

2012

2nd Pediatric Research Retreat

Frontiers in Pediatric Science

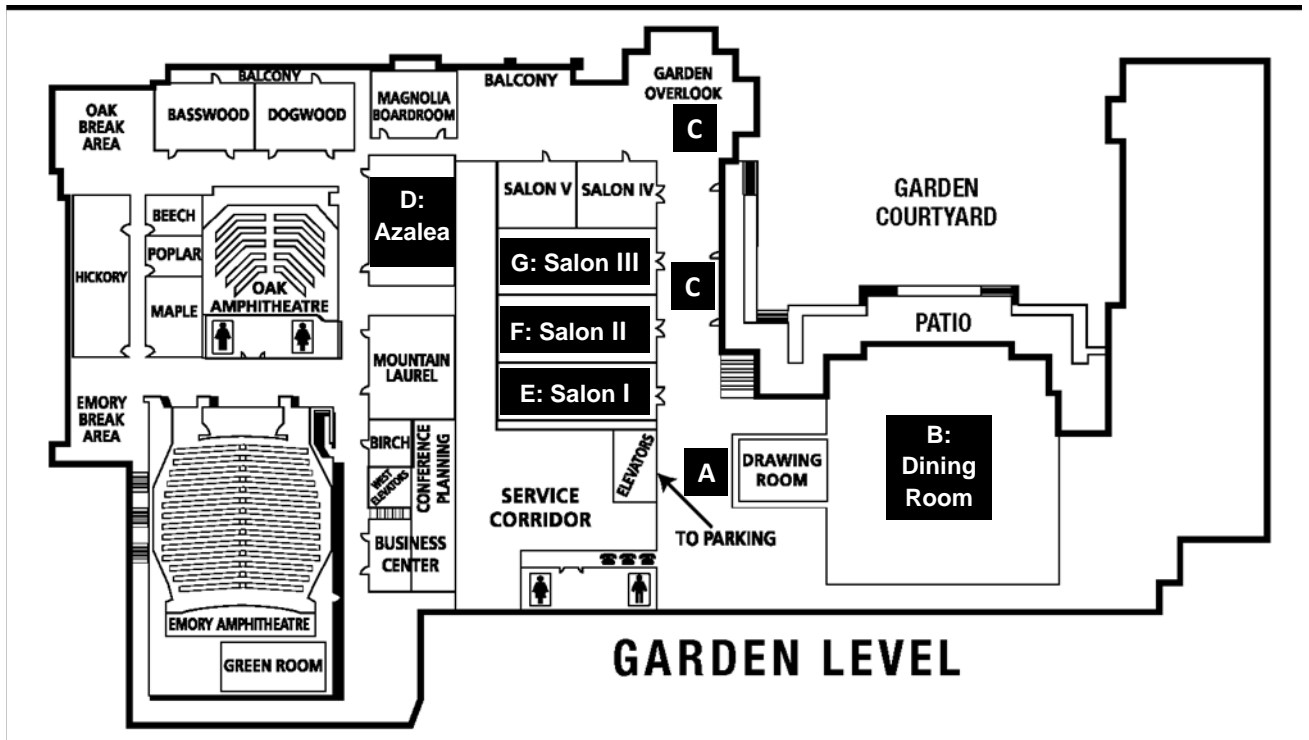
Friday, January 27, 2012

8:00 AM–5:30 PM

Emory Conference Center



Emory Conference Center Floor Plan



- A Registration and Information Desk
- B Lunch
- C Posters 1 – 45
- D Posters 46 – 99
- E Roundtables
 - Session 1: Pediatric Medical & Surgical Devices/Diagnostics
 - Session 2: IT and Informatics
- F Roundtables
 - Session 1: Medical Imaging as a Research Resource
 - Session 2: Orthopedics/Sports Medicine
- G Roundtables
 - Session 1: Environmental Exposures
 - Session 2: Cognitive Neuroscience and Disorders

Agenda

7:30 AM	REGISTRATION OPENS	
8:00 AM - 8:30 AM	Welcome	
	<p><i>Jeff Kilpatrick, Children's Healthcare of Atlanta</i> <i>Barbara Stoll, MD, Children's Healthcare of Atlanta, Emory University, and Emory-Children's Center</i> <i>Gilda Barabino, PhD and Paul Spearman, MD, Retreat Planning Committee Co-chairs</i></p>	
8:30 AM - 9:00 AM	Plenary Speaker	
	<i>Iñaki Sanz, MD, University of Rochester Medical Center</i>	
9:00 AM - 9:45 AM	Pediatric Nanomedicine	
	<p><i>Gang Bao, PhD, Georgia Institute of Technology</i> <i>Wilbur Lam, MD, PhD, Children's Healthcare of Atlanta, Emory University and Georgia Institute of Technology</i> <i>Philip Santangelo, PhD, Emory University and Georgia Institute of Technology</i></p>	
9:45 AM - 10:00 AM	Break	
10:00 AM - 10:45 AM	Poster Session 1 (Foyer, Garden Overlook, and Azalea Room)	
10:45 AM - 11:30 AM	A Systems Approach to the Pathophysiology and Treatment of Sickle Cell Disease	
	<p><i>Gilda Barabino, PhD, Emory University and Georgia Institute of Technology</i> <i>Wilbur Lam, MD, PhD, Children's Healthcare of Atlanta, Emory University and Georgia Institute of Technology</i> <i>Manu Platt, PhD, Emory University and Georgia Institute of Technology</i></p>	
11:35 AM – 1:30 PM LUNCH		Roundtable Session 1
	11:35 - 12:30	<ul style="list-style-type: none"> • Pediatric Medical & Surgical Devices/Diagnostics (Salon I) • Medical Imaging as a Research Resource (Salon II) • Environmental Exposures (Salon III)
		Roundtable Session 2
	12:35 - 1:30	<ul style="list-style-type: none"> • IT and Informatics (Salon I) • Orthopedics/Sports Medicine (Salon II) • Cognitive Neuroscience and Disorders (Salon III)
1:35 PM - 2:35 PM	Selected Short Talks	
	<p>Improved cell survival in steatotic hepatocytes undergoing ischemia reperfusion injury after treatment with GLP-1R agonist. <i>Vasantha Kolachala, PhD, Children's Healthcare of Atlanta and Emory University</i></p>	

	<p>Metabolic conditioning and reprogramming are hallmarks of neutrophilic inflammation in cystic fibrosis. <i>Julie Laval, MS, Emory University and Yerkes National Primate Research Center</i></p> <p>Quaternary organization of GPIb-IX complex (CD42) and insights into Bernard-Soulier syndrome revealed by the crystal structures of GPIb-beta ectodomain and a GPIb-beta/GPIX chimera. <i>Renhao Li, PhD, Emory University</i></p> <p>Correlating CNV and phenotype data in patients evaluated for congenital heart defects. <i>Eli Williams, PhD, Emory University</i></p>
2:35 PM - 2:50 PM	Break
2:50 PM - 3:35 PM	Poster Session 2 (Foyer, Garden Overlook, and Azalea Room)
3:35 PM - 4:35 PM	Selected Short Talks
	<p>Maternal smoking increases TGFb1 in the developing alveolar macrophage. <i>Theresa Gauthier, MD, Children's Healthcare of Atlanta and Emory University</i></p> <p>Cardiaplication as a novel antireflux procedure for infants: A proof of concept in an infant porcine model. <i>Sarah Hill, MD, Children's Healthcare of Atlanta and Emory University</i></p> <p>Novel biomarkers for assessing potential risk for stillbirth: Results from the Stillbirth Collaborative Research Network (SCRN) population-based case-control study. <i>Carol Hogue, PhD, MPH, Emory University</i></p> <p>Rare sequence variants at the X-linked AFF2 contribute to male autism susceptibility. <i>Kajari Mondal, PhD, Emory University</i></p>
4:35 PM - 5:30 PM	Informal Poster Session and Social Hour

Children's Healthcare of Atlanta is accredited by the Medical Association of Georgia to provide continuing education for physicians.

Children's designates this live activity for a maximum of 5.5 AMA PRA Category 1 credits TM. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Shaded abstracts present during Poster Session 1

10:00-10:45 am

Non-shaded abstracts present during Poster Session 2

2:50-3:35 pm

Poster Abstracts

Poster 1: Emotional Functioning in Children with Sickle Cell Disease

Aflac Cancer Center and Blood Disorders Service

Donald J. Bearden, MA, 1, 2; Thomas Burns, PsyD, ABPP-CN, 1, 2, 3; Clark Brown, MD, 1, 3; Richard Jones, PhD, 1, 3; Binjian Sun, PhD, 1; Jessica Huamani, MS, 1 (1: Children's Healthcare of Atlanta; 2: Georgia State University; 3: Emory University School of Medicine)

Sickle cell disease (SCD) is the most commonly occurring genetic disorder of the blood. An estimated 1,000 babies are born with SCD annually. Research suggests that children diagnosed with SCD are at greater risk for emotional dysfunction. Emotional disturbances among children with SCD are likely related to a variety of factors, including chronic pain, headaches, fatigue, and cerebral-vascular insults. The current study utilized parent report on the Behavior Assessment System for Children, Second Edition (BASC-2), as part of a comprehensive assessment, in an effort to understand the impact of SCD on areas of emotional functioning. This study included 18 children diagnosed with SCD and 14 demographically matched controls whose parents were administered the BASC-2. Results revealed significant differences in emotional functioning between children diagnosed with SCD and controls in areas of Anxiety, $t(28) = 2.57$, $p = .016$, Somatization, $t(28) = 3.84$, $p = .001$, and Internalizing Problems, $t(28) = 2.99$, $p = .006$. In sum, the current study provides information regarding specific areas of difficulty in emotional functioning associated with SCD. These findings may aid in tailoring intervention strategies for children with SCD aimed at improving specific areas of emotional functioning.

Poster 2: COMPARE (Choosing Opioid Management for Pain and Analyzing ACS Rates Equally)

Aflac Cancer Center and Blood Disorders Service

Iris Buchanan 1 Trisha Chan1 Saadia Khizer2 1.Morehouse School of Medicine, Department of Pediatrics, Atlanta, GA, USA 2.Children's Healthcare of Atlanta, Atlanta, GA, USA

Painful events are the most common cause for hospital care in patients with sickle cell disease. Acute Chest Syndrome (ACS) is the most common complication observed during painful episodes. It is the leading cause of death, contributing to increased morbidity and prolonged hospitalization. Prevention of ACS can improve outcomes and reduce healthcare costs. Morphine is the most frequently used opioid for the treatment of pain crisis, however, its use has been linked to the development of ACS. Nalbuphine is a mixed agonist/antagonist. It induces analgesia at both the spinal and supraspinal levels. Nalbuphine is equi-analgesic to Morphine in doses up to 30 mg. Its properties have not caused side effects observed with the use of Morphine. Most importantly, Nalbuphine has not been linked to the development of ACS. In a retrospective chart review, Morphine was three times more likely than Nalbuphine to be associated with the development of ACS. To evaluate the difference between Morphine and Nalbuphine in the rate of ACS and pain relief, we developed a multi-center, randomized, double-blind trial. Subjects are recruited in the emergency room when seeking relief for their pain. Once scheduled for admission and consented, participants are randomized in the pharmacy by a prearranged schema. Study medication is started on the inpatient unit and administered via continuous infusion with accompanying patient controlled analgesia. 32 subjects have completed the study. There have been no adverse events. 5 subjects changed to an alternate opioid for pain relief. ACS complicated the course of four subjects. The average inpatient stay was 4.2 days. 9 eligible candidates refused participation. Recruitment for a pain study in an emergency room is feasible and not coercive. The use of an alternative opioid, instead of Morphine, in the treatment of sickle cell pain can provide significant therapeutic benefit, fewer side effects and cost effectiveness.

Poster 3: Low Transcranial Doppler Velocity Associated with Stroke in Children with Sickle Cell Disease: A Case Series

Aflac Cancer Center and Blood Disorders Service

Iris Buchanan¹ Anne Herry² Ifeyinwa Osunkwo² 1. Morehouse School of Medicine, Department of Pediatrics, Atlanta, GA, USA 2. Emory University, Department of Pediatric Hematology/Oncology, Atlanta, GA, USA

The prevalence of cerebral vascular events (CVA) in sickle cell disease has been reported as 10 % by age 18 years old. Other cerebral events such as silent cerebral infarction, have been reported as high as 35%. Cerebral infarcts typically occur during childhood with a peak incidence between four and seven years. The cumulative risk of central nervous system events increases as patient age. Transcranial Doppler ultrasonography (TCD) is an established screening tool for detection of children with Hemoglobin SS and Sickle β^0 Thalassemia, at highest risk for having a stroke. TCD measures the flow velocity in the large intracranial vessels of the Circle of Willis. Velocities less than 170cm/sec are considered normal. Monthly red cell transfusions are indicated for those subjects with velocities greater than or equal to 200cm/sec or those who have had two consecutive conditional measurements. Transfusions have reduced the rate of CVA in this group by 90%. We will describe five children with sickle cell anemia and their antecedent screening Transcranial Doppler velocities measured as ≤ 70 cm/sec. Based on the criteria established by the Stroke Prevention Trial (STOP), these subjects were considered normal and therefore not at risk for a cerebral insult. All of these patients developed significant intracerebral insults. All patients are on chronic transfusion to prevent further progression. This is the second observation reporting low measurements, < 70 cm/sec, on TCD ending in cerebral insults. Based on these five cases and those previously reported, we suggest low Transcranial Doppler velocities < 70 cm/sec may identify another group of children at risk for cerebrovascular disease. We suggest that Transcranial Doppler velocities < 70 cm/sec, in major vessels, be considered conditional results and prompt clinicians to perform more sensitive evaluations, such as a brain MRI and MRA.

Poster 4: HDM2 promotes WIP1-mediated medulloblastoma growth.

Aflac Cancer Center and Blood Disorders Service

Meghan C. Buss¹, Tracy-Ann Read², Rosemary G. Maxwell¹, **Robert C. Castellino**¹ 1. Emory University, School of Medicine, Department of Pediatrics, Atlanta, GA, USA 2. Emory University, School of Medicine, Department of Neurosurgery, Atlanta, GA, USA

Introduction: Medulloblastoma is the most common malignant childhood brain tumor. We have previously shown that the protein phosphatase and oncogene WIP1 is overexpressed or amplified in a significant number of primary human medulloblastomas and cell lines. In the present study, we examine an important mechanism by which WIP1 promotes medulloblastoma growth using in vitro and in vivo models. **Materials and Methods:** Overexpression and knock-down constructs as well as small molecule inhibitors were used in human cell lines and intracerebellar, xenografted animal models to study the role of WIP1 and the major TP53 regulator, HDM2, in medulloblastoma growth. **Results:** Stable expression of WIP1 enhances growth of TP53 wild-type, but not TP53 mutated medulloblastoma cells compared to cells with stable expression of an empty-vector or mutant WIP1. In an animal model, WIP1 enhances proliferation and reduces the survival of immunodeficient mice bearing intracerebellar xenografted human medulloblastoma cells. Cells with increased WIP1 expression also exhibit increased expression of HDM2. HDM2 knock-down or treatment with the HDM2 inhibitor Nutlin-3a specifically inhibits the growth of medulloblastoma cells with increased WIP1 expression. Nutlin-3a does not affect growth of medulloblastoma cells with stable expression of an empty vector or mutant WIP1. Knock-down of WIP1 or treatment with the WIP1 inhibitor CCT007093 results in increased phosphorylation of known WIP1 targets, reduced HDM2 expression, and reduced growth specifically in WIP1 wild-type and high-expressing medulloblastoma cells. Combined WIP1 and HDM2 inhibition is more effective than WIP1 inhibition alone in blocking growth of WIP1 high-expressing medulloblastoma cells. **Conclusion:** HDM2 promotes WIP1-mediated medulloblastoma growth. **Impact:** Our preclinical study supports a role for therapies that target WIP1 and HDM2 in the treatment of medulloblastoma.

Poster 5: The role of miR-27a and PPAR γ in Enhanced Endothelin Signaling in Sickle Cell Disease-related Pulmonary Hypertension

Aflac Cancer Center and Blood Disorders Service

Bum-Yong Kang^{1,3}, Kathy K. Park^{1,3}, Fang Tan^{2,3}, Roy L. Sutliff^{1,3}, Solomon Ofori-Acquah^{2,3}, and C. Michael Hart^{1,3} ¹Department of Medicine, Atlanta Veterans Affairs and Emory University Medical Centers, Atlanta, GA 30033, ²Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, ³Center for Endothelial Biology, Children's Healthcare of Atlanta, Atlanta, GA

Pulmonary hypertension (PH), a serious complication of sickle cell disease (SCD), causes significant morbidity and mortality. We recently reported that the PPAR γ ligand rosiglitazone (RSG) attenuates hypoxia-induced PH and endothelin 1 (ET-1) expression. To examine these pathways in SCD, we hypothesized that increased levels of microRNA (miR)-27a reduce PPAR γ expression leading to increased ET-1 expression and PH. Our results demonstrate that levels of miR-27a, NF- κ B-p65, and ET-1 were increased in the lungs of 8-10 week old SCD transgenic mice compared to controls whereas PPAR γ levels were reduced. In parallel studies, C57BL/6 mice were exposed to control or hypoxic (10% O₂) conditions for 3-weeks \pm gavage with RSG (10 mg/kg/d) for the final 10 d of exposure. RSG attenuated hypoxia-induced increases in miR-27a in C57BL/6 mouse lung. In vitro, human pulmonary artery endothelial cells (HPAECs), were exposed to control (21% O₂) or hypoxic (1% O₂) conditions for 72 h. Hypoxia increased HPAEC proliferation, miR-27a, NF- κ B-p65, and ET-1 expression, and reduced PPAR γ expression. These alterations were attenuated by treatment with RSG (10 μ M) during the last 24 h of hypoxia exposure. In contrast, overexpression of miR-27a or knockdown of PPAR γ with siRNA increased HPAEC proliferation. Collectively, these findings suggest that miR-27a and PPAR γ regulate ET-1 signaling and that targeting PPAR γ may represent a novel therapeutic approach in SCD-PH pathogenesis.

Poster 6: Reconstitution of platelet glycoprotein Ib-IX complex in phospholipid bilayer nanodiscs

Aflac Cancer Center and Blood Disorders Service

Rong Yan^{1,2}, Xi Mo¹, Angel M. Paredes³, Kesheng Dai², Francois Lanza⁴, Miguel A. Cruz⁵, **Renhao Li**¹ ¹. Department of Pediatrics, Division of Hem/Onc/BMT, Aflac Cancer Center and Blood Disorders Service, Emory University School of Medicine, Atlanta, GA, USA; ². Ministry of Health Key Laboratory of Thrombosis and Haemostasis, First Affiliated Hospital of Soochow University, Suzhou, China; ³. Department of Pathology and Laboratory Medicine, The University of Texas Health Science Center at Houston, Houston, TX, USA; ⁴. Etablissement de Transfusion Sanguine, INSERM, Unite311, Strasbourg Cedex, France; ⁵. Thrombosis Research Section, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

Glycoprotein (GP)Ib-IX complex expressed on platelet plasma membrane is involved in thrombosis and hemostasis by initiating platelet adhesion to von Willebrand factor (VWF) exposed at the injured vessel wall. While most of the knowledge for GPIb-IX is obtained from studies on platelets and transfected mammalian cells expressing GPIb-IX, there is not an in vitro membrane system that allows systematic analysis of this receptor. The phospholipid bilayer Nanodisc composed of a patch of phospholipid surrounded by membrane scaffold protein is an attractive tool for membrane protein study. We show here that GPIb-IX purified from human platelets has been reconstituted into the Nanodisc. Nanodisc-reconstituted GPIb-IX was able to bind various conformation-sensitive monoclonal antibodies. Furthermore, it bound to VWF in the presence of botrocetin with an apparent K_d of 0.73 \pm 0.07 nM. The binding to VWF was inhibited by anti-GPIb α antibodies with epitopes overlapping with the VWF-binding site, but not by anti-GPIb β monoclonal antibody RAM.1. Finally, Nanodisc-reconstituted GPIb-IX exhibited similar ligand-binding activity as the isolated extracellular domain of GPIb α . In conclusion, GPIb-IX in Nanodiscs adopts native-like conformation and possesses the ability to bind its natural ligands, thus making Nanodisc a suitable in vitro platform for further investigation on this hemostatically important receptor complex. GPIb-IX reconstituted in Nanodiscs may also potentially be developed further for diagnostic purposes.

