made for transcatheter stent placement..

**Results:** Angiography confirmed severe stenosis of the superior and inferior vena cava due to obstruction from the TAH device. Stenting of the systemic veins led to immediate improvement in fill volumes and flows. The average right TAH cardiac output range increased from 3.4-4.2 LPM to 6.0-6.8 LPM with a 40% increase in maximum right fill volumes. There was a concomitant increase in left TAH flows and volumes. There were no further issues with the device and the patient was able to successfully rehabilitate. Six months after TAH implantation, she underwent successful re-transplantation.

**Conclusions:** Our case highlights use of TAH as a successful BTT in a pediatric patient with TAH function complicated by obstruction of the systemic veins. Transcatheter stent placement in the systemic veins, an intervention not previously described with TAH, led to effective, durable relief of venous obstruction. Multi-disciplinary collaboration for this patient provided a path to successful re-transplantation.

# ***The interface of mTOR and STAT3 signaling in the Th2 diathesis***

**Author: Maya Jean-Hillaire**

Additional Authors: Annelise Babcock, Glenn White, Cynthia Masson, Charles DeLuc, Vidhu Thaker MD

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Abstract:

**Objectives:** Metabolic and bariatric surgery (MBS) results in sustained weight loss – the most common being sleeve gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB). Rates of conception and pregnancy are known to increase after MBS, but less is known about offspring born after pre-pregnancy MBS. This study aims to profile the offspring longitudinal weight and height trajectory born after MBS compared to normal and high maternal BMI.

**Methods:** Data on gravidas with pre-pregnancy MBS and controls was obtained from the Ob/Gyn database and TRAC pull between Jan 2020-March 2023 at CUIMC. Maternal data included dates, location, and type of MBS, location, weight loss trajectory, ICD diagnoses, pregnancy complications. For offspring, longitudinal anthropometrics, laboratory results, ICD and CPT codes were extracted. Linear mixed models were used to compare the trajectories of weight and length.

**Results:** Data for 20,714 pregnancies (MBS n=422) was obtained. Longitudinal offspring data was available for 6865 unique offspring – 108 born following RYGB and 119 following SG. The birth weight after MBS was lower compared to gravidas with or without obesity ( $p < 0.001$ ). Offspring weight trajectories up to 24 months showed no difference between those born after RYGB and BMI  $< 27$  kg/m<sup>2</sup> ( $p = 0.8$ ), while those born after SG had persistent rise ( $p = 0.04$ ), adjusting for maternal age, parity, time since surgery and race/ethnicity. Boys had lower trajectories compared to girls. ( $p < 0.001$ ).

**Conclusions:** Pre-pregnancy RYGB, but not SG, was followed by favorable offspring weight trajectory that may have a role in long-term metabolic programming.



# ***Exercise Induced ECG Changes Predict Adverse Outcomes in Pulmonary Hypertension***

**Author: Maya Kailas MD**

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**Abstract:**

**Introduction:** Cardiopulmonary exercise testing (CPET) is an important tool in assessing the functional status of patients with pulmonary hypertension (PH). During CPET, ECG is used as marker of exercise induced ischemia. We hypothesize that ECG changes with exercise may be an early indicator of clinical worsening in PH and could predict adverse outcomes.

**Methods:** Clinical, hemodynamic, and CPET data of 101 PH patients who underwent CPET between 2013 and 2019 were included. ECGs were analyzed for ST depressions and T wave inversions during the earliest CPET in this time frame, along with coincident hemodynamic data. These data were correlated to adverse outcomes, including shunt creation (atrial septostomy or POTTs shunt), lung transplantation, and death.

**Results:** Median age was 19 y (7-40 y, IQR 12-26), 68% were female, and median follow up time was 3 y (1-8 y, IQR 1-5). Sixteen patients had an adverse outcome (8 shunt creation, 4 lung transplant, 7 death). Twenty-two patients demonstrated significant ST/T wave changes with exercise, 18 ST depressions and 9 T wave inversions. Multivariate regression, including pulmonary arterial pressure, revealed exercise induced ST/T wave changes to be an independent predictor of procedure-free survival (without lung transplantation or shunt creation) (hazard ratio 11.10, p=.006). Only 21% with ST/T wave changes demonstrated procedure-free survival vs 85% without.

**Conclusions:** ST/T wave changes on exercise ECG are significantly associated with adverse outcomes in PH on a medium term follow up study. These ECG changes with exercise can be used as early indicators of clinical worsening in PH and predictors of adverse outcomes.

# ***Exercise Induced ECG Changes Predict Adverse Outcomes in Pulmonary Hypertension***

**Author: Gokhan Kalkan<sup>1</sup> MD**

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**Abstract:**

**Background:** Cytomegalovirus (CMV) is an important cause of morbidity following pediatric orthotopic liver transplantation (OLT). We adopted a Cell Mediated Immunity (CMI) based approach to guide CMV prophylaxis (ppx) following pediatric OLT and sought to explore its implication on the rate of CMV infection, rejection, and valganciclovir (VGC) adverse reactions and cost in our population.

**Methods:** We conducted a retrospective review of pediatric OLT recipients on standard CMV ppx regimens (cohort 1, Jan 2017 – Dec 2018 ) vs CMI based ppx (cohort 2, Jan 2019-Nov 2020) and compared rates of CMV infection, CMV disease, rejection, duration and cost of valganciclovir (VGC), and drug attributable adverse. Fischer's exact test and student T-Test were used to assess differences in categorical and ordinal outcomes between the two cohorts, respectively.

**Results** Of 41 children (21 cohort 1, 20 cohort 2), Eight (19.5%) were HR (D+/R-), 21 (51.2%) were intermediate (IR) (D+/R+), and 12 (29.2%) were low (D-/R-) risk for CMV infection. All received VGC ppx. There was no increase in the incidence of CMV infection, disease, or rejection in cohort 2 compared to cohort 1. Mean duration of antiviral ppx decreased by 41%, and was associated with a 52% decrease in cost of antivirals. AE's associated with VGC were similar in both groups (19 vs 15%).

**Conclusion:** Implementation of a CMV CMI based protocol decreased the cost and duration of CM ppx following pediatric OLT, and was not associated with increased breakthrough viremia or disease. Incorporating CMV CMI to guide post-transplant CMV prophylaxis may reduce unnecessary antiviral use.

# ***Early Post-Operative Infections after Pediatric Liver Transplantation while in the Intensive care Unit***

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## **Abstract:**

**Objectives:** To identify the incidence of and risk factors for early post-operative infections (POI) after pediatric liver transplant (LT)

**Methods:** This is a multi-center retrospective cohort study amongst 12 pediatric LT centers. Pre- and peri-operative variables associated with POI were assessed. Continuous data were compared using the Wilcoxon rank-sum test and categorical data with chi-squared test. A multivariable logistic regression was used to identify independent predictors of infection for p-value>0.3.

**Results:** After LT, 76/327 (23%) patients developed POI (65% bacterial, 17% viral, 13% fungal, and 29% other). Abdominal/surgical site and bloodstream infections were most common at 29% and 26%, respectively. On multivariable analysis, independent predictors of POI included younger age (OR=0.92 (95%CI 0.87-0.98), p=0.006), history of immunodeficiency (OR=12.6 (95%CI 1.3-122.9), p=0.03), open fascia (OR=3.3 (95%CI 1.8-5.9), p<0.001), and hospitalization before transplant (OR=2.0 (95%CI 1.1-3.5), p=0.02). POI were associated with higher morbidity. POI patients had higher rates of open fascia (42% vs 20%, p<0.001), longer duration of mechanical ventilation (2.4d [0.5-8.5] vs 0.6d [0.0-2.1], p<0.001), allograft thrombotic complications (49% vs 18%, p<0.001), and receive blood products (74% vs 46%, p<0.001).

**Conclusions:** One in five LT patients developed POI in the immediate postoperative period. Predictors of POI included younger age, history of immunodeficiency, open fascia, and hospitalization before transplant. POI were associated with significant morbidity including prolonged length of stay, graft loss, and mortality. These data support the need for prospective studies to better characterize POI risk factors and develop protocols to prevent POI to optimize graft and patient survival.

# ***Early Post-Operative Infections after Pediatric Liver Transplantation while in the Intensive care Unit***

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Abstract:

**Objective:** By utilizing newly validated tools including the General Movement Assessment (GMA) and Hammersmith Infant Neurological Exam (HINE), providers can diagnose cerebral palsy (CP) in infants as early as three months old. The objective was to standardize screening practices for CP in a neonatal intensive care unit (NICU) and high-risk infant follow-up clinic to reduce age at CP diagnosis.

**Methods:** We combined plan-do-study-act cycles with implementation science methodology to reduce age at CP diagnosis by standardizing a screening process starting in the NICU over an 18 month period. Key stakeholders included pediatric providers, physical and occupational therapists, and clinic coordinator. Main process changes included routine administration of the GMA and HINE, first clinic visit at 3-4 months, and adoption of a high risk for CP designation. Means were compared using student t-tests. P value < 0.05 was considered statistically significant.