Poster 7: The Application of Nanoparticle Liposome-Impramine Blue in the Treatment of Medulloblastoma in SmoA1 Transgenic Mice

Aflac Cancer Center and Blood Disorders Service

Tobey MacDonald¹; **Jingbo Liu¹**; Jenny Munson²; Jaekeun Park²; Baowei Fei³; Barunashish Brahma⁴; Ben Roller²; Ravi Bellamkonda²; Jack Arbiser⁵

Medulloblastoma is the most common malignant brain tumor in children. Tumor invasion and metastasis is associated with poor survival and the side effects of radiation treatment used to prevent metastasis severely affect survivors' quality of life. Impramine blue (IB) is a new anti-tumor-invasion drug. In this study, IB is encapsulated with liposome to form a liposomal nanoparticle, i.e Liposome-IB, which has the advantage of reaching tumor cells via the enhanced permeability and retention effect. Our in vitro study demonstrated that Liposome-IB caused a dose-dependent decrease in growth of medulloblastoma cells, including human cell line Daoy and the mouse cell line Ps125 derived from the SmoA1 transgenic mouse model of medulloblastoma. To determine the responsiveness of medulloblastoma to liposome-IB in vivo, we carried out a preclinical survival study in the SmoA1 mouse. Magnetic resonance imaging (MRI) of the brain was utilized for screening and detecting cerebellar tumors in mice aged 10-12 week old based upon the imaging characteristics and pattern of tumor enhancement. Tumor bearing mice were divided into treatment and control groups randomly. The mice in the treatment group received two doses of Liposome-IB by tail vein injection with a 5 day interval. The dosage of Liposome-IB is 4.5mg/kg (liposome-IB /body weight). The mice in the control group received the same amount of Liposome-only. The tumor progression was monitored by MRI at the different time points after the Liposome-IB treatment. The results showed that the tumor volume increased dramatically in the control group compared with Liposome-IB treatment group. The Liposome-IB treated mice survived significantly longer (mean survival 100 days) than the control mice (mean survival 57 days; $P < 0.002$). In conclusion, the nanoparticle Liposome-IB is effective in the treatment of SmoA1 mouse medulloblastoma in vivo. It can significantly delay the tumor progression and prolong the tumor bearing mice's survival time. The results provide valuable data in supporting the translation from the preclinical animal model trial to the development of clinical trial and protocol to the cancer patients.

Poster 8: Inadequate Anti-thrombin III (ATIII) response in critically ill children on ECMO utilizing congenitally deficient ATIII patient dosing guidelines

Aflac Cancer Center and Blood Disorders Service

W. Bryan Gamble, MD Anne M. Winkler, MD Cassandra D. Josephson, MD James D. Fortenberry, MD Matthew L. Paden, MD

Published data on ATIII levels for healthy neonates and children exists, but little is described regarding the ATIII levels of children on ECMO. Critically ill children are known to have lower than normal ATIII levels, but the clinical significance is unclear. Replacement guidelines are based on use in patients with congenital ATIII deficiency based on the following formula, $ATIII \text{ Dose [IU]} = (ATIII_{\text{desired}} - ATIII_{\text{Measured}}) \times Wt \text{ [kg]} / 1.4$. We proposed a retrospective study to determine if administering ATIII to patients receiving ECMO support resulted in an increase in the ATIII activity level to the calculated goal. All patients receiving ECMO from 2000 through 2011 at our institution were reviewed. Neonatal and pediatric patients receiving ECMO in the CICU, the NICU, and the PCIU were included. Data collected included patient age, gender, weight, ICU of admission, ECMO type, admitting diagnosis, ATIII activity levels, and dosing details of ATIII replacement. From 2000-2011, 532 patients received ECMO. From 2000-2007, 358 patients received ECMO with 28 (7.8%) receiving ATIII replacement. Since 2008, 174 patients have received ECMO, and 94 (54%) received at least one dose of ATIII while on ECMO. Comparing the actual ATIII activity level to the expected ATIII activity level based on the standard formula yielded a correlation coefficient of 0.06. When the expected activity level change was adjusted based on a correction factor accounting for circuit volume with respect to total blood volume, again comparing the actual activity levels to the expected, correlation coefficient rose to 0.36. Current methods to supplement ATIII are insufficient to raise activity levels to normal range; however, by adjusting the expected activity level goal by including the ECMO circuit blood volume revealed an improvement in ATIII replacement. Prospective pharmacodynamic testing is needed to determine if the new method to supplement ATIII is effective at normalizing activity levels.

Poster 9: Pulmonary function in children with sickle cell disease following treatment with hydroxyurea

Aflac Cancer Center and Blood Disorders Service

Elizabeth Record, DNP (1,2); Tamara New, M.D.(1,2); **Jonathan Popler, M.D.** (3); LaTresa Lang, M.D. (3); LeRoy Graham, M.D. (3); Burton Lesnick, M.D. (3); Patricia Waters (1), Renee Mumford (1), Rhonda Copeland (1) 1) Aflac Cancer Center and Blood Disorders Service of Children's Healthcare of Atlanta, Atlanta, Georgia 2) Emory University School of Medicine, Atlanta, Georgia 3) Georgia Pediatric Pulmonology Associates, Atlanta, Georgia

Background: Acute chest syndrome (ACS) is a common and potentially fatal complication of sickle cell disease (SCD). Repeated episodes of ACS can result in chronic lung disease and persistently abnormal pulmonary function. Hydroxyurea (HU) therapy is believed to reduce the risk of ACS in SCD patients. The purpose of this study was to assess the change in pulmonary function of children treated with HU therapy. Methods: A retrospective review was performed to examine changes observed in pulmonary function tests (PFTs) of two groups of children with previously abnormal PFTs. Children were selected from a cohort followed in a multi-disciplinary specialty clinic with care provided by the hematology, pulmonary, and respiratory care services. Group 1 consisted of 40 children treated with HU therapy. Group 2 consisted of 25 children who did not receive HU therapy. Paired t-test was used to evaluate PFT and pulse oximetry changes. Results: In Group 1, the mean age of patients was 10.9 years. There were 18 female and 22 male patients. The mean duration of HU therapy was 19 months. In Group 2, the mean age of patients was 12.3 years. There were 13 males and 11 females. Mean duration of HU therapy was 18.9 months. PFT parameters assessed including Total Lung Capacity (TLC), Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), the ratio of FEV1 to FVC, and Forced Expiratory Flow 25-75%. Additionally, pulse oximetry was assessed. The group treated with HU therapy had statistically significant improvements in FVC, FEV1, and pulse oximetry. Group 2 did not show improvement in any PFT parameter or pulse oximetry. Conclusions: These findings suggest the consideration of HU therapy in SCD patients with abnormal PFTs. Prospective studies examining the clinical benefits of HU therapy may help identify an effective intervention for those children at risk for chronic pulmonary disease.

Poster 10: Cancer SurvivorLink™: Recruitment strategies for website utilization

Aflac Cancer Center and Blood Disorders Service

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Background: With an 80% cure rate in pediatric cancer, there is a need to empower pediatric cancer survivors to seek lifelong individualized surveillance and treatment for late effects to improve quality and length of life. Cancer SurvivorLink™(CSL)(www.cancerSurvivorLink.org)is a website designed to increase awareness and educate survivors, families and healthcare providers about survivorship care. Purpose: This analysis aims to determine the most effective method to increase website awareness and use in patients and families through 1.Standard Mailings 2.Community Events 3.Social Media Methods: 1. 250 pediatric cancer patients were randomized to receive information about CSL by standard mail. Patients/families that had not registered after the mailings received a phone call from CSL staff. 2. Community partners were contacted to increase utilization by attending 4 community events focused on cancer survivors. 3. Creation of a Facebook page. All registrations were tracked through the CSL website. Website traffic volumes were tracked using Google Analytics. Findings: 1. 11% of the randomized patient/families registered for the CSL website after a standard mail contact; 25% of those randomized registered after a follow-up call. 2. 21% of patients/families engaged by CSL staff at community events registered. Google Analytics showed an average 107% increase in new website visits immediately post-event. 3. Social Media, Facebook, recruitment has been live for 3 months. 38 people have 'liked' CSL on Facebook and the page has been viewed 2,920 times. Conclusions: Community engagement is the most effective method to increase website registration, use, and page views. Multiple users can be engaged using small amounts of staff time and budget. Standard mailings require the most staff time and cost, and show the least amount of registrants and page views. Facebook offers a cheap and easily accessible marketing tool, but may be difficult to encourage user registration.

Poster 11: Generation of purified cardiomyocytes from pluripotent stem cells using molecular beacons.

Center for Cardiovascular Biology

Kiwon Ban¹, Brian Wile², Sangsung Kim¹, Jaemin Byun¹, Talib Saafir³, Mary Wagner³, Gang Bao² and Young-Sup Yoon^{1,2} ¹Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA ²Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA ³ Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

Background: Pluripotent stem cells (PSCs), which include embryonic stem cells (ESC) and induced pluripotent stem cells, offer unprecedented hopes for myocardial repair; however, there are numerous technical hurdles for their clinical uses. Particularly, while various methods for CM differentiation from PSCs have been reported, all these methods were only allowed to produce heterogeneous population with undifferentiated or non-CM cells may cause negative outcomes. Therefore, it has been highly required to develop strategies to purify homogeneous populations of CM for their further clinical applications. Accordingly, we aimed to develop a novel system, in which CMs can be purified by cardiac specific molecular beacon (MB). MB is a dual-labeled antisense nano-scale probe with a fluorophore and a quencher. We hypothesized that MBs targeting CM-specific mRNA can specifically bind to CMs and allow to sort MB positive CM population by Fluorescence-activated cell sorting. Methods and results: At first, we generated two cardiac specific MBs targeting cardiac troponin T (cTNT) and myosin heavy chain (MHC). Next, to find the optimal way to deliver these MBs into living CMs, various transfection methodologies were examined with the HL-1 CM, which is an immortalized mouse CM cell line. As results, we found that a nucleofection method was highly efficient to deliver MBs into HL-1 CMs up to 98%. In addition, these MBs were selectively transfected into mouse ESC derived CM by 54%. Finally, cell sorting with an MHC MB allowed for the enrichment of CMs from mESC differentiation cultures yielding 97% of cTNT positive CMs. We further cultured these cells and verified their identity as CM by immunostaining (α -sarcomeric actinin and cTNT/I) and qRT-PCR analysis. Ca²⁺ transient analysis further verified that these purified CMs were functional. Conclusion: Our approach with cardiac specific MB will aid in the future success of using PSC-derived CM for basic and clinical applications.

Poster 12: Age and chamber specific differences in oxidative stress following ischemic injury

Center for Cardiovascular Biology

E. Bernadette Cabigas MD^{1,2}, Guoliang Ding MD/PhD^{3,4}, Tao Chen MD, ^{3,4}, Talib B. Saafir PhD^{3,4}, Karl D. Pendergrass PhD^{1,2}, Mary B. Wagner, PhD^{3,4} and Michael E. Davis PhD^{1,2,4,*}

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Each year, tens of thousands of children undergo cardiopulmonary bypass (CPB) to correct congenital heart defects. While necessary for surgery, CPB involves stopping the heart and exposing it to ischemic conditions. Upon re-oxygenation, the heart can experience effects similar to that of acute myocardial infarction. While much is known about adult injury, little is known about the effects of global ischemia on newborn ventricles. We studied newborn (2-4 days) and adult (>8 weeks) rabbit hearts subjected to ischemia-reperfusion (30 minutes ischemia, 60 minutes reperfusion). Our data demonstrate chamber and age-specific changes in oxidative stress. During ischemia, H₂O₂ increased in both right ventricular (RV) and left ventricular (LV) myocytes of the newborn rabbit, though only the RV change was significant. In contrast, there was no significant increase in H₂O₂ in either RV or LV myocytes of adults. There was a 5-fold increase in H₂O₂ formation in newborn RV myocytes compared to adults (p=0.006). In whole heart tissue, superoxide dismutase (SOD) activity was increased from sham vs. ischemia in the LV of both adult and newborn hearts, but only in the RV of the newborn heart. Catalase activity was significantly increased following ischemia in both adult ventricles, while no increase was seen in newborn hearts compared to sham hearts. Additionally, catalase levels in newborns were significantly lower, indicating less scavenging potential. Nanoparticle-encapsulated ebselen given as an intra-cardiac injection into the RV or LV of the newborn significantly increased functional recovery of developed pressure only in the RV, indicating the potential for localized antioxidant therapy during and after pediatric surgical procedures.

Poster 13: A rare genetic mutation (FBLN-4 mutation) found in a patient presenting with diffuse severe aortopathy.

Center for Cardiovascular Biology

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A 6-month-old female presented with acute onset difficulty breathing progressing to respiratory failure. Chest films showed a large mediastinum; chest MRI eventually detailed a severely dilated aorta from aortic root to aortic hiatus. The patient was diagnosed with RSV bronchiolitis as the etiology of the acute respiratory distress and compression of the main left bronchus by the dilated aorta as the etiology for failure to extubate. She thus required a tracheostomy prior to weaning from mechanical ventilation. The aorta was eventually surgically treated with an "elephant trunk" type ascending aorta repair and plication with reimplantation of the all of the strap vessels. Months after surgical repair, the patient was successfully decannulated and no longer requires any airway support. The eventual plan is a second and hopefully final surgery on her descending aorta to reduce its caliber. Otherwise, during the clinical progression, an ongoing attempt at defining an underlying genetic etiology was undertaken. Specific testing for Loeys-Dietz syndrome (TGFB2 and TGFB1) and arterial tortuosity syndrome (SLC2A10) was negative. DNA was sent to Dr. Bart Loeys in Brussels, Belgium for sequencing of the Fibulin-4 (FBLN4) gene that is a member of the fibulin family, a group of extracellular matrix proteins prominently expressed in medial layers of large veins and arteries. The result was a homozygous FBLN4 mutation (p.E126K) in this patient. Both parents who are consanguineous were heterozygous for the same mutation. Mutations in FBLN4 have previously been described in four patients including one patient from Australia with the identical mutation as this patient. This case report thus describes a severe clinical presentation of an extremely rare genetic mutation, which has to date been successfully surgically managed.

Poster 14: Determining changes in contractility, myofilament expression, and myofilament sensitivity in the developing human ventricle.

Center for Cardiovascular Biology

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As pediatric cardiac surgery is increasingly performed in the first year of life, the need for understanding contractility regulation becomes increasingly important. We examined contractility and myofilament changes in ventricular biopsies removed as part of the surgical correction of congenital heart defects from newborns (NB) (hypoplastic left heart syndrome, < 1 wk old) and infants (IF) (tetralogy of Fallot, 3-12 mo old). Sarcomere shortening and calcium (Ca) transients were measured in isolated ventricular cells stimulated at 0.5 and 1 Hz. Increasing pacing frequency caused a significant increase in sarcomere shortening ($p < 0.05$) in only the IF, but the Ca transient amplitude was relatively unchanged in both groups. Consistent with work in the developing rat heart, we found an isoform switch with increasing developmental age in myofilament proteins, troponin T (TnT) and troponin I (TnI). Western blot analysis revealed that total TnI (the sum of cardiac TnI (cTnI) and slow skeletal TnI (ssTnI)) was not significantly different between the two age groups. However, when comparing only the cTnI isoforms, we found that the NB had a significantly lower levels compared to the IF (11556 ± 789 a.u. vs. 21770 ± 1700 a.u., $p < 0.001$). Analysis of the RT-PCR revealed nearly significant lower levels of TnT isoform 1 in the IF group than the NB group ($p = 0.078$), no significant difference in the levels of TnT isoform 2 ($p = 0.536$), and significantly higher levels of TnT isoform 3 in the IF group than the NB group ($p = 0.039$). We also observed developmental changes in myofilament sensitivity to calcium as assessed by measuring the gradient of the fura-2 cell length trajectory on phase-plane diagrams during the late relaxation of the twitch contraction. These results collectively suggest that contractility and myofilament changes, or the lack of changes, may serve as targets for clarifying elements associated with cardiac dysfunction in the developing human ventricle.

Poster 15: Cardioprotection from oxidative stress in the newborn heart by activation of PPAR γ is mediated by catalase

Center for Cardiovascular Biology

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Introduction: Hydrogen peroxide (H₂O₂) has been shown to be an important metabolite produced during ischemia reperfusion in the heart and contributes to oxidative stress and cardiac injury. Catalase (CAT) plays a critical role in prevention of injury by ischemia reperfusion in heart. We investigate the regulation of CAT in heart by peroxisome proliferator-activated receptor- γ (PPAR γ) and determine if PPAR γ activation is cardioprotective from oxidative stress caused by H₂O₂ in newborn. **Methods:** Left ventricular development pressure (LVDP) was measured in Langendorff perfused rabbit heart, exposed to 200 μ M H₂O₂, with perfusion of rosiglitazone (RGZ, 1 μ M), a PPAR γ agonist. Lactate dehydrogenase (LDH) was measured in the effluent. The CAT activity was measured by fluorometric detection kit. The expressions of protein and mRNA were measured by western blot and qPCR. **Results:** (1) LDH release and cessation of beating occurred earlier in newborn than in adult heart stressed by H₂O₂ due in part to the lower expression of CAT in newborn heart; (2) RGZ increased CAT mRNA by 64 \pm 9% and protein by 46 \pm 11% as well as activity by 36 \pm 9% in newborn heart, not in adult heart. Higher expression of PPAR γ protein (156 \pm 12%) compared to adult heart (n=8, * p < 0.05) may lead to the increase in newborn; (3) RGZ inhibited release of LDH in H₂O₂ stressed newborn heart compared to untreated group (n=6 and 5, *P<0.05); (4) RGZ attenuated heart function deterioration in H₂O₂ stressed newborn heart. Left ventricular development pressure (LVDP) was significantly higher in newborn RGZ+H₂O₂ group than in H₂O₂ group (n=5, P < 0.05) with no difference in the adult; (5) The cardioprotection by RGZ was abolished by inhibition of CAT. **Conclusions:** Activation of PPAR γ is cardioprotective to hydrogen peroxide stress in the newborn heart by upregulation of catalase. These data suggest that PPAR γ activation may be an effective target against oxidative stress for the young surgery cardiac patient.

Poster 16: Differentiating "Athlete's Heart" from Hypertrophic Cardiomyopathy in Adolescent Patients: the Role of Exercise Stress Echocardiography

Center for Cardiovascular Biology

Brian Winn; Will Border, MBChB, MPH; M. Eric Ferguson, MD (Children's Healthcare of Atlanta, Emory University School of Medicine)

Background: Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden cardiac death in athletes. Exercise-induced LVH, or "athlete's heart," is felt to be a physiological adaptation state. Differentiating between HCM vs. "athlete's heart" can have significant ramifications for sports participation and for cardiovascular screening. **Objective:** To determine if certain resting and exercise-stress derived parameters are associated with LVH secondary to HCM versus LVH associated with "athlete's heart." **Study Design:** A retrospective review of two separate cohorts: HCM patients with prior genetic testing, and healthy individuals with suspected "athlete's heart." These two cohorts were compared with normal subjects. All subjects underwent resting and functional stress echo. **Results:** There were 27 subjects, including 16 males, 17 blacks, age ~14.8 years (range 9 yrs – 18 yrs). Nine subjects were identified for each cohort. There were no differences between groups in age, gender, ethnicity, height, weight, BSA, resting heart rate, or resting respiratory rate. Exercise testing brought out several differences between athletes and HCM patients. Athletes performed more work and consumed more oxygen. They had increased O₂ pulse values, indicating that stroke volume increases in athletes to a greater extent than in HCM patients. **Conclusions:** In adolescent patients with LVH, exercise echocardiography helps differentiate between athlete's heart and HCM. Athletes tend to perform more work overall, consume more oxygen, and increase stroke volume. HCM patients tend to perform less work, consume less oxygen, and fail to augment stroke volume. Furthermore, HCM patients have decreased TDI velocities at rest that do not augment much with exercise, compared with normal controls who have increased systolic TDI with exercise. Further study is warranted to refine TDI velocity and strain assessment during exercise in athletes.

Poster 17: CaMKII-dependent troponin-I phosphorylation contributes to the frequency-dependent acceleration of relaxation in ventricular myocytes

Center for Cardiovascular Biology

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Frequency-dependent acceleration of relaxation (FDAR) is an intrinsic mechanism in ventricular myocytes allowing a faster ventricular relaxation (and diastolic filling) at fast heart rates. Previous studies suggest that CaMKII activity is required for FDAR but the molecular targets remain elusive. We propose that CaMKII regulates FDAR by a mechanism that involves CaMKII-dependent alteration of myofilament sensitivity to Ca²⁺. We showed that increasing pacing rate from 0.5Hz to 4Hz in left ventricular (LV) myocytes accelerated Ca²⁺ decline and sarcomere relaxation time constants (from 152±13ms to 60±5ms and from 36±2ms to 18±1ms, respectively, p<0.05, n=27) and increased the length-fura2 trajectory gradient (ECa50 increased from 1.62±0.06 to 1.84±0.06, p<0.05) and shifted the trajectory loop to the right, indicating a consistency of FDAR with the reduction of myofilament sensitivity to Ca²⁺. Inhibition of PKA (H89, 1µM) or PKC (CHE, 1µM) had no effect on myofilament Ca²⁺ desensitization and FDAR, whereas CaMKII inhibitor KN93 (1µM) abolished frequency-dependent myofilament desensitization to Ca²⁺ and FDAR. Because cardiac troponin I (Tn-I) is the major regulator for myofilament sensitivity to Ca²⁺ and both PKA and PKC share the same phosphorylation sites Ser23/24, we determined the Ser23/24 phosphorylation in ventricular myocytes and found that Ser23/24 phosphorylation was largely reduced by PKA and PKC inhibitors but not by CaMKII inhibition. However, a phospho-Ser-antibody showed that CaMKII inhibitor KN93 significantly reduced Tn-I phosphorylation in the Tn-I immunoprecipitates, indicating that CaMKII phosphorylates Tn-I at sites different from the PKA and PKC sites. Indeed, a co-immunoprecipitation of CaMKII and Tn-I has been detected. Our results suggest that FDAR is regulated by a frequency-dependent desensitization of myofilament sensitivity to Ca²⁺, in which CaMKII-dependent Tn-I phosphorylation plays a major role.

Poster 18: Chronic CaMKII inhibition induces diastolic dysfunction

Center for Cardiovascular Biology

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Recent studies point to CaMKII as a novel therapeutic target in structural heart diseases. However, the role of CaMKII in maintaining normal diastolic function is under investigated. We have tested the effect of chronic CaMKII inhibition on diastolic function in physiological condition and in compensatory cardiac hypertrophy. We showed that moderate aortic thoracic banding (mTAB) induced similar hypertrophy in WT and CaMKII δ knockout (KO) mice. Left ventricle (LV) mass and ejection fraction (EF) were 109.2±7.4mg and 84±3.0% for KO hypertrophy and 112.8±12.2mg and 80 ±2.5% for WT hypertrophy, respectively (p>0.05). However, LV filling pressure and left atrium (LA) size were significantly increased in KO mice in baseline and in mTAB-induced hypertrophy characterized by increased transmitral inflow early diastolic velocity (E) to mitral annular early diastolic velocity (E') ratio (baseline: 34.5±1.3 vs. 29.9±0.8; hypertrophy: 41.7±1.5 vs. 33.8±2.0, p<0.05, KO vs. WT) and LA area (baseline: 4.3±0.2 vs. 3.3±0.2mm², p<0.05; hypertrophy: 6.1±0.2 vs. 5.1±0.2mm², p<0.05, KO vs. WT). Dynamic LV P-V loop showed that compared to WT hypertrophy, KO hypertrophy mice had nearly doubled LV end-diastolic pressure (10.6±1.9 vs. 5.8±1.1mmHg, p<0.05), slowed LV pressure decline time constants (8.10±0.51 vs. 6.76±0.34ms, p<0.05), and steeper LV end-diastolic pressure-volume relationship (0.11±0.02 vs. 0.05±0.01mmHg×ul⁻¹, p<0.05). Furthermore, 28% (5/18) KO hypertrophy mice with preserved EF had significant lung edema (doubled lung weight to body weight ratio) and doubled E/E' ratio, indicating diastolic heart failure (HF), whereas no diastolic HF was found in WT hypertrophy mice. Taken together these results showed that chronic CaMKII inhibition significantly impairs diastolic function. These results challenge recent idea that CaMKII inhibition is a beneficial treatment strategy in patients with structural heart disease by pointing to a caution of diastolic dysfunction.

Poster 19: Myocyte dysfunction in an immature model of right ventricular pressure overload

Center for Cardiovascular Biology

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Background: The response of the immature heart to hemodynamic stress is not well understood, thus limiting therapies designed for the pediatric patient. Thus, we investigated changes in right ventricular (RV) myocyte function and calcium handling after pulmonary banding (PAB) in very young rabbits. **Methods:** Ten day old rabbits underwent PAB and their hearts were harvested 5-7 weeks post surgery (n=5). Data was compared to age-matched controls. Isolated RV myocytes were paced at 0.5-2 Hz and sarcomere shortening and calcium transients were recorded to determine the force frequency response (FFR). Spatial distribution of calcium transients and t-tubule distribution was measured by confocal microscopy. **Results:** Heart weight was significantly larger in the PAB group compared to control, as was RV weight (1.83±0.18 g PAB vs. 0.82±0.03 g control, p<0.01) and RV/(left ventricle + septum) ratio (0.73±0.03 g PAB vs. 0.29±0.01 g control, p<0.001). The FFR was significantly diminished in PAB myocytes. In control cells, sarcomere shortening increased from 1.1±0.2% at 0.5 Hz to 6.41±0.8% (p<0.05) at 2 Hz. In contrast, in PAB cells, sarcomere shortening did not increase with the faster pacing rate (1.5±0.3% vs. 3.4±0.5%). The amplitude of the calcium transients was not different between PAB and control cells, but for all pacing rates tested, diastolic and systolic calcium levels were higher in PAB cells. Confocal line scan imaging showed that PAB cells had heterogeneous calcium transients compared to control and as well as decreased density of t-tubules. Furthermore, PAB cells had decreased colocalization of ryanodine receptors and caveolin-3 (to mark t-tubules) compared to control. **Conclusions:** PAB in an immature rabbit causes significant RV hypertrophy with cellular dysfunction and abnormal calcium handling. A better understanding of interactions between developmental age and hemodynamic stress may help identify improved therapies for the pediatric CHD patient.

Poster 20: Involvement of AMPK in right ventricular hypertrophy induced by pressure overload

Center for Cardiovascular Biology

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Background: Right ventricular hypertrophy (RVH) is an important problem in congenital heart disease (CHD), even after surgical repair. With the increasing size of the adult CHD population, a better understanding of RVH and failure is required. AMP activated protein kinase (AMPK) is a key energy sensor and regulates cellular metabolism to maintain energy homeostasis. Currently the detailed molecular mechanisms and signaling pathways like AMPK that are involved in RV dysfunction have not been extensively studied. We hypothesize that rat hearts exposed to chronic RV pressure overload secondary to pulmonary artery banding will demonstrate myocyte hypertrophy, changes of calcium handling proteins and involvement of AMPK. **Methods:** 16 eight week old male rats were randomly assigned to sham or pulmonary artery banding (PAB) groups. After 8 weeks, RV weight and the RV/LV+S (left ventricle+septum) ratio were measured. Expression of key calcium handling proteins and AMPK α activation was investigated by Western blot. **Results:** PAB increased RV weight from 0.24±0.01 g (sham) to 0.46±0.03 g (p<0.05, n=8). Left ventricular weight was not different between the groups indicating RVH. The RV/LV+S ratio was larger in the PAB group compared to the sham (0.58±0.04 vs. 0.29±0.01, p<0.05). Western blot results showed that SERCA was significantly decreased in PAB compared to sham but total phospholamban (PLB) was not changed. Interestingly, phospho-PLB (S-16) was significantly increased in PAB. The SERCA/PLB ratio decreased with PAB. NCX shows a trend to increase in PAB, but was not significant. Phospho-AMPK α (Thr172) was significantly decreased in PAB compared to sham, but total AMPK α was not changed. **Conclusions:** Chronic RV pressure overload by PAB demonstrates 1)RV hypertrophy; 2)decreased SERCA and increased phospho-PLB expression in RV; and 3) involvement of the AMPK pathway in development of RVH. Further studies are required to understand the functional implications of these findings.

Poster 21: Functional and Kinematic Advantages of Providing Knee Components in the First Prosthesis of Infants and Toddlers with High Level Lower Limb Amputations

Children's Clinical and Translational Research Center

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Purpose: To examine the advantages of providing a free flexing knee in the first prosthesis of infants and toddlers with amputations compared to the traditional provision of a knee locked in full extension. Methods: Five subjects, ages 13 to 23 months, with unilateral transfemoral or knee disarticulation amputations were exposed to crawling trials and selected functional tasks with prosthetic knees unlocked and locked in full extension while kinematic data were recorded. Subjects' emotions and performance during the functional activities were scored, and parents completed a questionnaire asking their perception of fit, function and appearance of their child's prosthesis. Results: All subjects showed the ability to flex the prosthetic knee. With the knee locked, most subjects demonstrated significant bilateral differences in knee flexion. In the unlocked knee, 4 of 5 subjects showed no significant bilateral knee flexion differences demonstrating greater symmetry in crawling. Similar symmetry results were recorded in hip ab/adduction. Subjects crawled faster in the unlocked condition. All subjects were able to perform all functional tasks in the unlocked knee condition. With the prosthetic knee locked, all subjects could crawl, none could assume tall kneel and 2 of the 5 could climb up steps each with varied degrees of frustration. All parents preferred the unlocked knee condition. Conclusion: This study validated that infants and young toddlers are capable of incorporating and controlling free flexing prosthetic knees during crawling and age appropriate tasks. Compensations were found in the contralateral limb when the knee was locked. All subjects demonstrated positive emotions and greater symmetry with the unlocked knee. Parent satisfaction was greater with the unlocked knee. Infants and toddlers should be provided the opportunity to develop early mobility and symmetrical movement by incorporating prosthetic knees at the initial prosthetic fitting.

Poster 22: Improving access to child health research in Downtown Atlanta: Building research infrastructure at Children's at Hughes Spalding

Children's Clinical and Translational Research Center

Beatrice E. Gee, Saadia Khizer

Children's Healthcare of Atlanta at Hughes Spalding (HSOC) is located in downtown Atlanta and provides care to a historically under-served and disenfranchised patient population with a high rate of health disparities. The six local zip codes encompass a 20 square mile area with about 135,000 individuals, 82% of whom are Black or Hispanic, with an average median income of \$31,000 (60% of the Georgia median income), and 34% with income below the poverty level. Thus, HSOC is a "safety net" pediatric healthcare facility. As part of the Clinical Interaction Network of the Atlanta Clinical Translational Science Institute (A-CTSI), HSOC has developed infrastructure to support child health research related to asthma, sickle cell disease, infectious disease and neonatal outcomes. Pediatric researchers from Morehouse and Emory University Schools of Medicine have collaborated with HSOC research personnel and clinical staff to see approximately 1000 research-related visits in 2011. Children's at Hughes Spalding has provided dedicated space for research personnel, confidential file storage, equipment for sample processing and storage. The A-CTSI will be assisting in integrating research activities at HSOC with existing scheduling, sample identification and storage systems, and clinical research nursing support services. Clinical research at HSOC is necessary to give children in this community the opportunity to participate in research conducted on-site that could directly improve their long-term health outcomes. This is an important step in reducing healthcare disparities related to ethnicity and socioeconomic status and integrates well with our campus's goal for developing comprehensive medical homes for our patients. There is opportunity for further research development in areas where we have clinical expertise, such as weight management, reproductive health, primary care, and injury prevention.

Poster 23: The role of a prosthetic knee in the kinematics of early walking.

Children's Clinical and Translational Research Center

Mark D. Geil, Ph.D., Georgia State University Colleen Coulter-O'Berry, PT, DPT, Ph.D., PCS, Children's Healthcare of Atlanta

For young children with limb loss who require a prosthetic knee joint, clinical protocols have historically placed the goal of stability over the goal of neuromotor development. The most stable knee is one that is locked into full extension at all times. However, an extended knee is a hindrance during crawling, walking, and age-appropriate functional activities. This study followed recent research on infants with unilateral limb loss crawling with locked and unlocked knees to determine the impact of the knee following the transition to walking. Seven healthy children (≤ 5 years old) who had been fit with an articulating knee in their first prosthesis participated. Kinematics were measured while each participant completed walking trials with the normally flexing prosthetic knee, with the knee mechanically locked into full extension, and with the knee flexing again. All subjects flexed the prosthetic knee effectively in the unlocked condition. In the locked knee condition, every subject exhibited one or more of the three analyzed accommodations: hip hiking, vaulting, and circumduction. Circumduction lingered after the knee was unlocked again [$p(U1 \text{ vs. } L) = 0.038$; $p(L \text{ vs. } U2) = 0.082$]. One subject exhibited the same accommodation in the unlocked condition, though the magnitude was decreased. The remaining six subjects showed none of the three analyzed clearance accommodations in the unlocked condition, although some other gait abnormalities were present, typically associated with hip flexion and extension necessary to articulate the prosthetic knee. The children in this study had been provided with an articulating knee joint in their first prosthesis, so the unlocked condition represents their developing gait pattern. The presence of acute accommodations in the locked condition and the general absence of any chronic clearance accommodations demonstrate the effectiveness of an "early knee" protocol in promoting more typical motor development.

Poster 24: Parental report versus laboratory data: which is more reliable in determining the most effective orthotic treatment for children with idiopathic toe walking?

Children's Clinical and Translational Research Center

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Background: Idiopathic toe walking (ITW) is a diagnosis commonly seen in the orthotic setting in which a muscularly normal child chooses to walk on their toes; it has been defined as the absence of a heel strike at initial contact (IC) during gait. ITW can lead to future problems including contracted Achilles tendon, deformities in the feet and decreased walking speed. Prevention of ITW is critical for the future development of a normal gait pattern. Methods: IRB approval for this study was obtained and 6 subjects were recruited and randomized to orthotic treatment: an articulated ankle foot orthosis (AAFO) or a carbon fiber footplate (CFF) with an attached custom foot orthosis. Three outcomes measures were compared before and after 1 month of orthotic treatment: 1) the L-test of functional mobility, 2) a parental satisfaction survey and 3) 3D gait analysis. Results: Parents of children in the AAFO group reported less incidence of ITW than parents of patients in the CFF group. Both the CFF and AAFO groups showed increases in speed after treatment. During 3D gait analysis, the AAFO group showed more frequent heel strikes at IC while wearing their AAFOs; however, when patients walked with shoes only, patients who wore the CFF showed more frequent heel strikes at IC than those who were randomized to the AAFO group. Interpretation: Parental report of time spent ITW is an important measure since children with ITW can walk normally if asked. A parental report of decreased time spent ITW is an excellent indicator of the effectiveness of the AAFO. Both devices led to increased speed showing orthoses may lengthen the Achilles tendon. The greater carryover effect seen in the CFF group during gait analysis indicates longer treatment times while wearing this device may lead to more normalized gait than an AAFO. The creation of a severity scale integrating parental feedback and clinical data may be an effective way to determine which orthosis would better suit certain patients.

Poster 25: Staphylococcus aureus Carriage in Children and How It Relates to Skin and Soft Tissue Infections
Children's Clinical and Translational Research Center

Shabnam Jain, MD Sarah Satola, PhD Robert C. Jerris, PhD Robert Mayberry, PhD, MPH Keming Yuan, MS Susan Ray, MD Robert S. Daum, MD

Objective. To determine the relationship between community-associated *S. aureus* carriage in children and skin and soft tissue infections (SSTIs) in the ambulatory setting. **Patients and Methods.** A case control study of patients younger than 21 years was conducted in a pediatric emergency department. Nasal and axilla swabs were collected, and participants were interviewed for risk factors for MRSA infections. The primary outcome was the proportion of MRSA and MSSA carriers among those presenting with and without SSTIs. The relatedness of MRSA and MSSA carriage isolates to *S. aureus* SSTI, molecular characterization of carriage isolates, and MRSA USA300 carriage risk factors were also determined. **Results.** The *S. aureus* carriage rate in children without SSTI was 2.4% (18/739) for MRSA and 20% (149/739) for MSSA. In children with SSTI, the carriage rate was 17% (42/247) for MRSA and 15% (37/247) for MSSA. From 247 SSTI, 166 were cultured and 64.4% (107/166) were MRSA. The pulsed-field types of MRSA carriers with SSTI were less clonal compared to MRSA carriers without SSTI and most were pulsed-field type USA300, and Panton-Valentine leukocidin positive. The risk for SSTI was almost eight times greater for MRSA USA300 carriers (OR: 7.74, 95% CI: 3.96-15.14), adjusting for age and other risk factors. Risks for MRSA carriage included age, previous medical condition, recent antibiotic use, previous SSTI, and household member with a SSTI. **Conclusion.** For children seen in the emergency department, those with MRSA USA300 type carriage are at increased risk for developing SSTI. MSSA carriage is not a risk factor for SSTIs in this population.

Poster 26: Mutations within a component of the oligosaccharyltransferase (OST) complex identified by whole exome sequencing are implicated in congenital disorders of glycosylation.

Children's Clinical and Translational Research Center

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Congenital disorders of glycosylation (CDG) are comprised of over 30 autosomal recessive disorders caused by deficient N-glycosylation. Multiple organs are affected in these disorders and symptoms can include ataxia, severe developmental delay, seizures, coagulopathies, liver fibrosis and retinopathy. Significant morbidity and mortality is associated with these disorders with 20% of children not surviving beyond 5 years of age. CDG patients are classified as having either Type I or Type II CDG depending on whether the defect resides in the synthesis (Type I) or modification (Type II) of glycans. A diagnosis of CDG is based on biochemical testing but this method cannot identify the specific gene defect. Over 40% of patients lack a confirmatory molecular diagnosis due to limited molecular diagnostic testing available for these disorders and patients having mutations in genes not yet known to cause CDG. We are using combined biochemical and whole exome sequencing approaches to identify new genes associated with CDG. With the use of next generation sequencing technology, we have identified a 22 bp deletion and a missense mutation in DDOST. The DDOST gene product is a component of the oligosaccharyltransferase (OST) complex. The OST complex is responsible for transferring the dolichol-linked precursor glycan onto nascent polypeptides in the ER lumen. N-glycosylation of three biomarkers was decreased in patient fibroblasts. Complementation with wild-type DDOST cDNA restored glycosylation showing that the mutations were pathological. Our results highlight the power of combining whole exome sequencing with detailed analysis of functional glycosylation to discover new types of CDG.

Poster 27: Genetic Therapies for the Lysosomal Storage Disorders – the Lysoman perspective

Children's Clinical and Translational Research Center

Dawn A. Laney, MS, CGC, CCRC Suma Shankar, MD, PhD Paul M. Fernhoff, MD

The Lysosomal Storage Disorders (LSDs) are a group of inherited conditions in which the decreased activity of an enzyme results in the intra-cellular storage of substrates and decreased organ functioning. Safe and effective treatment is now available for several of the LSDs, but there are still many pediatric onset conditions without a treatment. The Emory Lysosomal Storage Disease Center (ELSDC) provides diagnostic, evaluation, management, and treatment services for pediatric patients from all over the Southeastern United States. The ELSDC is involved in over 20 clinical research trials focused on different therapeutic treatment options including chaperone therapies, enzyme replacement therapy, and substrate inhibition therapy. Our goal is to provide information for clinicians and researchers on the leading and emerging therapeutic candidates for pediatric patients with LSDs.

Poster 28: Structural models evaluating novel potent HCV Inhibitors binding to NS5A

Children's Clinical and Translational Research Center

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Rapid selection of resistance-bearing mutations against the potent HCV inhibitor BMS-790052, suggests a highly specific binding site located in NS5A. Unfortunately, currently available X-ray structural data for NS5A are limited to the zinc binding domain, lack crucial N-terminus residues, thus are not sufficiently complete to describe drug binding. We hypothesized that novel modeling methods, constrained by distances between resistance bearing residues, could extend experimental data and provide 3D interaction maps for evaluation/prediction of structure-activity of this and related inhibitors of HCV replication. METHODS: Automated model building of NS5A domain 1 was performed using experimental structural data from X-ray and NMR as templates. A script was developed to rank the models for potential binding sites. Best models were selected and used to dock the symmetric inhibitor and analogs. A truncated small molecule analog library was synthesized and tested to evaluate activities and refine model building. Resistance selection data for the most potent new compounds was determined and correlated to the binding model. RESULTS: Over 40 potential binding sites were generated and sorted. A single best model was found to correlate SAR across the diverse compound class. The symmetric BMS inhibitor was found to bind simultaneously between two identical sites formed at the NS5A dimer/membrane interface. The binding sites are shallow, mostly hydrophobic, regions formed by mobile, proline-rich, sections of protein. Experimental resistance selection supports the prediction that novel asymmetric analogs are monodentate binders to one of these receptor sites. CONCLUSIONS: De novo 3D models of NS5A were built using experimental distance constraints. These models suggest high potency of BMS-790052 is due to simultaneous binding across two sites. We demonstrate small molecule inhibitors can bind at a single site. Novel are more effective than experimental structures alone.