**Results:** Since 2022, almost 80% of qualifying infants had a GMA done in the NICU, while 96% of infants seen at 3-4 months also had a GMA. In 2022, the HINE was performed in 80% of infants seen in clinic between 3-24 months of age. Age at CP diagnosis decreased from an average adjusted age of  $20.7 \pm 3.8$  months in 2021 to  $10.3 \pm 6.7$  months ( $p=0.008$ ).

**Conclusions:** Through successful implementation of a standard screening process in the NICU and follow-up clinic, the average age of CP diagnosis decreased by more than 10 months over an 18-month period allowing more time for earlier intervention and timely support for caregivers.

# ***Machine learning demonstrates that abnormal fetal umbilical artery Dopplers may be highly specific to necrotizing enterocolitis in preterm infants with fetal growth restriction***

**Author: Faith Kim<sup>1</sup> MD**

Additional Authors: Helen Field<sup>1</sup>, Marianne Garland<sup>1</sup> MD, Alex Lyford<sup>2</sup> PhD, Thomas Hays<sup>1</sup> MD

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Abstract:

**Objectives:** Necrotizing enterocolitis (NEC) is an ischemic intestinal disease that affects 10% of preterm infants and is associated with up to 50% mortality. Fetal growth restriction (FGR) is strongly associated with NEC. FGR infants are exposed to strategies intended to reduce NEC risk, but these strategies are associated with complications including mortality (e.g., delay of enteral feeds, bowel rest, antibiotic exposure, prolonged central line use). Risk stratification would allow tailored management and fewer complications. Machine learning is revolutionizing risk stratification for diseases with complex, non-linear risk factors. We sought to determine the utility of decision tree classification for NEC risk in FGR preterm infants. We included fetal umbilical artery (UA) Doppler assessment, hypothesizing that it might be an early marker of intestinal ischemia and NEC risk.

**Methods:** This was a retrospective cohort of 164 preterm (< 32 weeks' gestation) infants with FGR, 20 of whom developed stage II-III NEC. We used gradient boosted decision trees to classify NEC and to evaluate predictive value of gestational age, birth weight (sex and gestation normalized), and presence of abnormal UA Dopplers.

**Results:** Early gestational age and lower normalized birth weight strongly predicted NEC. The presence of a normal fetal Doppler was heavily weighted in classifying infants unlikely to develop NEC. Fetal Dopplers had a 95% specificity (15% sensitivity) for NEC in preterm FGR infants.

**Conclusions:** If validated, normal fetal UA Doppler may identify preterm FGR infants at low risk for NEC who may be spared conservative NEC-prevention strategies.

# ***The GUTSY Program: Gaining Understanding of Transition in Short Bowel Syndrome Among Youths***

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Additional Authors: Tanvi Verma, MA, Allison Geller, MSW, Elizabeth A. N. Berg, MD

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Abstract:

**Objectives:** Short Bowel Syndrome (SBS) requires life-long reliance on a multidisciplinary team. With increased survival, adolescents and young adults (AYAs) must prepare to transition to adult providers. Studies on health care transition (HCT) in AYAs with other chronic conditions suggest increased morbidity, mortality, and psychosocial impairment after transfer of care. Our program aims to guide AYAs with SBS through HCT by creating a structured curriculum that integrates ongoing assessments of transition readiness, health literacy, quality of life, resilience, mental health, goals and barriers to HCT.

**Methods:** We prospectively enrolled patients with SBS into our transition program, GUTSY: Gaining Understanding of Transition in Short Bowel Syndrome Among Youths. Participants complete six educational sessions that assess and teach topics relevant to HCT. Progress is measured using standardized tools, and barriers and goals for HCT are assessed through brief open-ended qualitative surveys.

**Results:** Participants (n=20 patients; n=16 patient-parent dyads), mean age: 17.4 years (range: 12-25 years); 55% female. To date, 68 sessions completed. AYAs report struggling with independence and self-management, reluctance to transfer care, and a desire to learn more about their condition, self-care techniques, and prognosis.

**Conclusion:** The GUTSY Program is an innovative program with targeted educational and psychological interventions to facilitate transition to adulthood in AYAs with SBS. Baseline data show a need for such a program, as AYAs with SBS have low transition readiness, health literacy, resilience, and positive screens for depression/anxiety. As patients progress through the program, we aim to measure changes in these baseline scores.

# ***Vitamin C is Mandatory for the TCA Cycle Production of Anti-inflammatory Itaconate***

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## **Abstract:**

**Introduction:** Sepsis-induced pro-oxidant conditions elevate vitamin C (VitC) demand, causing deficiency and potential immune impairment. Despite its recognized reductive role in mitochondria, the specific link between VitC and immune modulation remains unclear. Pro-oxidant susceptibility of citrate synthase (CS) and aconitase (ACO2) is noted, with ACO2's catalytic activity generating cis-aconitate, a precursor to the anti-inflammatory metabolite itaconate. We hypothesized that VitC is crucial for itaconate generation and maintaining its levels during systemic inflammation.

**Methods:** Using ODS rats lacking functional L-gulonolactone oxidase, we randomized them to VitC+ or regular (VitC-) water, subjected them to whole-body irradiation (WBI) or cecal ligation and puncture (CLP). Measurement of plasma VitC levels, enzymes' activity, and TCA cycle metabolite levels, along with blinded assessment of murine sepsis severity (MSS) scores, was conducted. Isotopic tracer [<sup>13</sup>C<sub>6</sub>]-glucose labeling in HEK293 cells explored VitC's role in TCA cycle metabolites.

**Results:** VitC+ rats showed increased kidney CS and ACO2 activity, higher cis-aconitate and itaconate levels in renal cortices, liver and ileum vs VitC- rats. [<sup>13</sup>C<sub>6</sub>]-glucose labeling showed a large fraction of cis-aconitate [M+0] was not derived from labeled glucose and higher reverse-TCA activity with increased itaconate and low  $\alpha$ KG levels in VitC+ vs Vit C- cells. WBI and CLP studies demonstrated higher MSS scores in VitC- rats corroborating with lower cis-aconitate and itaconate levels in ileum and renal cortex vs Vit C+ rats and increased NGAL in kidney cortices after CLP. Treatment of VitC- rats with itaconate attenuated CLP illness severity.

**Conclusions:** VitC has an essential role in itaconate production, mainly derived from glutamine via the TCA cycle, emphasizing its key role in generating the immunomodulatory molecule itaconate by protecting cis-aconitase activity during systemic inflammation.

# ***Health Equity Rounds: a trainee-led initiative to combat bias and racism in healthcare***

**Author: Thomas Kuriakose MD**

Additional Authors: Elorm Avakane MD MPP, Amanda Simard MD, Linda Aponte-Patel MD, Sumeet Banker MD MPH, Amanda Esteves MD MS, Katherine Nash MD MS, Patrice Pryce MD

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Abstract:

**Background/Objectives:** Disparities in healthcare access, experiences, and outcomes are rooted not only in individual-level behavior, but also in historical and current systems of oppression. As such, individual providers may lack confidence to address inequities.

Health Equity Rounds (HER) is a trainee-led curriculum that uses case-based conferences to examine the impact of bias and racism on patient care, understand current and historical drivers of inequities, and identify potential solutions. Beyond educating participants, HER empowers its trainee leaders to be career-long advocates for their most vulnerable patients, and fosters an interprofessional community in service of this work.

**Methods:** We will launch the trainee-led Health Equity Rounds curriculum for the Columbia Department of Pediatrics using Kern et al's 6-step curriculum development framework. Our AY2023-2024 pilot for the Division of Pediatric Critical Care, Hospital Medicine, and Palliative will include two presentations – each structured around a local clinical case, followed by a topic specific literature review with a focus on historical context, faculty and community expert panelists, and a discussion of tangible next steps. In parallel, we will aim to build a core group of trainees and faculty advisors across the Department of Pediatrics.

**Results/Conclusions:** The pilot program will be evaluated for feasibility, acceptability, and ability to meet conference-specific learning goals. In early 2024 we will incorporate HER into the pediatric residency program curriculum (in alignment with GME objectives and the American Board of Pediatrics' EPA 14). In 2025, we reach a departmental-level audience through presentations at the Department of Pediatrics Grand Rounds



# ***Ensuring the Success of Pediatric Cardiology Patients Through the Lifespan: Translating Current Transition Medicine Research Into Programmatic Implementation***

**Author: Hannah Y. Lee<sup>1</sup> MS CPNP**

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Abstract:

Purpose of review: This paper will introduce transition medicine implementation ideas to adapt and incorporate into every major pediatric cardiology center. By examining existing research that demonstrates effective strategies aimed at improving the transition process for young adults with chronic illness, we hope to engage major stakeholders in developing and sustaining transition of care clinics (TOCC).