Poster 29: The first signs of psychosis? Case study of a fourteen year old with parietal lobe epilepsy.
Children's Clinical and Translational Research Center

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Individuals with epilepsy are at increased risk of having psychotic symptoms that resemble those of schizophrenia. Although not a diagnosable disorder, Schizophrenia-Like Psychosis of Epilepsy (SLPE) has been characterized as a clinical condition with similar symptomatology but distinct pathophysiology from that of schizophrenia. Kindling has been offered as one potential mechanism for the association, bolstered by evidence that psychosis onset in SLPE is typically 14 years after seizure onset. This presentation examines a case study of a child with a history of parietal lobe epilepsy and ADHD, presenting with academic difficulties, unusual thinking, and social withdrawal. A full neuropsychological battery revealed high average intellectual functioning, intact receptive and expressive language abilities, and grade-level performance on academic achievement measures. The patient exhibited significant weaknesses in visual and auditory memory, as well as in executive functioning tasks, findings that were corroborated by parent report of poor executive skills. Finally, parent and self-report measures indicated difficulties in emotional and behavioral functioning, marked by atypicality, withdrawal, and poor functional communication. This profile of findings is consistent with the neuropsychological profile of SLPE, which is notable for deficits in auditory memory and executive functioning. The presentation will explore clinical and neuropsychological implications of the case.

Poster 30: Defining A Semantic Web Architecture for Long Term Follow Up (LTFU) of Children Positively tested with New Born Screening (NBS) Program.

Children's Clinical and Translational Research Center

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Background: Despite the success of Newborn Screening the understanding with respect to appropriate diagnostic methods, treatment and outcomes after screening as it relates to long term follow up (LTFU) data is lacking. This is hampered by the fact that these disorders are rare and comparatively little evidence-based data exists to evaluate available treatments and to develop management guidelines. Moreover, LTFU data that does exist often spans multiple, geographically separated sources (e.g. state labs, hospitals and local practices), further complicating the development of evidence-based guidelines. Recently, Semantic Web technologies have been successfully used for the integration of heterogeneous data in the biomedical domain. Its explicit semantics, the ability to express rich and well-defined models for data aggregation, and using logic to generate new knowledge has been quoted as being valuable. Here, we propose to develop a model demonstrating use of Semantic Web Technology to address the barriers associated with aggregating LTFU data from disparate sources. The methods include the development of Common Data Elements (CDE's) and application ontology with proper relationships for a specific domain Phenylketonuria (PKU). CDE's were developed by consensus of domain experts. The CDE's were evaluated for term availability using National Center for Biomedical Ontology's BioPortal. Based on established use cases, new application ontology for PKU was developed. Protégé with OWL language was used for defining and describing PKU ontology. Next steps include evaluating the functionality of the developed ontology by testing use cases to answer ad hoc research questions pertaining to PKU. Ultimately, the goal of this project is to develop a Semantic Web content repository populated with aggregate LTFU data of rare disorders from disparate sources. This will serve as a valuable resource for synthesis of evidence to make informed decisions that will improve health care.

Poster 31: Glycemic induced systemic oxidative imbalance in cystic fibrosis

Center for Cystic Fibrosis Research

Jason M. Hansen, Veranika Pazharskaya, Joy Luo, Amanda Castle and Arlene Stecenko

Cystic Fibrosis (CF) is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene leading to progressive lung disease and premature death. One of the most common CF comorbidities is CF related diabetes (CFRD) which occurs in 35% of patients. CFRD patients have increased pulmonary infections, a more rapid decline in lung function and even shorter lifespans compared to CF patients without CFRD. The etiology of CFRD remains unknown. CFTR also functions as a glutathione (GSH) exporter. Export of GSH into the extracellular (EC) space is an important regulator of EC redox environments and failure of export can lead to oxidizing EC environments. Oxidizing EC redox states increase intracellular reactive oxygen species (ROS) generation and thus perpetuate oxidative imbalance and damage. We hypothesized that in CF, the loss of GSH export creates an oxidizing EC environment which can alter cell function and promote CFRD pathogenesis. In vitro, oxidizing EC conditions cause a decrease glucose uptake and alter insulin secretion, promoting insulin resistance and inhibit insulin secretion, the two common most features in diabetes. Next, healthy and CF patients were given an oral glucose tolerance test. Plasma redox states were measured prior to and 2 h after an oral glucose challenge. Basal redox states were not significantly different between controls and CF with normal glucose tolerance (NGT) but CF with prediabetes or with CFRD showed basal differences that were significantly oxidized from either control or CF NGT. At 2 h, EC redox states in controls were unchanged. However, in all CF subjects, at 2 h after glucose load, EC redox states were markedly oxidized. Thus, loss of control of EC redox states sustains hyperglycemia, disrupts of insulin signaling and induces intracellular ROS generation. In CF, EC redox states are vulnerable during a glucose challenge, causing a chronic stress that promotes the pathogenesis of CFRD.

Poster 32: The Association of Cystic Fibrosis (CF) Outcomes with State Child Health Index

Center for Cystic Fibrosis Research

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Background: There is significant variation in CF outcomes, despite adjustment for known risk factors. This is demonstrated among the different CF centers in the CF Foundation(CFF) registry. This variation may be due to diverse care patterns, but regional differences in environmental exposures, education, public health infrastructure and other social determinants of health¹ likely also have some effect. We hypothesized that a Child Health Index (CHI)², generated by combining state-specific reports on measures of child health would be associated with CF center outcomes. Methods: We accessed CF Registry data and averaged patients' best FEV1% predicted (FEV1) and BMI percentile (BMI). We created linear regression models looking at the relationship between CHI alone and these outcomes by state. We then added CHI to a case-mix adjustment model, commonly used by the CFF, to evaluate the impact of CHI. Results: The CHI varied from a low of -2.69 for Mississippi (MS) to a high of 1.62 for New Hampshire (NH). In the full case-mix adjustment model, the regression coefficients were: 1.43 (95% CI 0.98, 1.88) for FEV1 and 1.54 (95% CI 0.98, 2.10) for BMI. Accounting for CHI would increase the mean FEV1 for centers in MS by 3.85% and the mean BMI by 4.14; it would decrease the mean FEV1 for centers in NH by 2.32%, and decrease the mean BMI by 2.49. Conclusion: There is an association between CF disease outcomes and CHI suggesting that state and regional characteristics have an influence on the health of CF patients. The mechanism is likely multifactorial and probably involves state differences within the social determinants of health. If this relationship is confirmed, it should be adjusted for when publically reporting outcomes. More importantly, the mechanism of this relationship may help to suggest interventions that may benefit all children, including those with CF. 1 Satcher D, et al. Am J Public Health. 2008 Mar; 98(3):400-3. 2 Goldhagen, J et al. Pediatrics. 2005; 116:e746-753.

Poster 33: Benchmarking to Accelerate Sustainable Improvements in CF Care (BASICC)

Center for Cystic Fibrosis Research

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Objective: In 2005, the CF Foundation sent a multidisciplinary team to visit pediatric CF centers with exceptional clinical outcomes, that identified clinical practices which were developed into a set of "signature themes" derived from observations during these visits. Our aim was to verify and validate these findings in a more quantitative way. **Methods:** An electronic survey regarding clinical practice was sent out to all accredited pediatric CF centers. We obtained published center averages of FEV1% predicted and BMI percentile. These were adjusted for sex, race, ethnicity, age, pancreatic enzyme use, age at diagnosis, and median family income. Centers were ranked and the top and bottom quartile centers for each outcome were identified and compared on their responses. **Results:** Respondents from high quartile BMI centers were more likely to agree that: clinic calls about medical questions are handled efficiently ($p=0.04$) and responsibility for clinic tasks are clearly defined ($p=0.007$). They also expect patients to be >50th percentile for BMI ($p=0.005$), express concern about small drops in weight/BMI ($p=0.03$), follow up patients of nutritional concern more often ($p=0.001$) and have high nutritional expectations ($p=0.007$). Respondents from top quartile FEV1 centers were more likely to: agree that good CF care requires active input ($p=0.02$) and participation by patients/families in treatment decisions ($p=0.02$). When presented with clinical scenarios on patients with new symptoms, low quartile respondents more frequently checked the option: "I cannot make this sort of generalization, every patient is different". **Conclusions:** Providers at high quartile centers compared to those at low quartile centers report better team function, value patient/family involvement, have higher expectations for outcomes and manage clinical compromise aggressively. These results suggest an approach to care that may be beneficial for centers to adopt in efforts to improve clinical outcomes.

Poster 34: The Effects of Socioeconomic Status on Outcomes in Pediatric Patients with Cystic Fibrosis

Center for Cystic Fibrosis Research

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Cystic fibrosis (CF) is one of the most prevalent, lethal genetic disorders in the Caucasian population. Approximately 30,000 individuals in the United States are currently diagnosed with CF. In the past 20 years, the life expectancy of a person with CF increased to a median age of 37.4 years. This may be contributed to extensive research, including the identification of the cystic fibrosis transmembrane conductance regulator gene and the development of the newborn screening tool. New therapies to prevent and treat pulmonary exacerbations, including the use of long-term medications, guidelines for airway clearance, and improvements in patient education have helped prolong the lifespan. The purpose of this systematic review is to identify significant modifiable factors relating to health outcomes of patients with CF and to explore appropriate patient education resources. Socioeconomic status (SES) was found to be the strongest predictor of health outcomes in patients with CF such that the risk of death increased for those in lower socioeconomic groups when compared to CF patients of higher SES. High mortality in the lower SES group may be related to environmental and socio-cultural stressors and disease management behaviors in addition to health care access barriers. Access to and/or use of educational programs present barriers for racial minorities, uninsured, those insured by Medicaid and the poor. Therefore, healthcare providers can create the greatest impact in the lives of CF patients by examining barriers and promoting patient education, especially in those with lower SES.

Poster 35: Hypogonadism in two patients with cystic fibrosis treated with megestrol acetate.

Center for Cystic Fibrosis Research

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Background: At least 20% of patients with Cystic Fibrosis (CF) are underweight. Weight gain and maintenance of weight are therapeutic parameters which correlate with improved pulmonary function and overall survival. As such, many patients with CF are treated with appetite stimulants. Megestrol acetate (MA) is a progesterone derivative used off label for appetite stimulation in patients with CF. It has been reported to cause adrenal suppression and hypogonadism at high doses in patients treated for cancer-related cachexia. Clinical Cases: Two 20 year old male patients with CF and CFRD who had achieved Tanner stage V of genital maturity complained of muscle weakness and fatigue. They were both being treated with low dose (1-2mg/kg/day) MA. They were found to have suppressed testosterone levels of 17.3 ng/dL and 22.7 ng/dL respectively (Nml range 100-970 ng/dL) without elevation of gonadotropin levels (LH/FSH 1.6/1.8 mIU/mL and 3.8/2.6 mIU/mL). Morning cortisol levels were also within normal range (10.0 ug/dL and 11.4 ug/dL). Patients were weaned off MA therapy. Both patients had recovery of their Hypothalamic-Pituitary-Gonadal (HPG) axis function on repeat testing 6-9 months after discontinuation of MA therapy (Testosterone levels 369 ng/dL and 273 ng/dL respectively). Conclusion: Our patients were on doses of MA lower than those associated with HPG axis suppression in the literature (40-100 mg/day vs. 200-800 mg/day). Nevertheless, they had clear evidence of HPG axis suppression which reversed with discontinuation of MA. They did not have suppression of the Hypothalamic-Pituitary-Adrenal axis. Hypogonadism secondary to MA therapy occurs young CF patients. This has the potential to negatively affect pulmonary function, lean muscle mass, pubertal progression, and bone health.

Poster 36: The cystic fibrosis (CF) neutrophil: a pivotal cell in accelerating lung decline in CF diabetes

Center for Cystic Fibrosis Research

Yue Luo, PhD, Arlene Stecenko MD, and Greg Gibson, PhD

A critical factor in the development of CF lung disease is inflammation. The major inflammatory effector cell in the CF lung is the neutrophil (PMN). These are the prime source of ROS which causes lung damage. CF related diabetes (CFRD) occurs in 35% of patients. Patients with CFRD have a significantly higher mortality than CF patients without diabetes and death is due to accelerated progression of lung disease. The focus of this proposal is to explore the role of the PMN in orchestrating accelerated lung decline in CFRD. Blood PMN were isolated using magnetic bead separation. Whole transcriptome gene expression profiles were generated using Illumina HT12 microarrays. 23 subjects (3 CF with normal glucose tolerance (NGT), 4 with CF prediabetes, 4 with CFRD, and 12 age matched controls, C) were studied. Contrasting PMN from CF and C, 412 of 15,000 expressed genes were differentially expressed at a significance level of $p < 0.01$ and 46 were significant at $p < 0.001$. The functional categories relevant to CFRD that were significantly up-regulated in CF were glucose transporter, glucose metabolism, and mitochondrial ribosome genes and those that were significantly down-regulated were DNA repair, mitochondrial iron-sulfur clustering, and anti-inflammatory genes. The transcript that showed the greatest difference was a glucose transporter which was increased 4.3 fold in CF. This increased expression appeared to be independent of the degree of glucose intolerance, suggesting a primary defect in the CF PMN. Since production of ROS in PMNs depends on glucose for energy, CF PMNs with increased expression of a glucose transporter placed in the CFRD hyperglycemic environment might be poised to increase production of ROS, accelerating lung damage. In summary, this pilot is uncovering major differences in the gene expression profiles of PMNs from CF patients compared to controls that could provide insights into the mechanism of CFRD.

Poster 37: Poverdine, the major siderophore of Pseudomonas aeruginosa, evades NGAL recognition
Center for Cystic Fibrosis Research

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Background: Cystic fibrosis (CF) patients develop chronic bacterial infections and *Pseudomonas aeruginosa* is the most common bacterial isolate that persists in the CF lung contributing to declining lung function. Bacteria secrete iron-chelating small molecules known as siderophores and the host limits bacterial growth by producing neutrophil gelatinase-associated lipocalin (NGAL) that specifically scavenges bacterial siderophores, therefore preventing bacteria from establishing infection. *P. aeruginosa* produces siderophores (pyoverdines) found to be important for biofilm development and bacterial virulence. The aim of this work is to determine if pyoverdine binds to the antibacterial protein NGAL. Methods: The binding of pyoverdine from *P. aeruginosa* and enterobactin from *E. coli*, to the recombinant NGAL protein was determined using the tryptophan fluorescence quenching method. Results: We found that pyoverdine did not bind to NGAL, neither in apo form nor when complexed with iron. We used enterobactin as a control, and as expected, enterobactin bound to NGAL causing strong tryptophan quenching. The data indicate that pyoverdine is a stealth siderophore that evades NGAL recognition. Further, upon phagocytosis of invading pathogens, respiratory burst is triggered as a defense mechanism that leads to release of reactive oxygen species (ROS) which is important for the oxidative killing of invading pathogens. We observed that pyoverdine decreased ROS release in a dose-dependent manner, when added at the peak of the respiratory burst in THP-1 macrophage-like cells exposed to *P. aeruginosa* LPS. The data suggest that pyoverdine dampens the respiratory burst possibly by scavenging released ROS to spare the oxidative killing of invading *P. aeruginosa*. Conclusions: *P. aeruginosa* persists in the CF host by evading both the iron-limiting innate defenses and the oxidative killing by macrophages.

Poster 38: Embryonic lung explants to model for paracrine actions of mesenchymal stromal cells in chronic lung disease of prematurity.

Center for Developmental Lung Biology

India C Brannan, M.D., Frank Harris, Theresa W Gauthier, M.D. and Ian Copland, PhD. Pediatrics/Division of Neonatology, Emory University, Atlanta, GA, United States and Department of Hematology and Medical Oncology, Emory University, Atlanta, GA, United States.

Chronic lung disease (CLD) is a serious complication of prematurity with potentially devastating consequences for the neonate. The pathophysiology is multifactorial but largely due to oxidative stress, pulmonary immaturity, volutrauma/barotrauma. An effective therapy is lacking but a potential therapeutic option for CLD is the use of Mesenchymal Stromal Cells (MSCs) as they have been shown to enhance tissue regeneration via paracrine-mediated neoangiogenesis and immunomodulation. Currently an appropriate model to analyze these effects on the developing lung is lacking. We hypothesize that MSCs secrete factors that are protective to the lung and aim to develop a lung model to demonstrate lung response in noxious conditions in presence of MSCs. Pregnant mice were sacrificed on gestational days 11-12 and their embryos harvested. Embryonic lungs were seeded on porous membranes in wells containing FBS or MSCs of mouse or human origin then exposed to normoxia or hyperoxia (60-80% oxygen/ 5% carbon dioxide) for 72 hours. Photographs were taken at 0, 24, 48 and 72 hours. Lungs were analyzed for growth and blood vessel densities. Under hyperoxic conditions, embryonic lung showed progressive deterioration compared to normoxic controls as evidenced by gross degradation and poor growth. Lung morphology appeared better preserved in presence of secreted factors from MSCs. Flow cytometry of explants suggests that MSCs may prevent the expansion of resident hematopoietic lineage cells. Hyperoxia is noxious to the developing lung and the effects are directly proportional to degree of hyperoxia as well as duration under these conditions. Furthermore, the presence of secreted factors of MSCs appears to mitigate the effects of noxious conditions. We propose that embryonic lung explants in transmembrane wells are an effective model to demonstrate alterations in growth and complexity. More data is still needed to delineate the effects of hyperoxia and presumed counter-effects of MSCs.

Poster 39: Systemic Glutamine, Asthma Severity, and Allergic Sensitization in Pediatric Patients A Possible Link

Center for Developmental Lung Biology

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Introduction: Severe asthma is characterized by increased inflammation and oxidant stress within the lung. While the mechanisms of severe asthma are not entirely clear, the disorder is likely related to oxidant stress from depletion of glutathione (GSH), a vital antioxidant, within the systemic circulation and airways. Hypothesis: Since GSH is a tripeptide synthesized from glutamine, cysteine, and glycine, the decreased availability of certain precursors may be responsible for decreased GSH concentrations in these children. Therefore, we hypothesized severe asthmatics will have decreased systemic glutamine levels that correlates with increased asthma symptoms and severity. Methods: systemic levels of glutamine, a precursor to glutamate that has been shown to correlate with GSH levels, were measured in plasma samples from 24 children with mild-to-moderate asthma and 36 children with severe asthma. Relationships between glutamine and clinical features of asthma severity, including lung function, asthma control, and markers of allergic sensitization were also assessed. Results: Children with severe asthma had significantly lower systemic glutamine levels ($p < 0.05$), when compared to children with mild-to-moderate asthma. Glutamine levels were not associated with lung function and asthma control. However, lower systemic glutamine levels were associated with increased exhaled nitric oxide concentrations ($r = -0.371$, $p < 0.01$), and a higher percentage of blood eosinophils ($r = -0.356$, $p < 0.01$). Conclusions: Glutamine concentrations are decreased in children with severe asthma and are associated with markers of allergic sensitization. These findings therefore suggest that decreased intake or altered metabolism of SAAs may be an important factor associated with severe asthma and allergic sensitization in children. Funded by: NIH RO1 NR 012021

Poster 40: Exhaled Breath Condensates and Tracheal Aspirates in neonates - a window into the lung

Center for Developmental Lung Biology

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Premature and ill newborns are at increased risk for oxidant-induced injury, particularly in the lung. Glutathione (GSH), an essential antioxidant in the lung is gestationally deficient in the premature newborn and is required for optimal functioning of resident cells in the lung, such as the alveolar macrophage (AM). Determining the GSH status of the neonatal lung requires invasive measurements such as collection of tracheal aspirates (TA) from intubated newborns. Exhaled breath condensates (EBC) have been described as a less invasive technique to evaluate oxidative stress markers in the lung, but little data exists of its use in the premature population. We hypothesized that GSH in the TA of mechanically ventilated newborns would directly correlate to the GSH found in EBC. Further, we hypothesized that the GSH status of the resident AM would be reflected in the TA and/or EBC. TA and EBC measurements were obtained after informed consent on stable neonates in the newborn intensive care unit. GSH and the percentage of oxidized glutathione disulfide (%GSSG) were measured via HPLC. AM were isolated from TA and cellular GSH status determined via immunofluorescence. Statistical analyses was performed via SPSS. Sixteen infants have been enrolled without any adverse events during sample collection. TA GSH and %GSSG significantly correlated with EBC GSH ($p=0.002$) and %GSSG ($p=0.002$). Furthermore, EBC GSH significantly correlated with AM GSH ($p=0.029$). Finally, TA and EBC GSH negatively correlated with the fraction of inspired oxygen on the ventilator. Our preliminary data suggests that redox measurements of a non-invasive EBC highly correlates to TA measurements and are indicative of cellular status. Further studies are necessary to determine whether EBC measurements in premature newborns are indicative of adverse clinical outcomes. Early identification of the premature newborn most at-risk for oxidant-induced injury may help tailor potential patient specific therapies.

Poster 41: NADPH oxidase regulates alveolar epithelial sodium channel (ENaC) activity and lung fluid balance in vivo via O₂- signaling.

Center for Developmental Lung Biology

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Departments of: 1 Department of Physiology 2 Department of Pediatrics 3 Department of Medicine and Cell Biology 4 Developmental Lung Biology Center at Children's Healthcare of Atlanta 5 Center for Cystic Fibrosis Research

Introduction: At birth, the lung transitions from a fluid secreting organ to an organ that must actively reabsorb salt and water in the alveoli in order for the newborn to breathe. In general, increases in epithelial sodium channel (ENaC) activity create an osmotic gradient for net water reabsorption in the alveoli. The specific mechanisms that regulate ENaC activity, however, remain unclear. We hypothesize that Rac1-mediated NADPH oxidase release of reactive oxygen species play a critical role in regulating ENaC activity (and hence alveolar fluid balance) at birth and throughout life. **Materials and Methods:** We used flow cytometry to purify alveolar type 1 and type 2 cells for western blot analysis of NADPH oxidases (Nox). Live lung tissue was used for both immuno-histochemical labeling and single channel patch clamp analysis in the cell-attached configuration. Live X-ray fluoroscopy quantified lung fluid content of C57Bl/6 mice challenged by tracheal instillation of saline or Nox inhibitor compound. **Results and Discussion:** Alveolar epithelial cells express Nox subunits (gp91phox, p22phox, p67phox, p47phox, and p40phox subunits) and small G protein Rac1. Since Rac1 is a known regulator of Nox2, and O₂⁻ release, we tested whether inhibition of Rac1 influenced ENaC activity. Indeed, 1 μ M NSC23766 inhibition of Rac1 significantly decreased ENaC activity from 0.87 ± 0.16 to 0.52 ± 0.16 in type 2 cells, and from 1.16 ± 0.27 to 0.38 ± 0.10 ($n = 6$) in type 1 cells. Tracheal delivery of NSC23766 lead to alveolar flooding in C57Bl/6 mice, and, consistent with a role for Nox2 in alveolar fluid clearance, Nox2^{-/-} mice showed increased retention of airspace fluid as compared to wild type controls. **Conclusion:** The data demonstrate that, in vivo, reactive oxygen species stimulate lung fluid clearance by increasing ENaC activity. The implication is that small G proteins, such as Rac1, may be an important point of pharmacological intervention for pulmonary disorders.

Poster 42: Hyperoxia decreases junctional proteins and promotes extracellular matrix in alveolar epithelial cells

Center for Developmental Lung Biology

S Vyas-Read, JC Dodds, TW Gauthier, LA Brown

Exposure to hyperoxia is often unavoidable in preterm infants and is implicated in the pathogenesis of bronchopulmonary dysplasia. The downregulation of junctional contacts between alveolar epithelial cells (AEC) is associated with a fibroproliferative response to injury. We examined how hyperoxia affects expression of junctional epithelial proteins and contributes to extracellular matrix. To assess changes in the lungs of animals exposed to oxygen in vivo, C57Bl/6 mice were exposed to room air or hyperoxia (85%) for 5 days and the lung was analyzed by immunofluorescence (IF) and RT-PCR. To evaluate the effects of hyperoxia on AEC, RLE-6TN were cultured under control or hyperoxia (85%) for 5 days and epithelial and mesenchymal proteins were evaluated by IF and immunoblot. The lungs of hyperoxia-exposed animals had 20% less E-cadherin and 40% less occludin mRNA when compared with controls ($p=0.03$). Whereas type II AEC cultured in room air expressed E-cadherin at cellular junctions, hyperoxia-exposed type II cells had minimal detectable E-cadherin protein and had 70% less claudin 18 protein expression. The lungs of hyperoxia-exposed animals had 1.8 times as much collagen I, 2.1 times as much collagen 5, ($p=0.03$), and 3.1 times as much fibronectin mRNA ($p=0.01$) as control animals. Alpha-smooth muscle actin, which was not detectable in the alveolar space of control animal lung, was expressed in the alveoli of hyperoxia-exposed animals. In culture, hyperoxia-exposed type II AEC expressed 3 times as much alpha-smooth muscle actin ($p=0.002$) and 1.9 times as much vimentin as controls ($p=0.04$). Hyperoxia exposure decreases normal alveolar junctional integrity and promotes extracellular matrix deposition in the type II AEC and in the mouse lung. A better understanding of the mechanistic relationship between oxidative stress, junctional proteins and mesenchymal phenotype may have significant implications for preterm infants at risk for bronchopulmonary dysplasia.

Poster 43: A novel method for interpreting prenatal behavioral responses to speech in autism research.

Marcus Autism Center

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Background: Autism is a neurodevelopmental disorder characterized by a deficit in communication that may derive from an early derailment of social engagement. Social engagement during critical periods of infant development begins with a preference for maternal speech over other speech and non-speech signals in utero. A failure to develop a preference for maternal speech in the womb could lead to aberrant social development in the infant with lifelong negative consequences. The aim of this study is to develop methods for investigating the precursors of social-vocal engagement by examining fetal attention to speech and non-speech. **Methods:** In this presentation, we describe a new methodological technique for detecting specific differences in cardiac response that indicate altered patterns of attention in the fetus. Our method applies time series analysis to accurately detect differences in the entire temporal profile of the cardiac response to an external stimulus, integrating key information about the local variability in heart rate known to indicate behavioral state, thus enhancing detection. We demonstrate the application of this technique to data derived from Doppler ultrasound recordings. **Discussion:** By allowing us to model inherent correlation across time within a single subject such that behaviorally-relevant cardiac responses to auditory stimuli may be considered separately from inherent fluctuations in fetal heart rate, we are able to identify with greater specificity which aspects of speech are perceptible in the womb and salient to fetuses. **Conclusions:** We have evaluated an innovative analytical and experimental technique for detecting behaviorally significant fetal responses to auditory stimuli as part of a new study to evaluate precursors to social engagement relevant to autism in utero.

Poster 44: Early vocal development in infants at risk for autism.

Marcus Autism Center

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Background: Autism is a neurodevelopmental disorder of early onset characterized by a three-fold deficit in social interaction, communication, and restrictive/repetitive behaviors. At present, clinical diagnosis of autism is not reliable before two years of age. Current research centers on the development of objective quantifiable biomarkers of risk within the first year of life. **Objective:** Focusing on the developmental unfolding of the communication deficit, the aim of this study is to quantify early vocal behavior and spoken language development in infants at risk of autism relative to typically-developing peers over the first three years of life, in order to test the hypothesis that early derailment of social vocal engagement may be predictive of later language and diagnostic outcome. **Methods:** As part of an ongoing pilot study, we recruited 4 low-risk infants, with no family history of autism, and 4 high-risk infants, with older siblings already diagnosed with autism. Using a miniature digital audio recording device (LENA) sent out to families in the mail and worn by each child all day, we made day-long audio recordings of each child's language environment at monthly intervals from 2 months onwards. Using automatic speech recognition technology, we extracted and labelled utterances by infant and caregiver, to derive longitudinal measures of (a) vocal interaction, (b) spectral features, and (c) developmental milestones. **Results:** Reporting on the first 12 months of our study, we present developmental profiles for all of our measures, derived from more than 600 hours of recordings, and quantify possible departure from typical behavior in two of our high-risk siblings, specifically in early vocal interaction. **Conclusions:** Automated vocal profiling of infants at risk for autism may enable us to shed light on the developmental unfolding of the communication deficit, with future implications for developing early targeted intervention.

Poster 45: Growth and nutritional status of children with autism spectrum disorder: A meta-analysis and comprehensive review of the literature

Marcus Autism Center

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Background: Autism spectrum disorders (ASD) and feeding problems are frequently linked; however, the impact of atypical feeding on growth and nutritional status in ASD is unknown. In the only literature review to date, Cermak and colleagues (2010) reported inconclusive results, with different studies suggesting nutritional deficiencies, excesses, or no deviation from normative comparison. The review also did not investigate anthropometric status. The current meta-analysis sought to provide a more comprehensive picture of the growth and nutritional status related to ASD by utilizing quantitative procedures for summarizing and synthesizing outcome data. Methods: A total eight studies involving 263 children with ASD were included in the meta-analysis on nutritional status. Key nutrients analyzed included vitamin A, C, D, & E, zinc, calcium, iron, fiber, energy, total fat, protein, and carbohydrates. Seven studies involving 426 children with ASD contributed to the growth analysis. Effect size (ES) estimates involved standard mean difference (SMD) with associated 95% confidence intervals. Results and Discussion: Findings indicated that children with ASD had significantly ($p < .05$) lower intake of calcium and protein. The ES estimates for both calcium (SMD: $-.65 (.28)$; 95% CI: -1.21 to -0.09) and protein (SMD: $-.58 (.25)$; 95% CI: -1.07 to -0.09) demonstrated medium differences in these nutrients when compared to comparison groups. Review of the anthropometric data indicated no difference in weight, height, and BMI between the groups. Conclusion: Results suggest that children with ASD fall within expected growth parameters; however, the population may be at risk for inadequate intake of calcium and protein. Findings emphasize the need to develop an empirical framework to guide research and clinical activities regarding nutrition and ASD, including the role of dietary insufficiencies in the pathology of the condition, as well as the use of dietary manipulation.

Poster 46: Inhibition of HIV-1 endocytosis allows lipid mixing at the plasma membrane, but not complete fusion

Center for Pediatric Nanomedicine

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We recently demonstrated that human immunodeficiency virus type 1 (HIV-1) productively enters epithelial HeLa-derived and lymphoid CEMss cells by fusing with endosomes, whereas its fusion with the plasma membrane (PM) does not proceed beyond the lipid mixing step. Here we extended our analyses of HIV-1 fusion to a larger panel of cell types including primary CD4+ T cells. Kinetic studies combined with time-resolved imaging of single virus fusion reinforced our initial findings that HIV-1 enters the cells via endocytosis and fusion with endosomes. In order to redirect HIV-1 fusion to the plasma membrane, we employed two experimental approaches. First, the viruses were allowed to engage CD4 and coreceptors at reduced temperature that is not permissive for virus uptake or fusion. Subsequent shift to a physiological temperature triggered accelerated virus uptake followed by entry from endosomes, but did not permit fusion at the cell surface. Second, the HIV-1 endocytosis was blocked by a small-molecule dynamin inhibitor, dynasore. Pretreatment with dynasore resulted in transfer of viral lipids to the plasma membrane without a detectable release of the viral content into the cytosol. Using the time-of-addition experiments, we found that higher doses of dynasore are required to block virus-endosome fusion compared to those inhibiting endocytosis. In conclusion, our results further support the notion that HIV-1 enters disparate cell types through fusion with endosomes. The block of HIV-1 fusion with the plasma membrane at a post-lipid mixing stage shows that the plasma membrane is not conducive to fusion pore formation and/or enlargement. Our results also implicate dynamin in facilitating the HIV-endosome fusion step.

Poster 47: Imaging Single Retrovirus Entry Through Alternative Receptors and Fusion with Endosomes

Center for Pediatric Nanomedicine

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The Avian Sarcoma and Leukosis Virus (ASLV) is a prototypic oncogenic virus that enters permissive cells via the two-step mechanism. First, ASLV Env glycoprotein binds a cognate receptor, which renders the Env competent to undergo refolding at low pH. Second, internalized ASLV undergoes fusion with the limiting membrane of acidic endosomes. We took advantage of the ability of the receptor-primed ASLV to remain fusion-competent for hours in the presence of NH₄Cl, which prevents fusion by raising endosomal pH. Following entry in the presence of this weak base, ASLV fusion can be synchronously initiated by removing NH₄Cl. We have fusion mediated through this arrest/release protocol in cells expressing either TVA950 (an integral membrane receptor) or TVA800 (GPI-anchored receptor), the two naturally occurring isoforms of cognate receptor. Early steps of single ASLV fusion were imaged based on the release of a GFP-based viral content marker. The full-length receptors supported faster release of the viral content into the cytosol, suggesting a more robust fusion compared to the GPI-anchored isoform. Synchronization of fusion through the NH₄Cl arrest/release protocol allowed detection of the viral core release following the transfer of a small content marker. The liberated viral cores were much more mobile compared to endosomes with which they fused. Strikingly, the viral cores moved twice as fast in TVA950 cells compared to TVA800 cells, implying that these cores were released into different compartments. Colocalization analysis further supported this notion. Viruses were primarily trapped in early Rab5-positive endosomes in TVA950 cells, whereas ASLV was mainly found in Rab7-positive compartments in TVA800 cells. Collectively, these findings reveal that ASLV is trafficked into distinct endosomal compartments by the alternative receptor isoforms and that the virus' itinerary has profound effects on the efficiency of fusion and on early post-fusion steps.

Poster 48: The clinical application of fMRI language mapping: Differential language activation and neuropsychological functioning in a pediatric population with seizures

Children's Center for Neurosciences Research

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Over the past 15 years, functional MRI (fMRI) has represented a popular tool for the study of brain localization. It has been useful in adult populations to study the neural substrates of cognition in both healthy individuals and those in disease states, and more recently extrapolated for use with pediatric populations. fMRI is most commonly used as a research tool in the following pediatric clinical populations: - Epilepsy (e.g., language and motor mapping) - ADHD (e.g., executive function) - Autism (e.g., facial and language processing) - Brain tumors/cancer The most used clinical application for fMRI is assessment of language processing in the context of a presurgical work-up for intractable epilepsy, neoplasms, and arteriovenous malformations.¹ Resection surgery for intractable seizures is considered when there is an identifiable focal lesion. Typical pre-surgical procedures²: - EEG - MRI - Neuropsychological Evaluation - Depending on area of dysfunction, Wada and/or fMRI can be completed to localize language function - Electrical cortical stimulation - Other newer procedures include Diffuse Tensor Imaging (DTI) - Neuroimaging less commonly used include PET, single-photon emission CT (SPECT), and magnetoencephalography (MEG) • Aim of the current study: •To determine the correspondence between neuropsychological and fMRI findings •To investigate the differences in neural and neuropsychological functioning between healthy controls and patients with seizures.

Poster 49: Selective deletion of Nav1.1 from forebrain expressing parvalbumin interneurons results in increased susceptibility to flurothyl- and hyperthermia-induced seizures

Children's Center for Neurosciences Research

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Voltage-gated sodium channels (VGSCs) are essential for the generation and propagation of action potentials in electrically excitable tissues. Mutations in the VGSC SCN1A underlie several forms of epilepsy including Dravet Syndrome (DS) and Genetic Epilepsy with Febrile Seizures Plus (GEFS+). Electrophysiological analyses of mouse models of DS and GEFS+ have led to the hypothesis that SCN1A mutations reduce the excitability of inhibitory cortical and hippocampal interneurons. We examined the expression of Nav1.1 in inhibitory parvalbumin (PV) interneurons and excitatory neurons from P22 mice using fluorescent immunohistochemistry. We found that 78% of PV immunoreactive interneurons in the neocortex were positive for Nav1.1. Likewise, 88% of PV immunoreactive interneurons were positive for Nav1.1 in the hippocampus. Specifically, PV immunoreactive neurons in CA1, CA3, and the DG regions of the hippocampus were 88%, 79%, and 98% positive for Nav1.1, respectively. In contrast, only 18% of Camk2a positive neurons (excitatory cells) in the P22 mouse neocortex were positive for Nav1.1. To examine the functional contribution of Nav1.1 in each cell type to seizure thresholds, we generated an Scn1a conditional knockout mouse. Selective deletion of Scn1a from PV interneurons and pyramidal cells was achieved by crossing mice with the floxed Scn1a allele to the Ppp1r2-Cre and Emx-Cre transgenic lines, respectively. Heterozygous progeny from these crosses were evaluated for alterations in thresholds to flurothyl-induced seizures. We found that selective deletion of Scn1a from PV expressing interneurons was sufficient to reduce thresholds to flurothyl-induced seizures, while thresholds were unaltered following deletion from pyramidal cells. Deletion of Nav1.1 from PV interneurons also resulted in increased susceptibility to hyperthermia-induced seizures, illustrating a role for this interneuron subtype in febrile seizure generation. These findings provide further support for alte

Poster 50: The Spinal Muscular Atrophy Disease Protein SMN Regulates the Assembly and Transport of mRNA Granules in Motor Neuron Axons by Interacting with mRNA-Binding Proteins

Children's Center for Neurosciences Research

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Spinal muscular atrophy (SMA) is a neuromuscular disease characterized by the specific degeneration of spinal motor neurons. SMA is caused by reduced levels of the survival motor neuron (SMN), a ubiquitously-expressed protein playing a housekeeping role in the assembly of small nuclear ribonucleoproteins. It is still unclear, however, why motor neurons selectively degenerate in SMA. We have shown that SMN is transported to the axons of primary motor neurons, where it colocalizes with mRNA-binding proteins. Also, defects in the localization of β -actin mRNA at the axon tip of SMA motor neurons have been observed. Thus, we hypothesize that SMN plays an additional role in motor neurons, possibly facilitating the assembly and transport of specific mRNAs and mRNA-binding proteins into RNA granules. To test this hypothesis, we investigated the interaction of SMN with the mRNA-binding proteins IMP1/ZBP1 and HuD. Both IMP1 and HuD bind and regulate several transcripts, including β -actin mRNA. We show that SMN colocalizes and is transported in granules containing IMP1 and HuD along the axons of motor neurons. We identified the SMN Tudor domain as necessary for SMN interaction with both HuD and IMP1, and we showed that a single point mutation in this domain disrupts the association. Importantly, shRNA-mediated knockdown of SMN leads to a significant reduction of HuD and IMP1 in the axonal compartment. This is also associated with a dramatic decrease in axonal polyA mRNA. The expression of SMN lacking the Tudor domain in SMA motor neurons failed to rescue this defect. We are now investigating the role of SMN in the mRNA/mRNA-binding protein association by using biochemical approaches such as RNA UV cross-linking. Taken together, these findings support a role for SMN regulating the association of mRNA-binding proteins with target mRNAs, providing a plausible model to explain motor neuron defects in SMA.

Poster 51: PI3K/mTOR signaling and protein synthesis as therapeutic target and biomarker in Fragile X Syndrome

Children's Center for Neurosciences Research

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Many genetic defects linked to autism spectrum disorders (ASDs) converge on the phosphoinositide-3 kinase (PI3K)/mTOR signaling pathway, which regulates protein synthesis. Recent studies furthermore support a significant role of PI3K signaling for the most frequent monogenetic cause of autism, the fragile X syndrome (FXS). A broad-spectrum PI3K inhibitor reverses dysregulated protein synthesis, excess GluA endocytosis and aberrant dendritic spine morphology in an FXS mouse model. Genetic and pharmacologic reduction of the PI3K catalytic subunit p110beta, which we have shown is specifically dysregulated in Fmr1 KO mice, rescues excess synaptic protein synthesis in Fmr1 KO mice. We furthermore show that increased and dysregulated PI3K/mTOR pathway activity and protein synthesis can also be detected in lymphoblastoid cells from FXS patients, and can be reduced with the same p110beta specific inhibitor. Our data suggest that excess PI3K/mTOR activity regulating protein synthesis may be a therapeutic target and biomarker for FXS, and possibly other ASDs.

Poster 52: Targeting the voltage gated sodium channel Scn8a for the treatment of refractory childhood epilepsies.

Children's Center for Neurosciences Research

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Voltage gated sodium channels (VGSCs) play an important role in the pathophysiology of epilepsy. Mutations in the VGSC gene SCN1A have been identified in patients with various subtypes of epilepsy including the catastrophic childhood encephalopathy Dravet syndrome and genetic epilepsy with febrile seizures plus (GEFS+). Similarly, mice with Scn1a mutations exhibit reduced seizure thresholds, severe spontaneous seizures and premature lethality. In contrast, we demonstrated that mice carrying mutations in the VGSC gene Scn8a display increased resistance to chemically and electrically induced seizures. Also, we were able to dramatically ameliorate the seizure phenotype of Scn1a mutants by co-expression of an Scn8a mutation, suggesting that Scn8a may provide a therapeutic target for the treatment of Dravet syndrome. To determine the feasibility of selectively targeting SCN8A as a treatment for epilepsy, it is necessary to establish that seizure protection can also be achieved when Scn8a expression is reduced at postnatal time points. We therefore employed two methods that provide temporal control over the reduction of Scn8a expression. First, the tamoxifen inducible Cre transgenic mouse line Ubc-CreERT2 was crossed to mice expressing a floxed Scn8a allele. Deletion of the Scn8a gene, initiated in 3-month-old mice by injection of tamoxifen, resulted in increased resistance to induced seizures. Secondly, we developed an adeno-associated virus (AAV) expressing an shRNA that effectively reduces the expression of the Scn8a protein. Intra-hippocampal AAV-shRNA delivery was found to increase seizure thresholds and prolong the survival of Scn1a mutants that model Dravet syndrome. These results 1) identify the hippocampus as a region critical for Scn8a-related seizure resistance, 2) demonstrate the feasibility of increasing seizure thresholds by reducing Scn8a expression postnatally and 3) provide support for the selective targeting of Scn8a for the treatment of Dravet syndrome.