Recent findings: Many barriers exist to implementing a successful transition of care program for pediatric chronic disease populations. The divergent goals of research findings and the nuances of institutional funding priorities serve as a big driver of delay in transition program implementation. Adequate funding streams for research are also limited, with child health outcomes and care throughout the lifespan not gaining sufficient attention. Investment from institutional, local, state, and federal funding as well as increased legislative priorities in child health may help gain more traction in establishing TOCC. Lastly, advocacy surrounding the importance of TOCC and comparative effectiveness data on which transition programs improve outcomes for pediatric chronic disease populations is critical for best care practice, as well as the ability to disseminate data that can be easily translated by and disseminated to institutions and lawmakers.

Summary: Engaging stakeholders, institutional prioritization, multi-level funding, and research translation are critical to enhancing and improving transition of care outcomes and experiences for pediatric chronic disease patients.

# ***Trends in Sedative Drug Utilization for Mechanically Ventilated Patients in US Pediatric Intensive Care Units, 2010-20***

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## **Abstract:**

**Background:** Sedatives are often administered in the pediatric intensive care unit (PICU) to facilitate the tolerance of mechanical ventilation (MV). Sedation management in PICU patients is variable with heterogeneity of clinical environments, patient-, and provider-related factors. To understand the current state of sedation practice in PICU patients, a description of sedative utilization patterns would be valuable, but is lacking.

**Objective:** To investigate trends in sedative use for MV patients in US PICUs.

**Methods:** A retrospective analysis was performed using the Pediatric Health Information System Database. Demographic, clinical, and pharmacy data were extracted, and descriptive statistics were summarized. Multivariable logistic regressions were performed to identify significant factors associated with receipt of <sup>3</sup>4 sedative classes or neuromuscular blockade (NMB). Sedative classes were defined as opioids (OP), benzodiazepines (BZ), alpha-2 agonists (AA), propofol (PF), barbiturates (BT), and ketamine (KT).

**Results:** Of 259,702 PICU discharges, there were 212,457 patients aged 2.0±10.0 years MV for 2.0±5.0 days (Table 1). 80.3% (n=170,652) received OP, 76.1% (n=161,748) BZ, 46.4% (n=98,518) AA, 37.5% (n=79,731) PF, 22.2% (n=47,251) KT, and 8.6% (n=18,167) BT, either alone or in combination with other sedatives. 64.3% (n=136,568) were given NMB. From 2010 to 2020, increased use of AA (+28.7%), KT (+12.3%), PF (+14.4%) was observed, and decreased use was seen with BZ (-14.4%), BT (-9.9%), and OP (-6.7%) (Figure 1). In 12.5% (n=26,469), no sedatives were documented. Only 6.9% (n=14,630) had a single class of sedatives with 17.9% (n=37,980) receiving 2 classes. 27.6% (n=58,561) had 3 classes; 35.2% (n=74,817) had <sup>3</sup>4 classes (Table 2). In those who had <sup>3</sup>4 classes, OP and BZ were administered to nearly all patients (99.6%, n=74,536). Compared to those >12 years, <3 years were less likely to receive <sup>3</sup>4 classes (OR=0.77, 95% CI 0.75-0.79, p<.001) and more likely to receive NMB (OR=1.56, 95% CI 1.53-1.60, p<.001) after adjusting for covariates (i.e. sex, race/ethnicity, discharge year, hospital census region, complex chronic condition, reason for admission, payor status).

**Conclusions:** OP and BZ were the most commonly administered sedatives to MV PICU patients; both were included when ≥4 classes were given. There has been a recent increase in the use of AA, KT, and PF with a reduction in the use of BZ, BT, and OP. Patients <3 years were more likely to have been paralyzed and less likely to have received <sup>3</sup>4 sedative classes.

# ***Management of Systemic to Pulmonary Shunts and Elevated Pulmonary Vascular Resistance***

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**Abstract:**

**Background:** Timing of repair of systemic to pulmonary shunts is aimed at preventing the development of irreversible pulmonary vascular disease. This was a retrospective study to assess outcomes of an individualized strategy for managing patients deemed borderline eligible for repair.

**Methods:** A retrospective chart review of patients with intracardiac shunts and a baseline  $PVRi \geq 3$   $WU \cdot m^2$  treated at a single centre from 1/1/2005-9/30/2019 was conducted. Data included demographics, WHO Functional Class, medications, and hemodynamic data at baseline and serial follow up.

**Results:** Thirty patients (18 females) met criteria for inclusion. Median age at diagnosis of PAH was 1.3 years (0.03–54) and at surgery was 4.1 years (0.73–56). Median follow up time was 5.8 years (0.2-14.6) after repair. The majority of patients received at least one targeted PAH therapy prior to repair. There was a significant decrease in mPAP ( $p < 0.01$ ), PVRi ( $p = 0.0001$ ), and PVR/SVR ( $p < 0.01$ ) between the baseline and pre-operative catheterization and a decrease in PVRi ( $p < 0.005$ ), mPAP ( $p = 0.0001$ ), and Qp:Qs ( $p < 0.03$ ) from baseline to most recent catheterization. WHO functional class improved from baseline FC II-III to FC I post repair in most patients ( $p < 0.003$ ). One patient died at the time of last follow up from a noncardiac cause.

**Conclusions:** In carefully selected patients with intracardiac shunts and elevated PVR considered borderline for operability, the use of preoperative targeted therapy in conjunction with fenestrated or partial closure of intracardiac shunts is associated with improvement in functional class and clinical outcomes.

# ***Cryo-electron tomography imaging of human parainfluenza virus fusion/entry complex glycoproteins on the viral surface.***

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Abstract:

Human parainfluenza viruses (HPIV) enter cells by fusing their envelope directly with the cell membrane in a process mediated by the viral surface glycoproteins HN (receptor-binding protein; hemagglutinin-neuraminidase) and F (fusion protein) — together forming the viral fusion complex. To successfully infect, the HN-F complex must first be prevented from activating prematurely in the absence of its cellular target. Prior to receptor engagement, HN helps retain F in an inactive, pre-fusion state. Upon engagement of a cellular receptor, HN triggers F to undergo a series of structural transitions, inserting in the target membrane and then refolding to mediate virus-cell fusion. This transition facilitates merger between the viral and cellular membranes and permits release of the viral genome into the target cell cytoplasm. Using cryo-electron tomography of authentic unperturbed viral particles, we characterized the viral fusion complex on the surfaces of viruses before and during engagement of host cell membranes. A high-resolution subtomogram average of the HN-F complex on the surface of intact virions reveals that within each HN dimer, one monomer's binding site faces the sialic acid receptor while the other monomer interacts with the apex of pre-fusion F. Subtomogram averaging refinements uncovered unanticipated interactions at the HN dimer interface, a domain that is key for HN's F-activation function during fusion activation. Specific domains of the HN globular head interact with the crown of pre-fusion F and suggest potential targets for interrupting HN's function. The structure of the complex formed by the receptor binding and fusion protein of paramyxoviruses has been elusive until now. These structures reveal several new interactions between HN and F in the pre-fusion state of the entry complex on the viral surface.

# ***Vascular Thrombosis after Pediatric Liver Transplantation: Is Prevention Achievable?***

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## **Abstract:**

**Objectives:** To identify risk factors for intra-abdominal vascular thrombosis (VT) after isolated pediatric liver transplantation

**Methods:** This is a multi-center retrospective cohort study amongst 12 pediatric liver transplant (LT) centers in the United States during 2-years. Univariable analyses were performed to assess for associations between anticoagulation therapy, vascular thrombosis, bleeding, unplanned return to the operating room, return to the intensive care unit, graft loss, and mortality. A regression model was built to identify independent risk factors for VT development.

**Results:** Within seven postoperative days, 31/331 (9.37%) patients developed intra-abdominal VT. Most VT were detected with a median day of diagnosis on postoperative day (POD) 1 (IQR POD 0-4). Open fascia occurred more commonly in patients with VT (51.61 vs 23.33%) and remained the only independent risk factor in multivariable analysis (OR = 2.84, p = 0.012). Patients with VT received more blood products (83.87 vs 50.00%), had significantly higher rates of graft loss (22.58 vs 1.33%), infection (50.00 vs 20.60%), and unplanned return to the operating room (70.97 vs 16.44%) compared to those without VT. The risk of bleeding was similar (p = 0.2) between patients on and off anticoagulation.

**Conclusions:** Prophylactic anticoagulation did not increase bleeding complications in this cohort. The only independent risk factor associated with VT was open fascia, likely a graft/recipient size mismatch surrogate, supporting the need to improve surgical techniques to prevent VT that may not be modifiable with anticoagulation.

# ***A Pediatric Population Health Dashboard to Support the Medical Home***

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## **Abstract:**

**Background:** Without comprehensive data, establishing a medical home for children can be challenging. There is a need to identify patients with chronic conditions, track utilization and understand care coordination.

**Objective:** To develop a pediatric population health dashboard to support the delivery of the medical home elements.

**Design:** A dashboard was created from EHR data of four, urban academic practices. It includes all patients empaneled to faculty and residents, and fields to filter by practice, pediatrician, social determinant risk, race, ethnicity, language, and zip code. It identifies children with special health care needs utilization<sup>1</sup>. The dashboard summarizes data of those not up to date with care. Finally, data on children diagnosed with ADHD, asthma, depression, and anxiety was incorporated to support outreach and monitor prevalence.