Poster 53: Maternal perinatal energy balance programs infant growth in rhesus monkeys.

Children's Center for Neurosciences Research

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Introduction: Environmental exposures during early life may program long term growth patterns and the risk for obesity. This project examined maternal influences on fetal and infant growth over 1 year in socially housed, rhesus monkeys that wean at 5-6 months of age. It was hypothesized that positive energy balance in mothers would be associated with faster infant growth. Methods: 18 randomly selected, pregnant rhesus monkeys underwent anthropometry and DEXA scans on gestational days 100 and 150 of their 165 day gestation and at 1 and 5 months post-partum (pp). Dams and their infants were weighed near pp days 2, 7, 14, 28, and then monthly. Serum leptin concentrations from dams at 1 month pp and infants at 14 and 28 days were measured by RIA. Peripartum was defined as the interval between gestational day 150 and 1 month postpartum. A multi-level model determined statistical associations. Results: Infant birth weight correlated best with maternal mid-gestational lean body mass ($r^2 = 0.60$, $p < 0.001$) and did not predict postnatal growth. Weight gain in the healthy progeny was linear over the first year and was significantly associated with maternal peripartum fat accretion ($r^2 = 0.62$; $p < 0.005$) and maternal circulating leptin 1 mo pp ($r^2 = 0.49$, $p < 0.006$). Infant growth, however, was not predicted by either later maternal fat accretion (between 1 and 5 months pp) or by infant circulating leptin concentrations at 14 and 28 days of age. Infant growth rate was independent of sex, maternal age and parity, and social status. Conclusion: Maternal energy balance during a critical perinatal period correlated positively with offspring growth rate. Endurance of this effect throughout the first year of life suggests that programming of growth occurred during this peripartum window.

Poster 54: Female HIV-1 transgenic rats manifest depressive-like behavior during adolescence.

Children's Center for Neurosciences Research

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Adolescents living with HIV/AIDS have an elevated incidence of clinical depression compared to the general population. The stigma of being HIV-positive has been proposed to account for this increased incidence of depression, despite a lack of evidence for similar associations between external stimuli and depression in other disease states. This study tested the hypothesis that developmental expression of HIV-1-related proteins causes depressive-like behavior in adolescent female rats. HIV-1 transgenic rats have circulating gp120 in their blood and develop pathology consistent with human AIDS. Here we compared affective-like behavior of female adolescent HIV-1 transgenic rats (PND 48; prior to manifestation of AIDS-like pathology) to wild-type littermates. Both genotypes were assessed with an extensive battery of neurological and motor tests. Adolescent HIV-1 transgenic rats exhibited normal motor behavior and general neurological function when compared to littermates ($p > 0.05$). HIV-1 transgenic rats spent more time floating than wild-type littermates ($p < 0.05$) in the forced swim test suggesting a more passive coping strategy. This behavioral difference is not related to motor behavior as locomotor activity did not differ between groups in the open field ($p > 0.05$). In order to assess social behavior, a novel female adolescent rat was introduced to each subject. HIV-1 transgenic adolescent females were slower to approach the novel animal, and HIV-1 transgenic adolescent females spent less overall time socially interacting than their wild-type littermates ($p < 0.05$). These data demonstrate a behavior pattern in adolescent female HIV-transgenic rats, which is consistent with a classification of depressive-like behavior, and suggests a biological source. Determination of the origin of increased depressive-like behaviors may provide alternate therapeutic angles by which to treat HIV-associated depression.

Poster 55: Stress and Absence Epilepsy: How a Voltage-Gated Sodium Channel (Scn8a) Mutation Affects the Stress Response and Seizure Outcome

Children's Center for Neurosciences Research

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Absence epilepsy is a common form of epilepsy affecting both adults and children. Stress has been reported as a seizure precipitating factor by absence epilepsy patients, suggesting that the physiological stress response has the potential to be a new therapeutic target for the treatment of epilepsy. Little is currently known about how a genetic predisposition to epilepsy interacts with the stress response to influence seizure outcome. In order to address this question, we have examined the effect of acute stress and early life stress on seizure outcome in mice with mutations in the voltage-gated sodium channel (VGSC) gene *Scn8a*. *Scn8a* mutants have putative deficits in excitatory pyramidal cell signalling and display spontaneous spike-and-wave discharges characteristic of absence epilepsy. Using EEG recordings, we have observed that the baseline frequency of absence seizures in the *Scn8a* mutants closely correlates with the diurnal activity of the hypothalamic-pituitary-adrenal (HPA) axis, a key player in the physiological stress response. A 20-minute acute restraint stress administered in the morning increases the frequency of spontaneous absence seizures immediately following the stressor. Seizure frequency returns to baseline levels within three hours after stressor exposure, but the subsequent evening peak in seizure frequency is delayed and broadened, changes which persist into the next evening. We also examined the effects of a 20-minute acute restraint stress on chemically induced seizures and found that acute stress increases the severity and duration of induced seizures in *Scn8a* mutants, changes which differ from wildtype littermates. We have also shown that early life experience changes the frequency of absence seizures in adulthood. Overall, our data show that a voltage-gated sodium channel mutation can alter the behavioral response to stress and can interact with the stress response to alter seizure outcome.

Poster 56: The impact of neonatal inflammatory injury on stress-related behavior and circuits in adult male and female rats.

Children's Center for Neurosciences Research

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Over 12.5% of infants born in the US are premature, requiring an extensive stay in the Neonatal Intensive Care Unit (NICU). Many NICU procedures are painful, inflammatory and performed without analgesics. Clinical studies reveal lack of analgesic therapy in the NICU is strongly associated with blunted pain and cortisol (CORT) responses and increased risk for affective disorders later in life. Our previous studies expand on clinical findings. Specifically, adult rats given inflammatory injury on the day of birth (PNO) are less sensitive to pain due to up-regulation of endogenous opioids, display decreases in anxiety- and stress-like behavior in the Open Field (OF) and Forced Swim Test (FST), respectively. Neonatal injury blunts CORT responses, alters protein expression of glucocorticoid receptor (GR), corticotrophin releasing factor (CRF) and receptors (CRFR) in stress-related brain regions suggesting dysregulation of the adult stress response. Endogenous opioids inhibit the HPA axis, but it is unknown whether they mediate the decrease in stress-like behavior observed in neonatally injured adults. Further, it is not known if changes in GR mRNA support changes in GR protein expression or if CRFR binding is altered. To answer these questions rat pups received an intraplantar injection of the acute inflammatory agent carrageenan (1%) on PNO; controls were handled identically. Adult animals either: 1) received opioid receptor antagonist naloxone (1 or 5 mg/kg or vehicle) then 5 min in the FST, 2) sacrificed and brains processed for in situ hybridization or receptor autoradiography. Our data from adults suggest: 1) injury-induced increase in endogenous opioid-tone decreased stress-like behavior in the FST, 2) injury altered GR mRNA and CRFR binding in stress-related brain regions. Collectively, our studies suggest neonatal injury alters adult stress behavior, circuitry and evidences long-term, polysystemic consequences of neonatal trauma in the absence of analgesics.

Poster 57: Phenotypic variability of DiGeorge and Waardenburg syndromes in one family.

Clinical Outcomes Research & Public Health

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Introduction: To evaluate the genetic etiology in a four generation African-American family with hearing loss, white forelock, heterochromia, congenital heart defect, developmental delay and ADHD. DiGeorge syndrome is caused by deletions at chromosome 22q11.2 resulting in variable clinical presentation including heart defects, cleft lip and palate, developmental delays, recurrent infection and characteristic facial features. Waardenburg syndrome (WS) presents with sensorineural deafness and pigmentation abnormalities of the hair, skin, and eyes. Both are autosomal dominant disorders. Methods: Clinical evaluation, chromosomal microarray analysis, fish for 22q and genetic testing of PAX3, a gene causing WS. Results: The proband had congenital hearing loss, characteristic facies with dystopia canthorum, blue iris, hypopigmented areas of skin and strands of white hair consistent with Waardenburg syndrome. His mother had facial features suggestive of WS with dystopia canthorum, broad nasal bridge, epicanthal folds and white forelock. In addition, she had a congenital heart defect, and developmental delays and had 22q11.2 deletion causing DiGeorge syndrome. History and evaluation of other family members revealed variable degree of hearing loss, premature graying and congenital heart defects. Fish for 22q and molecular genetic testing of PAX3 was negative in the proband. Conclusions: Two rare AD genetic syndromes can occur together in the same family rarely and should be considered when there are overlapping clinical features. Deletion of chromosome 22q11.2 accounts for DiGeorge syndrome in the proband's mother and her half sister. A mutation in a gene other than PAX6 likely causes the Waardenburg syndrome in this family. Additional gene testing of MITF and SOX10 are underway to determine the exact etiology for WS syndrome. Impact: Molecular genetic testing of family members with shared phenotypic features can help to personalize and provide optimal medical care.

Poster 58: Using SMS to Mediate Patient-Physician Communication between Regularly Scheduled Visits to Improve Chronic Illness Management

Clinical Outcomes Research & Public Health

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Several factors influence effective management of a chronic condition these include: open communication between patient and health care provider; a patient's awareness of symptoms and knowledge of her/his condition; and level of adherence to medical regimen. Best practices for patients with chronic conditions such as diabetes and asthma include visits to their physician 3 or 4 times a year. Despite the knowledge that communication is vital, there is often no communication between the patient and physician between regularly scheduled visits, unless there is an acute episode (e.g., asthma attack) that lands the patient in the emergency room. Here we present an approach that addresses all of the afore mentioned factors that lead to effective chronic care management.. We gathered symptom and management information from patients between scheduled medical visits using SMS. We also developed a visualization tool that presented the patient's SMS data in a clinically palatable format for the physician to utilize. Results from our randomized control study showed that the simple act of communicating knowledge and awareness information via SMS leads to improved pulmonary outcomes for pediatric patients. It also showed that the physician were able to use the data from the visualization tool to deliver patient-specific information during a follow-up medical visit. Although, the data we present is from pediatric asthma patients we believe that this approach can be tailored to other chronic conditions to improve patient-physician communication.

Poster 59: Readiness for Independence: Facilitation of the Transition to Adulthood for Teens with Acquired Brain Injury (ABI).

Clinical Outcomes Research & Public Health

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Introduction: Transition to adulthood, a move from dependence to independence, is a gradual process cumulating with less reliance on adults, increased personal responsibilities, and participation in community activities. Research describing transition outcomes for youth with ABI indicates that the presence of a medical home, self-determination and access to resources are skills that facilitate success. The goal of this paper is to describe a model intervention program that includes skill development in areas critical for transition to adulthood and outcomes for transition readiness. Materials and Methods: The BRAIN Program (Bringing Rehabilitation and Injury recovery to New Levels) is a two –week evidenced-based, intensive program to teach transition skills and offer access to resources to achieve post high school goal attainment. A peer coach model is utilized to provide skills training for communication, self-management, fitness and health/wellness. Access to resources is provided for school, vocational rehabilitation, leisure and health and wellness. Results and Discussion: Participants were 18 teens with acquired brain injury enrolled in the 2009, 2010 and 2011 programs. Qualitative data analyses from each year lead to the development of the Readiness for Independence Questionnaire (Haarbauer-Krupa & Gilleland, 2011) as an outcome tool for program evaluation. Findings from the 2011 pilot study of this measure will be presented as well as 3 month program follow-up. Conclusions: Teens with acquired brain injuries benefit from programs that offer training for skills important for the transition process and access to resources. Implications for outcomes for health and wellness will be discussed. Impact: Findings from program participants will inform the medical and educational communities about transition needs for adolescences with complex medical conditions.

Poster 60: Follow-up of Preschool Children with Acquired Brain Injury

Clinical Outcomes Research & Public Health

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Introduction: Compared to school aged children, infants and children under the age of 5 are particularly vulnerable to the effects of traumatic global brain injuries (Ewing-Cobbs & Barnes, 2003; Ewing-Cobbs & Barnes, 2002, Lowenthal, 1998). The goal of this study follow children who experience a brain injury before the age of 5 years to identify services accessed, school and community participation, developmental status, and parent burden and stress. Method: A mixed method study will be presented. Parents of children injured less than 5 years who were discharged from rehabilitation between the years 2004 - 2010 were contacted for a telephone interview followed by completion of questionnaires about their child's developmental level, school/community participation, and family burden/stress. Results: Following discharge from rehabilitation, children younger than age 5 do not have a single point of entry into school and community services. Caring for children required most parents to take time off from work resulting in lost income. An age effect was observed with parents of older children reporting increase number of concerns about their child. Conclusions: Children who sustain a brain injury before the age of 5 have increased risk for issues at a later age. Once discharged from the medical model, they do not have a single point of entry for school and community services and are often lost to follow-up by the time they are in elementary school. Increased stress and burden is on parents who manage their child's care. Findings from this study support increased education about long-term consequences during the hospital stay, screening for brain injuries during the early elementary years, and follow-up of preschool children during their school years. Impact: Understanding outcomes of preschool children with brain injuries provides insight into follow-up needed for complex medical conditions.

Poster 61: The Impact of Laparoscopy on Postoperative Small Bowel Obstructions in Children
Clinical Outcomes Research & Public Health

Sarah J. Hill, MD Emory University and Children's Healthcare of Atlanta Samir R. Pandya, MD Emory University and Children's Healthcare of Atlanta Mark L Wulkan, MD Emory University and Children's Healthcare of Atlanta

PURPOSE: There is limited published data regarding post-operative small bowel obstructions (SBO) in the pediatric patient population. In order to better characterize the impact of surgical technique on bowel obstructions, a retrospective review was performed. **METHODS:** After IRB approval, a retrospective chart review over ten years (2000-2010) was performed analyzing data of patients who were admitted to a tertiary care children's hospital with symptoms of a bowel obstruction. Patients without a history of prior abdominal surgery, with cystic fibrosis, or Hirschsprung's disease were excluded. Statistical analysis was performed using SPSS software and evaluated with a chi-square and non-parametric Mann-Whitney U test. A p value ≤ 0.05 was deemed as statistically significant. **RESULTS:** There were 250 qualifying admissions from 219 different patients. Of those, 21% had a history of prior laparoscopy (LAP) and 79% had undergone a prior laparotomy (OPEN). LAP patients presented with post-operative SBO significantly earlier when compared to OPEN (192 vs. 841 days. SD ± 378.8 and ± 1326.4 , $p=0.001$). The most common documented cause of obstruction for both LAP and OPEN was adhesive disease (78.2% and 62.5% respectively, $p=0.19$). Regardless of the type of prior surgery, there was no difference in the percentage of patients requiring operative intervention (LAP= 71%, OPEN= 72%, $p=0.405$). The type of prior operative technique (LAP vs. OPEN) did not impact the operative approach for postoperative SBO requiring surgical intervention ($p=0.12$). **CONCLUSIONS:** We conclude that minimally invasive surgery appears to impact the timing of presentation of post-operative SBO. However, the initial approach (LAP vs. OPEN) does not seem to have an impact on the need for surgical management of postoperative bowel obstructions.

Poster 62: Diabetes provider compliance with national standards nets improved clinical outcomes for patients.

Clinical Outcomes Research & Public Health

Margaret Jenkins, RN; Inger Hansen, MD; Maureen McGrath, NP; Karla Aleman, RD; Karen Lindsley, RN; Alan Kim, Student; Andrew Muir, MD; Emory Children's Center

The Pediatric Diabetes Center will continue a program of auditing and improvement to elevate our clinical outcomes, after achieving credentialing by the American Diabetes Association (ADA). The ADA National Standard for care includes assessment of markers for other key silent, co-existing, auto-immune conditions in children already diagnosed with Type 1 diabetes (T1DM), such as thyroid or celiac disease. We audit each patient's chart before his/her annual assessment visit for compliance with the ADA standard checklist in ordering/documenting lab tests and eye exams. During our initial assessment, we expected to identify standard screening tests not previously ordered. Based on the results, we plan to increase compliance by improved awareness, training, and timely reminders. We developed and vetted a 7 point assessment form capturing the most recent dates for the tests required based on age and years of diabetes. Alert information is entered into a visit reminder and placed at the front of the chart for the provider's awareness. Assessment results are entered into a tracking database. We analyzed compliance data on patient visits before initiating the program ($n=45$) and again at 6 months after initiating audits ($n=181$). We were less than 90% compliant in following ADA standards for each of the early detection tests. Testing for Celiac was the most frequently omitted test. Celiac disease is a damaging, often asymptomatic disease, which results in malnutrition and multiple complications. This outcomes assessment revealed that we need to increase our testing for celiac disease. Consequently we have diagnosed several children with celiac disease via increased screening. We have identified barriers to compliance in our providers and retrained staff. We will reassess our compliance and assess for appropriate follow-up of the newly diagnosed individuals. Enhanced management of co-existing conditions should also result in improvement in diabetes control.

Poster 63: Healthy-lifestyle camp intervention for obese children and their families

Clinical Outcomes Research & Public Health

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Parental self-efficacy, mindful eating, & attitude towards food restriction may affect their child's weight. The Healthy lifestyles Camp experience comprised a 5-day residential program for 8-12 year old obese children, sandwiched by family weekends that addressed these issues. Of the 18 families attending weekend-1 and camp, 12 attended weekend-2. Standardized questionnaires were completed concurrently in separate rooms by mothers (about their child and themselves) and by campers (about themselves) at the start of weekend-1 and the close of weekend-2: Pediatric Quality of Life (PQL), Weight Self Efficacy (WEL), Self-Efficacy Questionnaire for Children (SEQ-C), Child Feeding Questionnaire (CFQ), Mindful Eating Questionnaire (MEQ). Paired t-tests compared means of transformed data on the PQL and signed rank-sum tests compared medians otherwise. Campers' perceptions about themselves on the PQL, SEQ-C, and WEL before and after camp were not different. On the PQL, mothers reported higher psychosocial, but not physical health scores about their child after camp (62.4 vs 73.9; $p=0.05$). Mothers' WEL scores for themselves increased after camp in all test domains (101.5 vs 144.0, $p=0.001$). They reported more mindful eating in response to emotions (MEQ 2.5 vs 3.5; $p=0.002$), less concern about restricting their child's food (CFQ 4.3 vs 4.0; $p=0.02$), and less anxiety about their child's weight (3.6 vs 3.5; $p=0.05$). The results suggest that participation in camp instilled attitudes in mothers about themselves and their children that may promote weight control in the children. These hypotheses will be addressed in the subsequent camp in greater depth with a larger group of camp families.

Poster 64: Concentrations of polyfluoroalkyl chemicals during gestation and serum lipids in girls enrolled in the Avon Longitudinal Study of Parents and Children.

Clinical Outcomes Research & Public Health

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Background and aims. Polyfluoroalkyl chemicals (PFCs) are commercially synthesized chemicals used in consumer products. Exposure to PFCs is widespread and some PFCs may disrupt signaling processes involved in the control of lipid metabolism. We explored associations of maternal concentrations of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorohexane sulfonate (PFHxS) during gestation with serum lipid concentrations at age 7 in girls. Methods. Analyses were conducted on a sample of 227 singleton girls and their mothers participating in the Avon Longitudinal Study of Parents and Children. PFC concentrations were measured in serum samples obtained from the mothers at pregnancy. Cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides were measured in serum samples obtained from the girls at ages 7 and 15. Linear regression models were used to estimate the average change in lipids levels for each 1-unit increase in the natural logarithm (Ln) of the PFCs after adjustment for covariates. Results. PFOS (median 19.8 ng/mL), PFOA (median 3.7 ng/mL), and PFHxS (median 1.6 ng/mL) were detected in 100% of samples. A 1-Ln unit increase in PFOS was associated with a 13 mg/dL (95% confidence interval [CI]: 3, 22) increase in cholesterol concentrations and with a similar increase in LDL concentrations (11 mg/dL; 95% CI: 4,19) in girls. PFOA and PFHxS concentrations were not associated with any of the outcomes. We are currently exploring associations of maternal concentrations of PFOS, PFOA, and PFHxS during gestation with lipids concentrations at age 15 in the same girls. Conclusions. Gestational exposures to PFOS and PFOA may have a persistent influence in lipid metabolism during childhood.

Poster 65: The equity of pediatric healthcare accessibility: measurement and inference.