**Results:** The dashboard includes a population of 17,895 patients, stratified by level of special health care needs<sup>1</sup> and includes 1331 as a Level 3A (socially unstable), and 731 as a Level 3B (medically complex). It also includes 192 patients currently enrolled in the community health worker program, 327 working with a care manager, 1961 with a social worker, and 1581 with a mental health provider.

# ***A Pediatric Population Health Dashboard to Support the Medical Home***

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## **Abstract:**

**Background:** Standard of care anticoagulation for pediatric patients on Berlin Heart Excor or PediMAG ventricular assist device (VAD) support includes dual anti-platelet therapy in addition to primary anticoagulation with bivalirudin or heparin. With an increasingly complex patient population in pediatrics requiring VAD support, a growing subset of patients are unable to tolerate oral anti-platelet therapy. Cangrelor, an intravenous (IV) P2Y12 inhibitor, may be desirable as anti-platelet therapy in these patients to prevent clot formation leading to adverse events.

**Methods:** Retrospective chart review for all pediatric VAD patients receiving cangrelor from 2021-2022 at Morgan Stanley Children's Hospital at New York Presbyterian. Data analyzed using descriptive statistics.

**Results:** From 2021-2022, 4 patients aged 7 weeks-15 months, BSA 0.18-0.38, received cangrelor on VAD support as a bridge to heart transplantation. In all cases, there was long-term intolerance to enteral feeding limiting the ability to give oral antiplatelet therapy. In 3 of the cases, there was confirmed or suspected necrotizing enterocolitis. 2 patients were on VAD support with both PediMAG and Berlin Heart VAD, and 2 patients were supported only with PediMAG. 3 patients were supported with an SVAD configuration and 1 patient with an LVAD. Cangrelor dosing ranged from 0.3-2.7mcg/kg/min and duration of use ranged from 29-106 days. P2Y12 was used to guide dosing in all cases with a goal of <180 or <220. 3 patients were primarily anticoagulated with bivalirudin, and 1 patient with heparin. 1 patient had a stroke event on cangrelor, and 1 patient had pulmonary hemorrhage. 3 patients died while on VAD support, 1 patient survived to transplantation. Cangrelor was in use at the time of death for 2 of the cases that did not survive to transplantation.

**Conclusion:** The use of cangrelor as IV antiplatelet therapy for VAD patients where oral anti-platelets are contraindicated may be a viable option. More research is needed examining efficacy and outcomes.

# ***ATICUS: Application to Improve Corticosteroid Use in Pediatric Atopic Dermatitis Survey***

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Abstract:

Topical corticosteroids are a first-line treatment for pediatric atopic dermatitis (AD). Determining the appropriate amount for a child's affected body surface area (BSA) poses challenges. Caregivers often express uncertainty and concerns about topical steroid overuse and this is compounded by vague medical guidance and fluctuating BSA in young children. Providers may lack familiarity with straightforward and practical methods to recommend to caregivers for estimating the appropriate medication quantities, a challenge exacerbated by time constraints during busy clinical sessions.<sup>4</sup>The "fingertip unit" (FTU) offers a practical way to estimate required medication for AD treatment by equating the amount of medication dispensed to the length of one fingertip as an adequate treatment of areas of skin equivalent to the size of two adult hands.

This project aims to evaluate the validity and usefulness of a website developed utilizing the FTU methodology to assist caregivers and healthcare providers in estimating the appropriate quantity of topical steroids for a child's affected skin. Caregivers are prompted to input patient age, height, and weight, and to identify affected areas through an interactive mapping feature. The program then recommends the appropriate medication quantity in both FTUs and grams. A Qualtrics survey will assess participants' estimation accuracy before and after website use, with the ultimate goal of establishing the website as a valuable resource for caregivers and medical providers. This initiative aims to enhance treatment outcomes by ensuring ease of understanding and practicality for all users. We anticipate presentation of survey data at the time of the symposium.



# ***Survival in Symptomatic Tetralogy of Fallot Neonates with 22q11 Deletion Syndrome, Trisomy 21, and Other Genetic Syndromes***

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## **Abstract:**

**Objectives:** Neonates with symptomatic tetralogy of Fallot (sTOF) frequently have genetic abnormalities that may influence outcomes. We hypothesized that survival would be superior for sTOF patients without a genetic abnormality but would differ between genetic sub-types.

**Methods:** A multi-center retrospective cohort study of sTOF patients from 2005-2017 was performed at the 9 centers of the Congenital Cardiac Research Collaborative. Patients were categorized into 4 groups: normal genetics, 22q11 deletion syndrome (DiGeorge), trisomy 21 or "Other". The primary outcome was transplant-free survival. A multi-variable analysis was adjusted for prematurity, repair strategy (staged vs. primary repair), center, anatomic diagnosis (pulmonary atresia vs stenosis), and invasive ventilation pre-intervention.

**Results:** Among 572 neonates with sTOF, 151 (26%) had an identifiable genetic syndrome, including 22q11 deletion (n = 63, 42%), trisomy 21 (n = 28, 19%) and "Other" syndromes (n=60, 40%). Patients with 22q11 deletion more frequently underwent a staged repair strategy, otherwise patients with normal and abnormal genetics had similar baseline demographic and pre-operative characteristics. Unadjusted analysis at a median follow-up of 4.8 years demonstrated a survival advantage in patients without identified genetic abnormalities (p = 0.02). After adjustment, there was no demonstrable difference in mortality between the 3 groups with genetic abnormalities (Figure 1). Secondary end-points are displayed in Tables 1 and 2.

**Conclusions:** In neonates with sTOF, survival was not significantly different between non-syndromic and three major sub-types of syndromic patients. However, patients with abnormal genetics had longer hospital stays and were more likely discharged with tube feeds.

# ***Evaluation of Patient Outcomes Following Implementation of Enhanced Recovery After Surgery (ERAS) in Adolescents Undergoing Laparoscopic Sleeve Gastrectomy***

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## **Abstract**

**Objectives:** Enhanced recovery after surgery (ERAS) protocols are evidence-based, multimodal approaches to optimize patient recovery and minimize complications. Our team evaluated clinical outcomes following the implementation of an ERAS protocol for adolescents undergoing bariatric surgery.

**Methods:** We performed a single-institution retrospective review of adolescents who underwent laparoscopic sleeve gastrectomy between August 2021 and November 2022. Unpaired t-tests and Fisher's exact test were used to compare means between groups and categorical factors.

**Results:** 43 patients were included in the study, 21 who participated in the ERAS protocol and 22 control patients. ERAS cohort was 52% female, with a mean age of 17.1 years and a mean body mass index (BMI) of 44.5 kg/m<sup>2</sup>. The non-ERAS cohort was 59% female, with a mean age of 16.2 years and a mean BMI of 45.0 kg/m<sup>2</sup>. There were no significant differences between baseline characteristics. Patients in the ERAS group had a shorter time to oral intake (10.7 hours vs. 21.5 hours,  $p < 0.01$ ), lower morphine milligram equivalents (13.0 vs. 26.7,  $p = 0.01$ ), and shorter length of stay (1.5 days vs. 2.0 days,  $p = 0.01$ ). There were no significant differences between return visits to the emergency department (ED) within 30 days (3 vs. 2,  $p = 0.66$ ) or readmissions (0 vs. 0,  $p = 1.0$ ).

**Conclusion:** The described ERAS protocol is safe and effective in adolescents undergoing laparoscopic sleeve gastrectomy and is associated with shorter time to oral intake, reduced opioid requirements, and shorter hospital lengths of stay with no increase in return ED visits or readmissions.

# ***Developing accessible patient educational materials for children and their families undergoing stem cell transplantation***

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**Abstract:**

**Objectives:** Hematopoietic stem cell transplantation (HSCT) is increasingly used for pediatric patients with hematologic and oncologic conditions. While HSCT can be curative, it is a considerable commitment for the child, family, and healthcare system. Thus, patient education is important. Our children's hospital serves a diverse population, many of whom have risk factors for limited health literacy, which can impact health outcomes and quality of life. The aim of this project was to revise an existing handbook of HSCT educational materials (last updated 2012) to improve accessibility and usability.

**Methods:** A multidisciplinary group was convened including those with expertise in HSCT and psychology. Key stakeholders were identified and timing for input determined. Existing patient materials served as a foundation and were examined for accuracy and readability. We followed CDC and Federal Plain Language guidelines.

**Results:** The handbook incorporates medical and psychological patient education materials. It is conceptualized as a living document that is personalized for each child/family. It incorporates easy to read information, medical illustrations, and photographs of commonly visited areas of the hospital. Quotes from former patients/caregivers collected from qualitative studies are included.

**Conclusions:** The initial handbook is a promising patient education tool that includes the expertise of specialists and follows principles of clear and simple communication. Next steps for this handbook include conducting interviews with parent-caregiver dyads for feedback, revising the materials, and disseminating the handbook to practitioners to provide to families. In the future, we plan to culturally adapt and translate the handbook

# ***De novo truncation mutants in IRF8 associated with mild natural killer cell deficiency***

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Abstract:

IRF8 is a transcription factor that is important for B cell, NK cell, and myeloid cell function. IRF8 deficiency leads to susceptibility to mycobacterial disease in a dominant inheritance pattern and recessive mutations can lead to monocyte and dendritic cell deficiency and/or NK cell deficiency (NKD). Here using next generation sequencing on our cohort of NKD patients we identify de novo truncating variants at the C-terminal region of IRF8 in two female adults with chronic EBV infection, decreased NK cell frequencies, and impaired NK cell cytotoxic function.

Association of C terminal-truncation variants are also observed in B cell lymphomas, suggesting a possible gain-of-function (GOF). How GOF leads to NKD remains to be elucidated, nevertheless our preliminary data using YTS cell lines suggest the defect associated to the C-terminal truncations in NK is not functional but rather a developmental defect. In conclusion, our data suggest that the C-terminal region of IRF8 is important to modulate the proteasomal degradation of IRF8 and that in its absence, the up-regulation of the protein is deleterious for the proper NK cell maturation.

# ***Transition of Care in Adolescents with Epidermolysis Bullosa: The Provider Perspective***

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**Abstract:**

**Objectives:** The characteristics of Epidermolysis Bullosa (EB) demand higher than average provider support for transition from pediatric to adult care. Our objective was to examine existing barriers from the providers' perspective of their current practices for a more complete understanding of how to improve the transition process.

**Methods:** We administered an online Qualtrics survey to members of the Epidermolysis Bullosa Clinical Research Consortium, a group of providers who care for patients with EB.

**Results:** Sixteen of twenty-four EBCRC participants completed the survey, with a response rate of 67%. Six of sixteen (38%) respondents reported having a formal TOC program, 5 of which (83%) were supported at the institutional, rather than departmental, level. All 6 TOC programs

had a social worker and a dermatologist as key members of their TOC team. Five of the six (83%) providers with a formal TOC program reported difficulty finding a receiving provider.

Ten of sixteen (63%) respondents reported that they did not have a formal TOC program, however, seven of those ten (70%) reported utilizing some kind of informal transition effort. The majority of providers (7/10, 70%) reported their patients could benefit from a formal transition program.

**Conclusion:** Our findings support the need for a team-based approach and, in particular, identification of adult providers to participate in the transition of patients with EB to achieve improved quality of care during this often challenging time. Increasing understanding of the current landscape of both patient and provider perspectives provides foundational information for the development and implementation of future TOC programs.

# ***Gastrointestinal Endoscopic Electroincision Therapy for Children***

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## **Abstract:**

**Background:** Anastomotic strictures can be successfully treated by endoscopic balloon dilation (EBD); however, the emerging modality of stricturotomy with electroincision therapy (EIT) and strictureplasty (stricturotomy followed by endoscopic clipping) may achieve superior outcomes. Endoscopic stricturotomy has been shown to have greater efficacy than EBD in adult patients with IBD. While the rate of perforation is lower in EIT as compared to EBD in IBD, stricturotomy has a 4-10% rate of delayed bleeding, with a smaller proportion requiring blood transfusion. EIT can delay the need for surgical intervention and in many circumstances obviate the need indefinitely. This study is to describe the use of EIT for luminal strictures in children.

**Methods:** Retrospective cohort study of 10 pediatric patients (including 18 procedures) with anastomotic and primary luminal stricture who underwent endoscopic EIT with stricturotomy or strictureplasty. Outcomes and complications were documented.

**Results:** Among 18 performed, 14 stricturotomy and 4 strictureplasty, 2 patients did not require further intervention and had no stricture recurrence at time of follow-up. 3 patients required repeat stricture therapy but the time duration between interventions, previously EBD, extended. There were 2 procedural complications, tension pneumoperitoneum managed by needle decompression and microperforation, neither of which required surgical repair or resection. There were no episodes of GI bleeding.

**Conclusion:** EIT for luminal stricture in children may offer an alternative to EBD or surgical resection and re-anastomosis. The relative risk in children remains to be delineated.

# ***Cell therapy in regionally conditioned rat lung in vivo as novel therapeutical approach for chILD treatment***

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## **Abstract:**

**Objectives:** Childhood interstitial lung disease (chILD) resulting from defective surfactant protein genes poses a significant challenge, leaving lung transplantation, hampered by severe organ shortage, as the only definitive treatment. This study explores cell therapy as alternative but facing two challenges: removing damaged epithelial cells while preserving lung architecture and selecting suitable cells for treatment. In an ex vivo rodent model, we successfully addressed the first challenge, employing a detergent to remove epithelial cells while preserving the surrounding lung structure. Human pluripotent stem cell-derived lung epithelial progenitors (DLEPs) generated from lung organoids represent a potential candidate for the second challenge.

**Hypothesis:** In vivo regional de-epithelization of rat lung will create a favorable environment for engraftment, differentiation of transplanted DLEPs and potentially lung repair.

**Methods:** To assess the therapeutic potential of DLEPs, a xenogeneic model was established in pharmacologically immunosuppressed rats. Locoregional de-epithelialization targeted 20% of the left lobe, followed by a delivery of 106 DLEPs after inhibiting endogenous repair.

**Results:** The analysis at 48 hours post-injury validated the de-epithelization in vivo (n=21), while evaluation at 10 days post-engraftment (n=18) showed successful engraftment of DLEPs contributing to both rat alveolar epithelial cells and formation of 'KRT5-pods', demonstrated to be involved in distal lung repair. Importantly, engrafted DLEPs prevented regional lung injury induced by the conditioning regimen in the transplanted regions.

**Conclusions:** This approach provides an animal model for understanding lung regeneration and repair by human lung progenitors, essential for preclinical development of cell therapy to treat lung injury and disease in humans

# ***Thermostable measles fusion glycoprotein as a new vaccine strategy***

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**Abstract:**

Measles (MeV) causes disease worldwide despite efforts towards eradication by vaccine, primarily because it is readily spread between people. Acute MeV infection causes immune amnesia, increasing susceptibility to other infectious diseases. In addition, rare but severe neurological complications can develop several years after measles due to persistent MeV infection of the central nervous system. People with impaired cellular immunity are at increased risk of developing severe measles but often cannot be vaccinated since the vaccine virus itself can

lead to fatal illness. There is no specific therapy for acute or persistent MeV manifestations. A successful vaccination campaign could have eradicated MeV more than 20 years ago. As of today, eradication is not in sight, and the resurgence of measles highlights the need for a vaccination strategy that is safe for immune-compromised people and easy to be delivered around the world without the need for a cold chain. We have designed a thermostable measles fusion protein. We have obtained structural data showing that our stabilized MeV F is in the expected pre-fusion state. We present here data that immunization with our stabilized MeV F induces protective immunity and neutralizing antibodies in vivo.



# ***Evaluating the Impact of a Novel Beta Actin Variant as Cause of a functional Natural Killer Cell Deficiency***

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**Abstract:**

Natural killer (NK) cell deficiency (NKD) occurs when an individual's major clinical immunodeficiency derives from abnormal NK cells and is associated with several genetic etiologies. Three categories of  $\beta$  actin-related diseases with over 60 ACTB variants have previously been identified, none with a distinct NK cell phenotype. An individual with mild developmental delay, macrothrombocytopenia, susceptibility to infections, molluscum, and EBV-associated lymphoma had functional NK cell deficiency for over a decade. A de novo ACTB variant encoding G342D  $\beta$  actin was identified and was consistent with the individual's developmental and platelet phenotype. This novel variant also was found to have direct impact in NK cells, as its expression in YTS (YTS-NKD) cells caused increased cell spreading in lytic immune synapses created on activating surfaces. YTS-NKD cells were able to degranulate and perform cytotoxicity, but demonstrated defective serial killing owing to prolonged conjugation to the killed target cell and thus were effectively unable to terminate lytic synapses. G342D  $\beta$  actin results in a novel mechanism of functional NKD via increased synaptic spreading and defective lytic synapse termination with resulting impaired serial killing leading to overall reductions in NK cell cytotoxicity.

# ***Tissue-specific X-Chromosome Inactivation Skewing Affects iPSC Reprogramming In HNRNPH2-Related Neurodevelopmental Disorder***

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Abstract:

**Objectives:** The ultra-rare, X-linked HNRNPH2-Related Neurodevelopmental Disorder (HNRNPH2-RNDD) is due to de novo pathogenic missense variants in HNRNPH2, a gene encoding for an RNA-binding protein. Symptoms include developmental delay, intellectual disability, severe language impairment, autistic behaviors, motor disturbances, and limited independence. We are modeling this disorder using patient-specific induced pluripotent stem cells (iPSCs) to identify pathogenic mechanisms and develop precision medicine therapeutics.

X-chromosome inactivation (XCI) is an epigenetic modifier for dosage compensation of X-linked genes in females. It is unclear if different tissues maintain similar or skewed XCI ratios. Different tissue skewing patterns may have consequences on the choice of donor tissue for reprogramming.