Clinical Outcomes Research & Public Health

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Background: The U.S. Department of Health and Human Services identifies increasing accessibility of healthcare services as a key step in mitigating the widening disparities of health outcomes in children. Traditional measures of access are overly simplistic and few studies have examined factors that predict access at a local level. We develop a measure that considers three aspects of access: the percentage of children served by a pediatrician, the average distance children travel to reach their pediatrician, and the congestion children encounter for their pediatrician, then quantify the measure and statistically explain the results. Methods: A linear optimization model uses demographic data and the location of physicians to estimate access for children covered by Medicaid or by private insurance in each census tract in Georgia. The model assigns children to pediatricians to minimize the total distance traveled with constraints for provider capacity and willingness to take Medicaid patients and patients' mobility and insurance status. We use regression with spatially varying coefficients to determine if the following factors explain patterns of access: income, race, education levels, population density and percent of children in the population. Findings: We present maps to show how each dimension of access varies over the state of Georgia for Medicaid or other patients, and where unexplained variation remains. Access is more uniform in urban areas and more variable in rural areas. Children covered by Medicaid are less likely to be served by a pediatrician and more likely to experience high congestion. We find education levels, percent of population that is non-white, and percent of children in the population as significant predictors of access. Interpretation: Disparities in access to health care are prevalent in Georgia, particularly for the Medicaid population. Our work points to locations ripe for additional recruitment of providers or remote health services.

Poster 66: A Model Curriculum in Global Child Health for Pediatric Residents

Clinical Outcomes Research & Public Health

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Background: In response to the increasing engagement in global health (GH) among pediatric residents and faculty, academic GH training opportunities are growing rapidly in scale and number. However, consensus regarding best practice guidelines or model curricula has not been established to guide residency programs. Objective: To highlight critical components of well-established GH tracks and to develop a model curriculum in GH for U.S. pediatric residency programs. Methods: We identified 43 existing formal GH curricula offered by U.S. pediatric residency programs in April 2011 and selected 8 programs with GH tracks based on our inclusion criteria. Led by Emory University faculty and trainees, a working group composed of GH track program directors and global child health experts collaborated to develop a consensus model curriculum. The model curriculum included GH core topics, learning modalities, and approaches to evaluation within the framework of competencies for residency education outlined by the Accreditation Council for Graduate Medical Education. Results: Common components among the identified GH tracks included didactics in various topics of global child health, domestic and international field experiences, completion of a scholarly project, and mentorship. The proposed model curriculum identifies strengths of established pediatric GH tracks and utilizes competency-based learning objectives. Conclusions: Implementation of this proposed pediatric GH curriculum will support residency programs in creating and sustaining successful programs in GH education. The curriculum can be adapted to fit the needs of various programs, depending on their resources and focus areas. Evaluation outcomes need to be standardized so that the impact of this curriculum can be effectively measured.

Poster 67: Fathers, Sons, and the Human Papillomavirus (HPV) Vaccine: Perceived Vulnerability to HPV Infection in Boys Ages 9 to 13

Clinical Outcomes Research & Public Health

Tami L. Thomas, PhD; Ora Strickland, PhD, Ralph Di Clemente, PhD and Melinda Higgins PhD

Increasing prevalence of Human Papillomavirus (HPV) infection in the United States is often overlooked in men secondary to the focus on cervical cancer. But the incidences of HPV – related cancers in men are on the rise and prevalence of HPV infection in young U.S. males is estimated to be between 65 and 93%, see table 1. When boys and men ages 9 to 26 years of age are vaccinated against HPV infection, quality of life and a reduction in healthcare costs occur. In December of 2009, the Centers for Disease Control and Prevention (CDC) approved the use of the HPV vaccine in boys as young as age 9 and now the ACIP has recommended HPV vaccination for boys starting at ages 10 or 11. In January 2010 data was collected to determine parents' knowledge, attitudes and beliefs about HPV vaccination for their sons ages 9 to 13. Parents with children ages 9 to 13 participated in a descriptive research study from 2009 – 2011 in elementary and middle school settings. The Parental HPV Survey (PHPVS), a 42-item survey based on the constructs of the Health Belief Model developed by the Principal Investigator was used for data collection. Responses by fathers were of particular importance as the prevalence of HPV infection was reported to be increasing in the United States. Only 35 % of fathers answered that they would vaccinate their son with the HPV vaccine. Results also imply that parents (fathers and mothers) who self-identify as Baptist are very likely to choose or intend to vaccinate their sons with the HPV vaccine. This is a significant finding, as it is in sharp contrast to previous reports that indicate conservative religious groups may be more resistant to HPV vaccination. In conclusion, HPV vaccination should be discussed with parents, especially fathers, during primary care visits. Future health policy should include HPV vaccination for boys during routine well-child checkups and sports physicals.

Poster 68: Quantifying physical therapy metrics through robotic assistance.

Center for Pediatric Healthcare Technology Innovation

Douglas Brooks, Georgia Institute of Technology Yu-ping Chen, Georgia State University Ayanna M. Howard, Georgia Institute of Technology

In recent years, robot-assisted rehabilitation has gained momentum as a viable means for improving outcomes for therapeutic interventions. Such therapy experiences allow controlled and repeatable trials and quantitative evaluation of impairment metrics. Typically, though, these robotic devices have been focused on adult-based rehabilitation. In these traditional robot-assisted rehabilitation studies, participants are required to perform goal-directed movements with the robot during a therapy session. This requires physical contact between the participant and the robot to enable precise control of the task, as well as a means to collect relevant performance data. For child-based rehabilitation, alternative means of extracting the control data needs to be developed to enable individualized therapy between child and robot. As such, this research uses a single camera coupled with computer vision techniques to quantify upper-limb rehabilitation metrics. The results are compared with ground truth data retrieved via a Vicon Motion Capture System for the purpose of assessing the efficiency of this approach. The overall goal is to incorporate this method of data extraction with a humanoid robot to provide a play scenario for a child during a physical therapy session. Utilizing a mimicking based game, the robotic playmate will interact with the child and capture the child's movement so that specific physical therapeutic metrics such as range of motion, velocity, and acceleration may be quantified while simultaneously keeping the subject engaged in the session.

Poster 69: Click-hydrogel therapy to provide controlled delivery in pediatric model of re-synostosis
Center for Pediatric Healthcare Technology Innovation

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Craniosynostosis is the pathologic fusion of cranial sutures early in development and can lead to severe craniofacial deformities and complications related to increased intracranial pressure. Treatment involves complex calvarial remodeling, frequently resulting in rapid re-closure of the skull that requires additional surgical intervention associated with an extremely high incidence of life-threatening complications. To address this need we developed a novel injectable hydrogel therapy to deliver therapeutic proteins in a pediatric specific animal model of re-synostosis. Under approval of the Georgia Tech IACUC, a 1.5 mm by 2.5 mm defect was created to remove the posterior frontal suture in 21 day old male C57Bl/6J mice. We have shown that this defect undergoes rapid re-closure in these young mice, but not in adult mice with an identical defect. The mice were randomized to receive an empty defect, a defect containing a fluorescently protein only, or a defect treated with our novel click-hydrogel containing a fluorescently labeled protein to monitor in vivo release of the proteins. The mice were imaged 2, 5, and 14 days following surgery with micro-CT to assess bone regeneration and the fluorescent intensity was imaged using the IVIS imaging station. Bone in-growth was assessed using our algorithms and the results showed that the regenerating bone grew rapidly around the hydrogel in the defect beginning on 5 days post-op. By 14 days the bone was able to fully regenerate and there was no difference between the animals that received the hydrogel or the empty defect. Quantification of the fluorescent images showed that the defects containing the hydrogel had retained more of the fluorescent protein at the 5 and 14 day time points, indicating that the hydrogel was able to provide controlled delivery of proteins. In conclusion, the click-hydrogel provides the ability to have controlled release of incorporated proteins in a pediatric specific cranial defect.

Poster 70: Rapid re-synostosis in mice is both location and age dependent
Center for Pediatric Healthcare Technology Innovation

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Craniosynostosis is the premature fusion of the cranial sutures and commonly requires complex calvarial reconstruction. In up to 40% of cases, the bones re-fuse resulting in re-synostosis that requires subsequent surgical intervention associated with a high incidence of serious complications. The objective of this study was to determine if the regenerative ability of a murine cranial defect varies with age and location. Under approval of the GA Tech IACUC, a 1.5 by 2.5 mm calvarial defect was created in C57Bl/6J mice removing the posterior frontal suture or a bone region lateral to the suture. The surgery was performed on either post-natal day 21 or 50 for the juvenile or adult groups, respectively. On post-operative days 2, 5, and 14, five mice were randomized into each group for imaging with micro-CT and histology. The mean defect distance and bone volume in the defect was quantified using our novel snake algorithm previously validated with serial histology. A $P < 0.05$ was considered statistically significant by ANOVA and Bonferroni post-test. The defects over the juvenile suture had a significant decrease in defect distance by 5 days post-op followed by an increase in bone volume by 14 days post-op. The adult suture group had a decrease in defect distance later at 14 days post-op while there was no increase in bone volume. None of the bone defects lateral to the suture showed any decrease in distance by 14 days post-op; however the bone volume adjacent to the edges of defect increased for the juvenile group only. There were no changes in either the defect distance or bone volume in the adolescent lateral defect group. Our algorithm shows that the rapid re-synostosis in a murine model is both location and age dependent. All the defects created over the posterior frontal suture went on to nearly complete bridging while any increase in bone volume was specific to the juvenile animals.

Poster 71: Gene Expression Analysis of Coronal Craniosynostosis

Center for Pediatric Healthcare Technology Innovation

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Introduction: Craniosynostosis is the premature fusion of cranial sutures. It is divided into two categories: syndromic, linked to a syndrome with an identified gene mutation, and non-syndromic, in which the cause of the genetic abnormality is unclear. Coronal craniosynostosis commonly presents as syndromic synostosis. Different gene mutations have been identified in coronal synostosis, most commonly in FGFR2, FGFR3, TWIST, and MSX2. The aim of this study was to elucidate whether cells isolated from different syndromic craniosynostosis present the similar gene expression. **Methods:** Five bone samples were received from Children's Healthcare of Atlanta (CHOA) under IRB approval from CHOA and Georgia Tech. Of these samples, three were confirmed syndromic craniosynostosis and a fourth had a family history of syndromic craniosynostosis. The patient's ages ranged from 4 to 16 months and four of the five samples were from female patients. Cell isolation was performed on each sample and cells were then used for RNA isolation, RNA quantification, and cDNA synthesis via reverse transcriptase PCR. The resulting cDNA was analyzed by real-time qPCR for expression of BMP, Wnt, integrin, and hormone receptor molecules. **Results:** Members of the BMP family, particularly BMP2, were highly up-regulated in fused sutures in comparison to normal and open suture cells. BMP4 and Noggin were lower in fused sutures than in normal bone. Wnt molecules Axin2 and Dkk1 were down-regulated in fused sutures in comparison with normal and open sutures. Angiogenic factors were also differentially regulated, with FGF2 highly expressed in open sutures and VEGF highly expressed in fused sutures. **Conclusions and Impact:** The data suggest that while gene expression of coronal craniosynostosis does not reveal a single gene responsible for craniosynostosis; however, several genes important development are differentially regulated in fused sutures, which may provide candidates for future therapeutic approaches.

Poster 72: Is Virtual Reality Gaming An Effective Adjunct To Traditional Therapy In Children and Adolescents With Traumatic Brain Injury?

Center for Pediatric Healthcare Technology Innovation

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Purpose/Hypothesis: To compare the use of commercially-available virtual reality games with traditional therapy as a treatment intervention to improve functional mobility in the pediatric population with traumatic brain injury (TBI). **Number of Subjects:** 11 inpatients from Children's Healthcare of Atlanta Comprehensive Inpatient Rehabilitation Unit, aged 8-18 (4females/ 7 males) years with TBI and a Rancho Los Amigos rating of V or VI. **Materials/Methods:** The participants were randomly assigned to the virtual reality (VR) group or the traditional therapy (TT) group. Each group received 20-30 minutes of their respective intervention for a minimum of 6 sessions. The VR group practiced balance exercises using the PlayStation II Sony TM Eye Toy® Play 2 while the TT group participated in conventional dynamic balance activities. Outcome measures included, Pediatric Berg Balance Scale (PBBS), Multi-Directional Reach Test (MDRT), WeeFIM II SM and Intrinsic Motivational Inventory (IMI). **Results:** Significant differences from baseline to post intervention were found within groups for PBBS, MDRT and WeeFim II SM, however there were no differences shown between groups. The IMI showed trends of improvement for the Interest/Enjoyment subscale. **Conclusions:** Video games are equally effective to traditional balance training as an adjunct to traditional therapy for children and adolescents with TBI on an inpatient pediatric rehabilitation setting. **Keywords:** Brain Injury, Inpatient Rehabilitation, Virtual Reality, Pediatrics.

Poster 73: Understanding child's play by sequencing play primitives and planning turn-taking strategy for a therapeutic robot playmate

Center for Pediatric Healthcare Technology Innovation

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Background: In recent years, new approaches have been taken in applying robotic platforms as an assistive therapeutic device. We focus on robot's ability to provide consistent and repetitive exposure to interaction plays, and believe that the synergy between "play therapy", and "robot playmate" broadens the concept of social interaction training. Methods: Our system extracts and sequences low-level play primitives, and plans turn-taking strategies during a robot-child interaction. Play primitives study has been conducted with videos of children playing with toys in order to analyze the most frequently observed play elements. The first module involves the extraction of play primitives based on observation of motion gradient vectors computed from the image sequence. Hidden Markov Models (HMMs) are then used to recognize 14 different play primitives during play. The second part introduces a novel attempt in applying Case-Based Reasoning (CBR) for planning human-robot turn-taking strategies. By comparing the child's play in the current scene to past play cases stored in memory, we retrieve the best solution bypassing a long complicated decision process. Both Play Behavior Recognition (PBR) module and Turn-Taking CBR (TTCBR) system are then evaluated for stacking and inserting tasks with adult and child subjects. Evaluation: In order to train HMMs, we collected 20 play scenarios from three adults. To verify the system, 100 play scenarios were gathered from three child and three adult subjects. Play primitive data sets for each primitive were extracted from 20 training play scenarios, and were tested with the remaining test scenarios. The average play primitive recognition rate was 86.88%, with 100% accuracy in sequencing. TTCBR module's training phase consisted of five of each stacking and inserting plays. Initial play case-base is created during this time. The proposed framework was able to deduce a solution within a second with a successful solution rate of 82.36%.

Poster 74: KIDS-CRRT: Development and in vitro testing of a pediatric continuous renal replacement device with a novel fluid balance mechanism.

Center for Pediatric Healthcare Technology Innovation

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Background: Nearly 3,600 critically ill children per year with acute kidney injury receive life-saving continuous renal replacement therapy (CRRT) in the United States. There is currently no pediatric CRRT device approved by the Food and Drug Administration, and thus adult devices are adapted for this use. The adult adapted CRRT devices operate with unsafe extracorporeal blood volumes and provide inaccurate fluid balance between ultrafiltrate (UF) removal and replacement fluid (RF) infusion rates. The research herein addresses this unmet clinical need through the design, fabrication, and testing of a pediatric specific Kidney Injury and Dysfunction Support (KIDS) – CRRT device. Methods: As opposed to adult CRRT devices where fluid balance is based on measurements of the weight of UF and RF, the KIDS CRRT design is based on a "conservation of volume" approach that exploits the physical property of fluid incompressibility. The fluid is displaced via a miniature bladder pump that functions similar to a cardiac ventricle to achieve highly accurate and controlled pumping, and this reduced the extracorporeal circuit volume to a pediatric-safe level of 34 mL. Findings: Flow rate and fluid balance accuracy of the KIDS CRRT prototype was experimentally evaluated over driving pressures of 50-120 mm Hg and flow rates of 600-4800 mL/hour. Device flow rate error was calculated as the difference between the prescribed and delivered flow rates. Fluid balance accuracy was calculated as the difference between the UF and RF flow rates. The KIDS CRRT prototype produced < 5 mL/hour flow rate error and fluid balance accuracy as compared to the average 20 ml/hour error obtained in the traditionally used intravenous (IV) pump method system. Interpretation: We have thus demonstrated the highly accurate fluid balance produced using the conservation of volume principle, and the pediatric specific KIDS CRRT device is nearly an order of magnitude more accurate than adult adapted CRRT devices.

Poster 75: Automated physician schedule generation for a pediatric ICU using integer programming to enhance continuity.

Center for Pediatric Healthcare Technology Innovation

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Introduction: Continuity of care can improve patient satisfaction and outcomes, but care is increasingly fragmented (hour restrictions and lifestyle choices by physicians (MDs)). Manual MD duty schedule construction is complex and time-consuming. An automated tool could be more efficient and effective in generating schedules with greater continuity and compliance with requirements/preferences. An integer programming model (IP) can efficiently generate a schedule meeting all constraints and with a better Handoff Continuity Score (HCS) (Crit Care 2011, 15:R256) than a manually generated schedule. Methods: A 6-month duty schedule was generated manually by an MD group with the goal of achieving a high HCS and conforming to a predefined staffing model and MD requests. Another schedule was generated using an IP with the same goals. Time spent generating schedules was estimated. An HCS was calculated for each schedule. Results: Manually constructed schedule required a solution time of approximately 4 person-hours vs. approximately 2 computer-hours and 5 minutes preparation for IP model to generate schedule (using CPLEX 12.2). Entering IP solution into Excel and using a Macro to generate user-friendly duty schedule required < 5 minutes. HCS for the IP-generated schedule improved by 11% over manual schedule. When a change in MD staffing occurred (one MD removed from schedule pool), IP took < 5 seconds to reassign shifts to other MDs. Manual reassignment required approximately 30 minutes. Conclusions and Impact: The IP generated an MD schedule in less time and with a better HCS than the manually constructed schedule. IP development required a lengthy period of time for fine-tuning constraints/debugging, but the resulting model is general (i.e. can easily accommodate varying MD groups/requests, or can be adapted to other MD groups, without requiring extensive changes to underlying code). The model can be used for future schedules for this MD group or others.

Poster 76: Feasibility and efficacy testing of autologous Mesenchymal Stromal Cells (MSCs) for the treatment of Crohn's in Pediatric patients.

Children's Transplant Immunology & Immune Therapeutics Center

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Crohn's disease (CD) is a chronic, life-long disorder with devastating consequences. Chronic inflammation and ulcerations of the intestine not only results in malnutrition and intestinal failure but also progress to fibrosis that results in complications such as obstruction (stenosis), fistulas and bowel perforations. IBD results in substantial morbidity and increased mortality. Standard anti-inflammatory regimens such as corticosteroids and 5-ASA, are only effective in controlling the inflammation but do not halt the progression of the disease nor change the natural history of IBD. Thus more aggressive, mucosal healing agents such as biologic therapies have been developed with the belief that sustained healing of mucosa may halt the progression and fibrostenosis. These newer treatments and more aggressive algorithms have shown promise over the short term, but a significant portion of IBD patients become medically refractory over time due to immunogeneity. Enthusiasm over the use of these agents is further tempered by the concerns of serious side effects including life-threatening infections, severe allergic reactions and malignancies such as lethal form of hepatosplenic T cell lymphomas. These concerns are magnified in young IBD patients with early onset of disease who are known to harbor severe & aggressive disease phenotype and are at a higher risk for surgery. Mesenchymal stromal cells (MSCs) have emerged as a novel approach for immune related disorders like IBD. MSCs are a cellular product that can be derived from a patient's own body (autologous) or from a donor (allogeneic). MSCs have been shown to have a broad spectrum of immunomodulatory actions on both the innate and adaptive immune systems. Despite promising pre-clinical and limited clinical data, clinical dosing of MSCs remains to be established in CD. We believe this lack of clinical efficacy is directly related to MSCs being derived from a MHC-unmatched donors, propagated in xenogenic expansion

Poster 77: Portal vein and hepatic artery flow abnormalities are present and are accentuated after ischemia reperfusion injury of a steatotic liver

Children's Transplant Immunology & Immune Therapeutics Center

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Background: Ischemic insults to a fatty liver lead to extensive hepatocellular damage and cell death. This is becoming a burgeoning problem due to the rising incidence of non alcoholic fatty liver disease. Identification of factors contributing to hepatocellular damage will help in developing therapeutic targets to mitigate this injury. **Aim of our study** was to determine the effect of ischemia reperfusion injury (IRI) on hepatic vascular flow in mice with steatotic liver as compared to lean mice. **Methods:** C57BL/6 mice were fed a high fat diet (HFD) for 12 weeks. They were subjected to 20 minutes of ischemia. Portal venous and arterial blood flow was evaluated using Vevo 2100 high frequency, digital, linear array, color doppler machine prior to the IRI and after 24 hrs of reperfusion. **Results:** Prior to IRI, the ratio between the systolic and diastolic peak of the portal venous blood flow was higher in the HFD fed mice as compared to the lean mice (2.9 ± 0.3 vs 2.0 ± 0.1 , $p < 0.009$). After IRI, there was a further increase in this ratio in mice with fatty liver (3.6 ± 0.21) as compared to the lean mice (2.4 ± 0.38 , $p < 0.01$). The resistive index was significantly higher in HFD fed mice compared to lean both post IRI (0.74 ± 0.01 vs 0.52 ± 0.04 ; $p < 0.001$) and pre IRI (0.58 ± 0.02 vs 0.46 ± 0.03 ; $p < 0.01$). Pulsatility index (PI) showed a similar trend with HFD fed mice compared to lean mice post IRI (1.35 ± 0.09 vs 0.77 ± 0.12 ; $p < 0.01$) and pre IRI (0.75 ± 0.04 vs 0.53 ± 0.04 ; $p < 0.01$). Mice fed a HFD showed a significant increase in serum ALT levels compared to lean mice. **Conclusion:** Our study demonstrates that hepatic blood flow abnormalities are present in mice with fatty liver and are further accentuated after IRI. We postulate that these blood flow abnormalities contribute to the increasing hepatocellular damage which is seen after IRI in a steatotic liver.