**Methods:** We investigated XCI patterns in the Androgen Receptor locus in female HNRNPH2-RNDD probands in blood, buccal tissue and skin fibroblasts (Sanger sequencing). PBMCs and fibroblasts were reprogrammed using Sendai virus, iPSC characterized and evaluated for wild type and variant allele expression (allele-specific qPCR).

**Results:** XCI skewing was detected, with ~85% of probands' blood (n=41) highly or highly/moderately skewed towards wild-type allele expression. The majority of probands displayed a random or randomly/moderately skewing pattern in buccal tissue (n=44) as well as in fibroblasts (n=7). We found that blood is a poor donor tissue for iPSC derivation in this disorder, with no variant allele expression in blood-derived iPSCs, while fibroblast-derived iPSCs expressed the pathogenic variant.

**Conclusions:** To our knowledge, we generated the first patient-specific female-derived iPSCs expressing the most common HNRNPH2-RNDD variant. XCI skewing and tissue source may be critical for iPSC reprogramming in some X-linked disorders.

# ***Initiating mental health screening for caregivers of patients attending the Columbia Neonatal Growth and Development (GraD) Clinic***

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## **Abstract:**

**Objective:** The Growth and Development (GraD) clinic follows children who were in the neonatal intensive care unit (NICU). Families whose infant was in the NICU are 20-30% more likely to experience perinatal mood and anxiety disorders (PMADs). In GraD clinic, there was no formal mental health screening process. The goal was to screen 100% of primary caregivers attending appointments in 2023.

**Methods:** The Patient Health Questionnaire-9 (PHQ-9) was chosen to allow the same screening tool to be administered at all appointments and to provide continuity from our inpatient NICU and with our ACN clinics. A workflow was established based on the cut-off scores, ranging from no depression to severe depression. Initially, screening was performed for caregivers at the earliest visit on paper. After 4 months, the screening was expanded to all visits. After 7 months, the PHQ-9 was sent to caregivers in Epic before their appointment. If it is not filled out in Epic, it is administered on paper at their appointment. The results and action taken are documented in the visit note.

**Results:** As of August 2023, 85% of caregivers were screened and 15% were missed. Eight percent have been positive. Out of the positives, 60% in the mild depression range, 28% in the moderate depression range and 12% in the severe depression range. Current limitations include caregivers not completing the PHQ-9 on paper if not completed in Epic due to limited time and virtual visits.

**Conclusion:** Putting routine screening practice in place enabled 85% of caregivers to be screened for PMADs. Of those, 8% were positive

# ***Identification of Doubly-polyunsaturated Phosphatidylethanolamines as Essential Initiating Substrates of 15-Lipoxygenase for Biosynthesis of Ferroptotic Hydroperoxy-Signals***

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Abstract:

Ferroptosis is a regulated cell death program in which generation of hydroperoxy-polyunsaturated fatty acid containing phospholipids (HOO-PUFA-PL) occurs due to insufficiency of glutathione peroxidase/glutathione system. While sn2-HOO-PUFA-phosphatidylethanolamines (HOO-PUFA-PE) were identified as biomarkers of ferroptosis generated by 15-lipoxygenases (15LOX), there are several unresolved inconsistencies cloudifying the mechanisms of phospholipid peroxidation in ferroptosis. Among them is the strong dependence of the ferroptotic outcome on the contents of arachidonoyl-PE as the substrate provided by long chain acyl-CoA synthetase 4-driven (ACSL4) reaction. Paradoxically,

complete execution of ferroptosis occurs well before exhaustion of arachidonoyl-PE substrates. We reasoned that there are yet unrecognized limiting factors acting as true substrates initiating 15LOX-catalyzed formation of HOO-PUFA-PE. We hypothesized that very low-abundance doubly-sn1/sn2-PUFA-PE species are in fact the real peroxidation-initiating factors. By using biochemical, cell biology, computational, and redox lipidomics protocols, we discovered that doubly-PUFA-PEs are oxidized by 15LOX at strikingly higher (by > an order of magnitude) rates than mono-PUFA-PEs. Our computational studies revealed that this is due to absence of non-productive enzyme-substrate complexes with 15LOX in which non-oxidizable saturated/monounsaturated fatty acyls of PE are positioned in the proximity of catalytic iron. We further established that 15LOX-catalyzed peroxidation of doubly-PUFA-PEs occurs preferably at earlier stages of ferroptosis in several different cell types. Notably, elevated levels of doubly-PUFA-PEs and increased sensitivity to ferroptosis were observed in wild-type cells, but not in ACSL4-deficient cells thus explaining the ACSL4-paradox of ferroptosis. The identified doubly-PUFA-PE phospholipid peroxidation substrates represent new therapeutic targets in many disease conditions whose pathogenesis is associated with ferroptosis.

# ***Patient derived iPSC-based modeling of GINS4 deficiency reveals NK cell specific replication stress and increased apoptosis leading to NK cell deficiency***

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Abstract:

Cell proliferation is a ubiquitous process required for organismal development and homeostasis. However, individuals with partial loss-of-function variants in DNA replicative helicase components, including MCM and GINS proteins, often present primarily with immunodeficiency due to specific loss of natural killer (NK) cell immune subsets. Such lineage-specific disease phenotypes suggest cell type-specific characteristics of cell cycle and proliferation and raise important questions about the regulation of helicase function and cellular responses to its impairment. We aimed to understand NK cell-specific proliferative dynamics and vulnerability to impaired helicase function using iPSCs from individuals with NK cell deficiency (NKD) due to compound heterozygous GINS4 variants. In the 42-day process of NK cell differentiation from iPSCs, we observed the emergence of CD34<sup>+</sup> hematopoietic and endothelial progenitors on day 6, granulocytes and monocytes on days 14 and 21, and NK cells emerging primarily on day 28. In

this process, we defined two primary waves of cell proliferation, one on day 6 in the CD34<sup>+</sup> precursors and one on day 28 in the committed NK cell precursors. GINS4 protein expression was high in pluripotency and CD34<sup>+</sup> progenitors but decreased significantly with differentiation. In the patient-derived NKD lines, GINS4 protein expression was lower relative to controls at all time points, and the most significant difference was observed on day 6, prior to the emergence of the NK lineage cells on day 28. Interestingly, on day 28, we observed a higher frequency of NK progenitors from the NKD line in G2/M phase of cell cycle accompanied by increased apoptosis. Further investigation identified upregulation of apoptosis-related genes following commitment of cells to the NK cell lineage.

Ultimately, impaired cell cycle progression coupled with an NK cell specific sensitivity to apoptosis led to a lower frequency of mature NK cells in the NKD lines, recapitulating the clinical phenotype. Other lineages, including granulocytes and T cells, were unaffected, underscoring the specific vulnerability of NK cells. Together, our results demonstrate that maturing NK cells have a lower threshold for apoptosis than other lineages and replication stress results in apoptosis of NK precursors, leading to NKD.

# ***Female mice with low nephron endowment are more sensitive to salt-induced hypertension than males revealing sex dimorphisms***

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Abstract:

**Background:** Humans born preterm have low nephron endowment and an increased risk for hypertension (HTN), yet the pathogenesis of HTN due to nephron deficits is poorly understood.

**Objective:** To test the hypothesis that nephron deficits are an independent risk factor for HTN and that salt intake modifies this response using a new mouse model of congenitally low nephron number (40-60% nephron reduction, named RetUB del mice, Good et al, JCI Insight, 2023).

**Methods:** Male and female control and RetUB del mice (9-10m old) had continuous systolic and diastolic blood pressure (SBP and DBP) monitoring for 72h using radiotelemetric methods. Mice were fed high salt chow (8% NaCl) for 10d before another 72h of BP measurements. We collected blood, urine, and kidneys at the end of the study and analyzed BP with mixed effects models.

**Results:** In females at baseline, control and RetUB del mice had no significant differences in SBP, DBP, or mean arterial pressure (MAP) (n=4 per group). High salt intake resulted in insignificant increases in SBP, DBP and MAP in both groups, but the rise in SBP was significantly greater (excess of 5.8 mmHg, p<0.001) in RetUB del vs. controls. Similarly, rises in DBP (excess of 4.7 mmHg) and MAP (excess of 5.2 mmHg) were significantly greater in RetUB del vs. controls (p<0.001). Both groups had normal serum creatinine (Cr), blood urea nitrogen (BUN), hematocrits (Hct), sodium (Na), fractional excretion of sodium (FeNa), and urine Na:Cr. Similarly, in males at baseline, RetUB del and control mice had no significant differences in SBP, DBP or MAP (n=4-6 per group). High salt intake also resulted in insignificant increases in SBP, DBP and MAP in both groups. Although rises in SBP were similar, there was a significantly greater rise in DBP (excess of 2.0 mmHg) and MAP (excess of 0.8 mmHg) in RetUB del vs. controls (p<0.01). RetUB del males had higher serum Cr, BUN, FeNa and urine Na:Cr, while serum Na and Hct were similar to controls. Morphologically, RetUB del females had focal CKD whereas males showed more widespread CKD changes.

**Conclusion:** RetUB del mice did not have HTN under basal conditions, yet high salt intake caused a greater rise in BP in females. This response is independent of renal function and unlikely attributable to pathological changes of CKD given that males had a more severe CKD phenotype yet less of a rise in BP. Our results reveal sex dimorphisms in salt response and emphasize the need for lifestyle modifications in humans born preterm. Further studies will focus on mechanisms of sex dimorphisms in HTN.

# ***Impact on Patient Adherence and Post-Transplant outcomes with the introduction of Medication Blister-Packing***

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Abstract:

**Introduction:** One of the major barriers to medication adherence is the number of medications pediatric heart transplant patients are required to take. Medication non-adherence leads to transplant organ rejection, resulting in lengthy hospitalizations and tremendous burdens on healthcare systems due to costs associated with rejection treatment. Blister packing is one way to improve adherence to the medication schedules.

**Methods:** We will examine a patient's date of blister-packaging initiation and determine if this intervention helps maintain therapeutic drug levels. We will also evaluate the rates of admissions due to rejection treatment and trend immunosuppression trough levels leading up to hospitalizations for rejection treatment. Using statistical analyses, MLVI will be calculated as the standard deviation of a set of at least three tacrolimus trough blood levels for each patient observed.

**Results:** One limitation of this intervention is the small cohort of patients currently enrolled in medication blister-packaging. Another limitation is a patient selection bias relating to the assumption that the patients enrolled include those who do not require frequent titrations of medication dosages for immunosuppression.

**Conclusion:** The overwhelming medication burden for pediatric heart transplant patients can perpetuate the cycle of medication non-adherence. Therefore, it is imperative for transplant programs to adopt interventions that have shown promise related to increasing medication adherence. The simplicity of weekly blister-packaging has shown to be effective in helping patients better manage their medication regimen compared to taking pills directly from the bottle or filling up pill boxes.

# ***Broad-spectrum inhibition of human coronaviruses by lipopeptides derived from the C-terminal heptad repeat of SARS-CoV-2***

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## **Abstract:**

Prior to the outbreak of SARS-CoV-2, human coronaviruses were already distributed globally and caused 15-29% of all common colds. Although there is limited serological cross-reactivity between strains, rationally designed treatments targeting conserved viral mechanisms may confer broad-spectrum inhibitory activity. We previously demonstrated that daily prophylactic intranasal lipopeptides derived from the C-terminal heptad repeat of SARS-CoV-2 completely prevent ferret-to-ferret transmission of SARS-CoV-2. The lipopeptides also inhibit SARS-CoV-2, SARS-CoV-1, and MERS-CoV infection in vitro and cell-to-cell fusion mediated by the respective spike proteins. Here we assessed the ability of these lipopeptides to inhibit the growth of common human coronaviruses (HCoVs), e.g. HCoV-229E, in primary human airway epithelial (HAE) cells grown at an air-liquid interface. Treatment with lipopeptides significantly reduced virus production in HAE cultures infected with common HCoVs. The broad-spectrum inhibition of human coronaviruses by SARS-CoV-2 HRC derived lipopeptides highlights potential applications of the compounds for inhibiting common HCoVs and supports assessing their antiviral efficacy on newly emergent strains.



# ***Proteases required for primary infection and propagation of human parainfluenza virus 3 bearing the fusion protein cleavage motif of clinical isolates***

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Abstract:

Entry by human parainfluenza virus 3 (HPIV3) into a target cell is dependent on highly specialized viral fusion machinery that has been honed by evolution to have a balance of receptor binding affinity, membrane fusion activation, and neuraminidase driven release of virus, that favor spread within and between hosts. The regulatory contributions of host factors necessary for the activation of viral proteins remain undefined yet are key for host and tissue tropism and pathogenesis. HPIV3 infection is driven by the coordinated action of viral surface glycoproteins hemagglutinin-neuraminidase (HN) and fusion protein (F). Upon HN binding to sialic acid bearing proteins on the target cell, HN triggers F to insert into the target cell membrane and drive virion-cell membrane fusion. To facilitate fusion, the fusion protein precursor (F0) must first be cleaved by host proteases into its active form, composed of the disulfide-linked subunits F1 and F2. F0 cleavage has been thought to be executed during viral glycoprotein transit through the trans-Golgi network by the ubiquitously expressed furin, because F0 contains a dibasic cleavage site. However, our laboratory found that the dibasic cleavage site underlying the assumption is an artifact of laboratory adaptation, whereas circulating strains of HPIV3 have a monobasic cleavage site that is cut by an unidentified protease. As a consequence, furin-cleaved laboratory adapted strains promiscuously infect hosts and cell types, but authentic clinical viruses exhibit tight tropism for human lung. To study viral tropism, we sought to identify the protease responsible for authentic F0 cleavage in vivo. We assessed protein expression in tissues and cell culture models that support the growth of authentic HPIV3 to identify candidate proteases that may process HPIV3 F in vivo. Gain-of-function experiments revealed candidate proteases that are sufficient to cleave F0 and produce infectious virions. The preliminary data suggest that F0 protein cleavage may occur at the cell surface facilitated by transmembrane proteases, in distinction to the previous notion of F0 processing by furin in the trans-Golgi network. These preliminary findings support an alternative mechanism of F activation in vivo, reliant on host factors expressed in a narrower subset of cells. Understanding how F is processed in the human lung is important for understanding viral tropism and host factors involved in regulating infection.

# ***Intrauterine Exposure to Environmental Endocrine Disrupting Chemicals and Risk of Hypospadias***

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Abstract:

**Background:** Hypospadias is a common congenital malformation; the etiology is largely unknown. Hypospadias may be caused by a disruption of hormone signaling during embryonic development. Endocrine disrupting chemicals (EDCs) are exogenous substances that cross the placenta and can interfere with hormone synthesis and metabolism. Meconium begins accumulating at 13 weeks gestation, allowing for insight into early intrauterine exposure. Ano-genital distance (AGD) is a marker of androgen exposure; lower androgen levels are associated with shorter AGD.

**Objective:** To determine whether intrauterine exposure to EDCs is associated with a higher rate of hypospadias.

**Methods:** This is a multi-center case-control study of full term ( $\geq 37$  weeks) infant males with and without hypospadias. Placement of urethral opening, stretched penile length (SPL), AGD, locations of testes, and any other genitourinary (GU) abnormalities were determined by physical exam. Family history and potential environmental exposures during pregnancy was obtained via survey. Meconium was collected from diapers on day 1 of life and tested for concentrations of bisphenol-A (BPA), bisphenol-S (BPS), and bisphenol-F (BPF).

**Results:** BPA, BPS, and BPF were detectable in approximately 30% of meconium samples. Concentrations of BPA were higher in cases versus controls, though this difference was n.s. Higher BPA was associated with shorter AGD and SPL.

**Conclusions:** BPA, BPS, and BPF concentrations are detected in meconium using this novel lab procedure. Our data suggests an emerging pattern of higher BPA in cases of hypospadias compared to controls, though not statistically significant. Higher levels of BPA were associated with smaller SPL and AGD, two measures that are sensitive to hormone exposure.

# ***Real-World Pediatric Outcomes of Hybrid Closed-Loop systems at a Large Urban Academic Center***

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Abstract:

**Background:** Hybrid closed-loop (HCL) technology is increasingly utilized in the management of pediatric patients with type 1 diabetes (T1D). HCL systems use continuous glucose monitoring (CGM) to adjust insulin doses to keep blood glucose within a target range of 70-180 mg/dL and avoid diabetes complications. Previous real-world studies of HCL users have shown improvement of TIR, however these studies largely represent early technology adopters and lack patients from underrepresented minorities.

**Objective:** To study the impact of two new HCL devices on glycemic control indices and quality of life (QOL) in pediatric patients with T1D at a large urban diabetes center.

**Methods:** Participants aged 2-20 years with T1D of at least one year duration were recruited at the time of initiation of t:slim x2(TS) or Omnipod5 (O5). Glycosylated hemoglobin (HbA1c) and TIR were collected at baseline and 3, 6, and 12 months. Two surveys (Diabetes Distress Scale and Insulin Device Satisfaction survey) were administered pre- and post-initiation of the HCL system.

**Results:** For all participants using HCL, TIR improved by 8% after 3 months ( $p < 0.001$ ) and 7% at 6 months ( $P < 0.001$ ) while time with glucose  $< 70$  mg/dL and  $< 55$  mg/dL were unchanged after 3 and 6 months. HbA1c improved from 7.2% to 6.9% at 3 months and 6.8% by 6 months of use ( $p < 0.001$ ).

**Conclusions:** In this real-world study, HCL systems improved TIR and HbA1c at 3 and 6 months without significant change in hypoglycemia. Additional enrollment and data collection, including QOL questionnaires and 12-month data, are ongoing.

# ***Mapping the proteome of the NK cell Immunological synapse***

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## **Abstract:**

NK cells are innate immune cells that provide protection against virally compromised or transformed cells. Direct killing occurs through the release of lytic granules onto the target cell at the Immunological Synapse (IS). The IS is a unique structure formed at the site of contact between the immune and target cell. While some key components regulating the dynamics of the IS have been identified, its complete composition remains unknown. To identify new molecular components mobilized on the NK cell side of the IS during cytotoxic activity, we developed a method to extract and purify the portion of the NK cell cortex engaged in the IS. To attest to the specificity and efficacy of our purification approach we assessed our lysates for a series of known markers for the IS. Additionally, by immunofluorescence we observed that actin was maintained as a patch on the beads following sonication of the whole cell. The fingerprint left behind by the effector cell on the bead suggests that the architecture of the IS was preserved by our extraction protocol, increasing the probability of purifying intact actin cortices. Having validated our approach, future experiments will focus on proteomic analysis of the “Immune Synapsome”. The IS will be compared between activated (ligation of CD18 and NKp30) and tethered-only NK cell conditions (ligation of CD18 only). This approach enables identification of new proteins essential to the formation of the immune synapse of NK cells, opening the path to uncover novel key regulators of NK cell cytotoxic function

# ***Fumarate metabolism is an unexpected factor in the success of Staphylococcus aureus as a pulmonary pathogen***

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**Abstract:**

**Rationale:** *S. aureus* is a major cause of healthcare-associated pneumonias. Within the lung, there is substantial selective pressure for *S. aureus* variants optimized to persist within the inflammatory milieu, which consists of phagocytes and cytokines, but also immunometabolites. We hypothesize that the metabolite fumarate generated by host cells exerts a strong selective pressure on *S. aureus* which drives adaptive processes for survival.

**Methods:** The impact of *S. aureus* fumarate regulation via *fumC* expression was examined using a murine model of MRSA pneumonia. We assessed the transcriptional effects of fumarate on *S. aureus* by RNA-Seq and the importance of fumarate regulation on bacterial metabolic fitness using phenotype microarrays.

**Results:** Fumarate is highly abundant in the lungs of cystic fibrosis (CF) patients chronically infected with *S. aureus*. Using a mouse model of MRSA pneumonia, we show that a *S. aureus* USA300 mutant lacking the ability to degrade fumarate (*DfumC*) was attenuated compared to the WT strain despite stimulating a similar immune response. The lower *DfumC* burden was observed in both BL/6 mice and the *Ptenl*<sup>-/-</sup> background, a model of heightened inflammation whereby fumarate accumulates in the lungs. This suggested that the ability of *S. aureus* to persist in the lung is dependent upon

its ability to metabolize fumarate. Our survey of published staphylococcal genomes from clinical isolates confirmed that *fumC* is exceptionally highly conserved and upregulated in CF isolates worldwide.

**Conclusions:** We show that fumarate imposes a strong selective pressure on *S. aureus*, driving *fumC* conservation to regulate the increasing amounts of airway fumarate. *FumC* is critical for *S. aureus* to cause chronic infection.

# ***Fibulin Genes Regulate Outflow Tract Caliber and Extracellular Matrix Integrity***

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Abstract:

Critical developmental roles for matrix molecules in proliferation and differentiation and in generating tissue structural integrity are evident by the range of clinical disorders induced by mutations in extracellular matrix (ECM) genes. In the cardiovascular system, recent data underscore the dynamic nature of ECM composition during embryogenesis. This emerging focus on the function of ECM in cardiac development and disease has advanced our understanding of the morphogenetic basis of congenital heart defects (CHD). Yet, we have limited appreciation of the cellular and biophysical mechanisms regulated by individual ECM proteins during formation of the cardiac outflow tract (OFT). Our data reveal that Fibulin molecules, a family of glycoproteins that regulate cell behaviors and structural contributions to the ECM, have previously unrecognized requirements in establishing the proper dimensions of the vertebrate OFT. Zebrafish fibulin mutants also exhibit decreased TGF- $\beta$  signaling in second heart field (SHF) progenitors of the linear heart tube. Consequently, fibulin-deficient SHF progenitors supply fewer endothelial and smooth muscle cells, resulting in a narrower arterial pole. In addition to effects on SHF progenitor differentiation, we find that deposition of Elastin, a crucial ECM component of the OFT, is impaired as evidenced by decreased expression, fiber number and alignment in fibulin mutant embryos. Importantly, tissue stiffness of the OFT auxiliary chamber is impaired by disrupted ECM integrity and these factors govern biomechanical function. Our insights will yield valuable strategies to improve engineered biomaterials for surgical intervention in congenital OFT anomalies and will fuel further identification of novel disease genes in CHD.

# ***Assessment of management and outcomes of afebrile neonates who received a pediatric dermatology consultation for pustules and/or vesicles***

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## **Abstract:**

**Objectives:** To assess the management and outcomes of afebrile neonates who received a pediatric dermatology consultation for pustules and/or vesicles.

**Methods:** Medical records were reviewed for all neonates who received a pediatric dermatology consult across 6 academic institutions between September 1, 2013 and August 31, 2019 to identify those neonates with pustules and/or vesicles.

**Results:** Of the 879 consults, 183 afebrile neonates presented with pustules and/or vesicles. No cerebrospinal fluid cultures or blood cultures were positive for bacteria. No concordant positive urine cultures were identified in neonates with cutaneous infection. Nine infants were diagnosed with herpes simplex virus (HSV). Five preterm infants were diagnosed with angioinvasive fungal infections.

**Conclusion:** No serious bacterial infections (SBIs) attributable to a skin source were identified, yet 53% of these infants received parenteral antibiotics. HSV was diagnosed in 7% of this cohort, 77.8% (7/9) of whom were term infants and 22.2% (2/9) of whom were preterm. Angioinvasive fungal infection was diagnosed in 3%, all of whom (100%, 5/5) were extremely preterm at <28 weeks gestational age. These findings suggest that full-term, afebrile, well-appearing neonates presenting with pustules and/or vesicles may not require a full SBI workup. HSV testing is recommended for all infants with vesicles, grouped pustules and/or punched-out erosions. In full-term infants, the likelihood of a life-threatening etiology of isolated pustules or vesicles is low once HSV infection is excluded. In preterm infants with pustules and/or vesicles, a high index of suspicion must be maintained, and broad infectious evaluation is recommended.

# ***Paramyxovirus fusion mechanisms revealed through the perturbation of a crucial interaction site of the fusion complex***

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**Abstract:**

Human parainfluenza virus 3 (HPIV3), and paramyxoviruses generally, have two surface glycoproteins that form a complex to mediate fusion with host cells. For HPIV3, this complex consists of a receptor binding protein (hemagglutinin neuraminidase, HN) and a fusion protein (F) whose dynamic interaction allows the virus to enter at the appropriate time and location. Both glycoproteins and their interaction are essential for regulating entry, and the specific mechanism by which they interact is of great interest. One key site of interaction between HN/F, in which a loop on the HN globular head interacts with the apex of F, was elucidated by cryo-electron tomography. This site at the F apex overlaps with the binding site of a previously discovered anti-F neutralizing antibody. During HPIV3 evolution under the selective pressure of this anti-F neutralizing antibody, two mutations in F that confer resistance to neutralization independently arose. One residue is at the apex of F where the antibody binds, suggesting a direct change to the antibody binding site. The second mutation is distal to the antibody binding site and may alter antibody binding allosterically. The two discrete alterations that shift F conformation to avoid antibody neutralization have distinct functional consequences on the virus. The F mutated at the apex is less easily triggered by HN but more unstable in the absence of HN compared to parental F, suggesting altered interaction with HN. The second mutation resulted in an F that was cleaved less efficiently on viral particles and on transfected cells. This evolution of HPIV3 F in response to an antibody directed to the site of HN-F interaction in the prefusion complex suggests a central role for interaction between HN and F at the apex of F.



# ***Screening for neutralizing conformation-specific MeV F antibodies***

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**Abstract:**

Measles virus (MeV) is a highly infectious respiratory virus and a re-emerging global public health threat. Inadequate vaccine coverage, decline in herd immunity, and vulnerable populations of immune compromised people who cannot be vaccinated have created an increased need for effective interventions. Monoclonal antibodies can both act as valuable antiviral therapeutics and aid in structural and mechanistic studies of the virus. Most neutralizing antibodies against measles are against the receptor binding protein (MeV H). We aimed to elicit neutralizing monoclonal antibodies against various conformations of the measles fusion protein (MeV F). Antibodies that recognize the pre-fusion, post-fusion, or some intermediate state of MeV F may have different mechanisms of neutralization and may also aid in capturing different states of MeV F for structural analysis. We generated monoclonal antibody producing hybridomas from mice vaccinated with stabilized soluble MeV F and characterized them. We screened the antibodies for neutralization of live virus, recognition of pre-fusion and post-fusion MeV F, and mechanism of fusion inhibition using in vitro functional assays. Among neutralizing antibodies, the ones that recognize only the pre-fusion state or the pre- and post-fusion state all blocked fusion by stabilizing the F protein in an extended intermediate state after its activation. On the other hand, neutralizing antibodies that primarily recognized the post-fusion state did not block fusion in our in vitro experiment despite neutralizing live virus. Screening antibodies for conformational specificity as well as mechanism may provide a strategy for selecting or specifically eliciting the most potent neutralizing mAbs for MeV treatment or prophylaxis.