Poster 78: Health-related quality of life and perceived need for mental health services in adolescent solid organ transplant recipients.

Children's Transplant Immunology & Immune Therapeutics Center

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With increased survival in pediatric transplant recipients, there is increasing interest in health-related quality of life (HRQOL) following organ transplantation. Data from our 18-month investigation of HRQOL in adolescent transplant recipients has resulted in points of intervention to improve HRQOL. We have identified predictors of HRQOL change including demographic, transplant-related and environmental factors (Devine, et al.). This paper examines the relationships between adolescent and parent reported HRQOL and parents' perceived need for types of mental health services. The sample consisted of 63 parents, 51 adolescent ($M = 17.1$ years, $SD = 2.4$) solid organ transplant recipients. Adolescents completed the Child Health Questionnaire-Child Form 87 and parents completed the Child Health Questionnaire-Parent Form 50, HRQOL (Landgraf, Abetz, & Ware, 1999). Parents rated their perceived need for 10 different mental health services for their adolescent and themselves including counseling, parent training, and communication skills. On average, 57% of parents endorsed interest in mental health services. Parent and adolescent reports of HRQOL across physical, behavioral, and psychosocial domains were found to be negatively associated with parent perceived need for mental health services. Counseling for emotional/adjustment issues and training to help adolescents develop independence had the highest number of significant associations with HRQOL. The HRQOL subscales most frequently associated with need for mental health services included parent and adolescent reports of adolescent behavior problems and parent report of low family cohesion. Results offer initial guidance about the mental health services needed by adolescent solid organ transplant recipients and parents that may improve HRQOL. In conjunction with our past work demonstrating stability of poor HRQOL without intervention, these results suggest possible mental health interventions that parents are open to receiving.

Poster 79: A randomized double blind placebo controlled trial of vitamin D to ameliorate sickle cell chronic pain

Children's Transplant Immunology & Immune Therapeutics Center

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Pain is the hallmark symptom of sickle cell disease (SCD) and accounts for the majority of morbidity and healthcare utilization associated with the disease. Low vitamin D status has been linked with osteoporosis, increased fracture risk and chronic back and extremity pain in adult populations however there is a limited data on its clinical correlates in SCD. Objective: To determine the efficacy and safety of vitamin D in improving chronic pain in SCD. Eligibility: Age 7- 21y, any sickle genotype. Exclusion: sickle nephropathy, serum Cr>1.5, ALT>3ULN, malabsorption, serum Ca <8.0 >11mg/dL, oral steroids, thiazide diuretics, depot provera, phenobarbital, phosphenytoin or previous treatment with high dose vitamin D. Following informed consent, subjects were randomized to receive either high dose vitamin D (240,000-600,000IU) or placebo. Number of pain days was monitored prospectively using a daily diary. Serum 25-hydroxyvitamin D (25OHD) was measured at weeks 8, 16, 24; Peds QoL v4 was administered at similar intervals. Statistical analyses used SAS 9.2 (Cary, NC). Results: Serum 25OHD levels increased briskly from 22.1 to 52.7ng/ml at week 8 in the treatment arm, drifting down to 30.4ng/mL by week 24 with no change in placebo arm. Vitamin D levels were significantly negatively associated with number of pain days ($r = -0.680$; 95% CI [-0.90, -0.10]), indicating that higher serum 25OHD were associated with fewer pain days. Vitamin D levels were also significantly positively associated with physical QoL score ($rs = 0.22$; 95% CI [0.14, 0.41]), indicating that higher 25OHD levels were associated with higher physical quality of life measures. In contrast, the number of pain days was significantly negatively associated with physical QoL scores ($rs = -0.25$; 95% CI [-0.43, -0.04]). Conclusion: This suggests a benefit of vitamin D in improving pain and quality of life in SCD. Larger prospective studies with longer duration are needed to confirm these effects.

Poster 80: Evidence for quantitative and functional immune deviation in pediatric patients with sickle cell disease.

Children's Transplant Immunology & Immune Therapeutics Center

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Bone marrow transplantation (BMT) is a curative for sickle cell disease (SCD). These patients are at increased risk of graft rejection particularly with non-myeloablative BMT suggesting baseline immune activation. Objective: to describe extent & character of immune deviation in pediatric SCD. We evaluated quantitative immunity in 23 children 10 -16y with SCD (SS or Sb0-thalassemia) at steady state (≤ 21 days from acute illness; ≤ 8 weeks from RBC transfusion) compared to 18 ethnic matched controls in a cross sectional study. Baseline demographic indices were similar in both groups for gender & age. After informed consent, blood was drawn for quantitative immune analysis: WBC, ANC, ALC, T cell (CD4/8 subsets), B cell & NK cell, and CD4/8 T cells for memory subpopulations. Functional immune assessment was done on a subset 18 patients/6 controls (Invitrogen 25-plex human cytokine panel). Quantitative/qualitative flow-cytometric analysis used FloJo software & Prism statistical package. Results: SCD patients had increased WBC & ANC (1.9-fold & 1.7-fold $p < 0.05$); higher total lymphocytes, monocytes, cytotoxic & cytokine-secreting NK cells (2.9, 2.4, & 2.2-fold $p < 0.01$); higher B cells (3.3 fold, $p = 0.0005$), CD4+ T cells (1.7-fold, $p = 0.002$) and an increased memory CD4+ subpopulations, with both central and effector memory CD4+ T cells affected (1.9-fold & 2.5-fold, respectively, $p < 0.01$). There was also evidence of functional immune activation at with higher circulating CXCL10, CCL4, IL-15 (2.4, 2.1, & > 10 fold $p < 0.05$). These cytokines secreted by activated endothelial cells & monocytes are implicated in promoting proliferation (IL-15) and activation (CXCL10 & CCL4) of both T & NK cells. Implications: Our results confirm that pediatric SCD exhibit significant quantitative and functional immune deviation. Targeting immune pathways impacting NK, B, and CD4 T cell function may be required for successful engraftment of SCD patients during non-myeloablative BMT.

Poster 81: Dietary intake of vitamin D amongst children and adolescents with sickle cell disease compared to ethnic controls

Children's Transplant Immunology & Immune Therapeutics Center

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Vitamin D deficiency (VDD) is highly prevalent in sickle cell disease (SCD) approaching 100% depending on season. This is significantly higher than reported for African Americans in the US. There are no published reports on dietary intake of vitamin D in SCD compared to controls that could adequately account for these differences. Our objective was to determine the differences in dietary intake of vitamin D between children with SCD and ethnic controls. We quantified dietary intake of various nutrients in 26 children 10 -16y with SCD (SS or S β 0-thalassemia) at steady state (\leq 21 days from acute illness; \leq 8 weeks from RBC transfusion) compared to 21 ethnic matched controls in a cross sectional study. There were no differences in age and gender between the two groups. After informed consent, subjects were given a 3-day food diary to complete. Food record was assessed and entered into the Nutrition Data System for Research (NDSR; University of Minnesota, Minneapolis, MN) program for analysis of average daily dietary intake of vitamin D. Blood was drawn for serum 25-hydroxyvitamin D (25OHD). Results: Mean daily dietary intake of vitamin D was similar between subjects and controls (161.7 ± 21.9 v.s 161.4 ± 26.3 IU/d $p=0.99$) and lower than the recommended 600IU/d. Surprisingly, the mean serum 25OHD level was low and also similar between subjects and controls (18.2 ± 1.9 versus 20.8 ± 1.4 $p=0.295$). The range of daily vitamin D intake varied widely in both groups, subjects had the lowest recorded intake compared to controls (8.3 v.s 42.0 IU/day). Similarly, the range of serum 25OHD varied widely in both groups; subjects had lowest 25OHD levels 6.96 v.s 11.99 ng/ml. We did not assess for non-dietary sources of vitamin D intake and at least 2 subjects were known to be on vitamin D therapy. Conclusion: Dietary intake of vitamin D is similar among subjects with SCD and ethnic controls. Other etiologies for the higher rates of VDD in SCD need to be investigated.

Poster 82: Iron-deficiency anemia in children with malaria and helminth co-infection

Children's Center for Immunology and Vaccines

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Background: Anemia affects approximately 25% of the world's population, with young children in developing countries being disproportionately affected. Infections due to malaria and helminthes play a major role in development of anemia in this population, with iron-deficiency anemia and anemia of inflammation being the main etiologies. Iron deficiency anemia is treatable with oral iron supplementation while anemia of inflammation is unresponsive to iron therapy. In order to determine the best method of treating anemia in a population, it is important to define the underlying causes of anemia. Methods: We constructed Luminex analytes to measure ferritin and soluble transferrin receptor levels from blood spots taken from 320 school-aged children co-infected with malaria and helminths in four semi-urban villages in Nigeria. As serum ferritin is affected by inflammation, C-reactive protein was measured to allow correction of ferritin level for inflammation. Results: An average of 42.05 ± 11.46 ug/mL of protein was successfully extracted from the blood spots and studies are underway to determine the proportion of children with anemia attributed to iron-deficiency, and whether this is disproportionately influenced by malaria and / or helminth infections. Conclusion: Iron deficiency has been associated with delayed mental and physical development; therefore knowing the underlying cause of anemia in these school age children will allow therapy to be better directed and will give them a better chance at a productive life.

Poster 83: The PI3-kinase pathway is activated in dendritic cells responding to rodent malaria parasites.

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The main signaling pathways activated in dendritic cells and macrophages responding to malaria parasites are currently unknown, particularly with respect to intact infected red blood cells. The surface of infected red blood cells is decorated with parasite-exported proteins which can be recognized by innate immune cells. Upon replication, parasites burst from red blood cells in a process known as schizogony and this is accompanied by the release of parasite molecules such as free GPI anchors that induce an inflammatory response via ligation with TLR2. Indeed the fevers associated with malaria infection are the result of the acute phase response triggered during schizogony. Finally malaria will be coated with antibodies, the Fc region of which is recognized by Fc receptors on antigen presenting cells. Dendritic cells and macrophages secrete the pro-inflammatory cytokine IL-12 in malaria infection, and the production of this cytokine by dendritic cells has previously been shown to be inhibited by signaling pathways involving the PI3-kinase pathway. Therefore, it was our hypothesis that the PI3-kinase pathway may be activated by malaria parasites and / or their products in dendritic cells and macrophages to reduce the induction of a pro-inflammatory immune response and the activation of anti-parasite inflammatory immune responses. We have collected evidence that the PI3 kinase pathway is activated, and that selective inhibition of the PI3-kinase pathway modulates the cytokine balance produced by antigen presenting cells detecting malaria parasites.

Poster 84: Analysis of the expression of ephrin ligands on different CD4+ T cell subsets

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Ephrin ligands bind Eph kinase molecules, the largest known family of receptor tyrosine kinases. Naïve T cells have been shown to express several ephrin ligands (A1, B2, and B3) on the surface and published studies indicate that they may be important for T cell activation and migration. It is unknown whether ephrin ligands are differentially upregulated on CD4+ T cell subsets (Th1, Th2, Th17 and T reg cells) or on memory cells. If ephrin ligands are differentially expressed they may be a new target for therapeutic interventions (such as monoclonal antibody therapies) whereby some T cell subsets could be specifically targeted, leaving beneficial T cell subsets intact. Here we have purified naïve CD4+CD25- T cells from mouse splenocytes and differentiated them into distinct subsets in vitro by adding different combinations of recombinant cytokines and blocking antibodies. The phenotype of each cell subtype was verified by intracellular FACS staining. The expression of ephrin ligands was measured using qPCR and compared to naïve undifferentiated cells. Th1 cells differentiated in vivo were also purified from the splenocytes infected with rodent malaria to assess whether the expression of ephrin ligands was an artifact of in vitro culture. Lastly, we have also examined ephrin ligand expression on human CD4+T cells purified from the peripheral blood and differentiated in vitro to assess whether human CD4+T cells behave in a similar way to mouse CD4+T cells.

Poster 85: Defining the minimal requirements for paramyxovirus fusion.

Children's Center for Immunology and Vaccines

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Paramyxoviruses are responsible for significant upper respiratory disease in the pediatric population. Understanding the mechanism of viral fusion and the conformational changes that occur during viral entry will produce new targets for drug therapeutics. Members of the paramyxovirinae rely on the concerted action of two glycoprotein complexes to complete membrane fusion for viral entry; the attachment (H) protein that binds to the cellular receptor and the fusion (F) protein that forms the fusion pore. Previously we identified three groups of H mutants which when expressed in pairs could complement each other and restore fusion. Utilizing these mutants we developed a bimolecular complementation (BiC) assay for MeV H, based on the hypothesis that physical interaction of H with F complexes, F triggering, and receptor binding constitute distinct events. Implementation of H-BiC revealed that a high affinity receptor-to-paramyxovirus H monomer stoichiometry below parity is sufficient for fusion initiation and that F binding and fusion initiation are separable in H oligomers. H-BiC activity profiles confirm that H functions as a tetramer. Recent co-crystal structures of MeV H with SLAM also reveal tetrameric oligomers of H. To further define the necessary constituents and functions of the minimal fusion complex we build upon the BiC assay by forcing homo-dimer formation with di-sulfide bond engineering. Utilizing the di-sulfide bonds that form between the covalently link H dimers, we forced our three mutants to form homo-dimers and determined if complementation occurs when homo-dimer-hetero-tetrameric complexes form. While receptor binding and F triggering complemented in this setting, the F interaction mutations did not. Native-PAGE analysis suggests the F interaction mutant, H-F111A, assumed a different conformation than the other H proteins. Further studies examining the conformation of parental and H-F111A proteins are ongoing.

Poster 86: Target cell restriction: one mechanism to explain the rarity of mother-to-infant transmission of SIV in naturally infected sooty mangabeys.

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Background: Mother-to-child transmission of HIV occurs in utero, intrapartum, and through breastfeeding, with a cumulative rate of transmission of 35-40%, that results in ~400,000 infected children each year. In contrast, nonhuman primate species that are naturally infected with SIV in the wild ("natural hosts", including sooty mangabeys) rarely transmit SIV from mothers to infants. The mechanisms underlying this protection are unknown. **Methods:** Using a thirty-year history of births in the colony of naturally SIV-infected sooty mangabeys at the Yerkes National Primate Research Center, we previously investigated the rates of SIV infection in infants by serological and virological methods. We here performed flow cytometric analyses of post-necropsy tissue samples from infant sooty mangabeys to quantify targets (CD4+CCR5+ T cells) for SIV infection. **Results:** Examination of 163 sooty mangabey infants born to SIV-infected mothers revealed that 152 (93.2%) were not infected by mother-to-infant transmission. Interestingly, quantitative real time RT-PCR showed a ~2-log reduction in the median viral load in the rare 11 mangabeys who were infected as infants compared to animals infected as adults. By analyzing tissues (lymph nodes, spleen, gastrointestinal tract) and blood from 7 infants, we found that CD4+CCR5+ T cells comprised less than 5% of the total CD4+ lymphocyte population. This low frequency of CD4+CCR5+ T cells in infants was found in all sites and involved all memory subsets, representing a previously unrecognized feature of the evolutionary adaptation to reduce the levels of SIV target cells that has been described in adult mangabeys. **Conclusions:** Mother-to-infant transmission is substantially less frequent in SIV-infected sooty mangabeys than in HIV-infected humans, and is associated with low SIV viremia. A potential mechanism to explain the protection from transmission in this natural host species is the low level of target cells present in blood and tissues.

Poster 87: Placental hofbauer cells limit HIV-1 replication and potentially offset MTCT by induction of th2-cytokines

Children's Center for Immunology and Vaccines

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Background: Despite readily detectable levels of the HIV-1 (co)-receptors CD4, CCR5 and DC-SIGN on placental macrophages (Hofbauer cells, HCs), the rate of HIV-1 infection in utero in the absence of interventions is only 7% of exposed infants. We hypothesize that HCs may act as mediators of protection at the feto-maternal interface during HIV-1 exposure. Methods: These observations prompted us to examine the replication kinetics of isolated human HCs to the HIV-1BaL. We also determined the infectivity of HIV-1-exposed HCs by co-culturing with cord and peripheral blood mononuclear cells [CBMCs, PBMCs]. To understand the limiting nature of HCs to viral replication, we examined their phenotype and cytokine profile. In addition, we measured the migratory ability of HCs and determined their presence in the neighboring fetal circulation by flow cytometry. Data were analyzed by using Student t test (two-tailed) and Mann-Whitney U Test. Results: We established that HCs have a reduced ability to replicate HIV-1 in vitro compared to standard infections of MDMs ($p < 0.01$). Interestingly, HCs had a marked reduced ability to infect CBMCs and PBMCs compared to MDMs ($p < 0.001$ for both). Furthermore, un-stimulated HCs constitutively expressed higher levels of TH2-type cytokines, IL-10 and TGF- β , compared to MDMs ($p < 0.01$), which may contribute to TH2-predominance at the placenta and account for the down-regulation of HIV-1 replication and infectivity in HCs. We further demonstrate that these TH2 cytokines inhibit HIV-1 replication within HCs in vitro. HCs exhibited migratory properties similar to MDMs. Despite this potential for migration and infectivity, HCs were not detected in fresh cord blood. Conclusions: Our data suggest that HCs may shift the TH1/TH2 cytokine balance within the feto-maternal interface to favor TH2 predominance thereby offsetting MTCT of HIV-1. These novel observations may be important in defining correlates of protection during on-going HIV-1 exposure in utero.

Poster 88: A novel method for newborn screening for 22q11 Deletion Syndrome using dried newborn blood spots.

Children's Center for Immunology and Vaccines

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Keywords: Newborn Screening, 22q11 Deletion Syndrome, Copy Number variation, MALTI-TOF

Background: A hemizygous deletion in 22q11 causes 90% of DiGeorge Syndrome, occurs in 1:3000 children, causing heart defects, hypocalcemia, T cell lymphopenia, speech, cognitive delays, and other birth defects. Newborn screening for SCID/severe T cell lymphopenia uses quantitative PCR on DNA from newborn dried blood spots (NDBS), but cannot identify the 22q11 deletion. I have developed a novel method to measure absolute copy number of UFD1L, located in the deleted segment, using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALTI-TOF). An internal competitor (2N), on chromosome 18, differs in 2 nucleotides from the target gene (1N). Methods: Punches from normal cord blood DBS, and DBS from blood of patients with 22q11 DS were washed. Mastermix for primary amplification was added directly to the DBS, with forward and reverse primers for a 97bp amplicon in the UFD1L gene and chromosome 18. After 45 cycles, the PCR product was treated with shrimp alkaline phosphatase and a multiplexed extension PCR was performed using 2 primers, one for each SNP. A nested PCR reaction added a single base at the 3' end. The salts from the mastermix are removed, the product is spotted on a glass chip and analyzed using the MALTI-TOF mass spectrometry. Results: 22q and chr.18 SNPs have distinct masses. The mean ratio of the peak intensities is 1.12 (SD 0.17) for SNP1 and 0.94 (SD 0.07) for SNP2 for normal controls and 0.6 (SD 0.04) for SNP1 and 0.58 (SD 0.04) for SNP2 in deleted patients. Conclusions: The MALTI-TOF MS assay can reliably detect a hemizygous deletion of the UFD1L gene on chromosome 22q11 using DNA obtained from NDBS. This assay can be multiplexed to include other regions in the 22q11 deletion segment to characterize the size of the deletion, and is suitable for high throughput using automated dispensers. Impact: This test would be a useful addition to the newborn screening panel and permit early detection of this disorder.

Poster 89: Functional domains in paramyxovirus L protein.

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Paramyxoviruses such as respiratory syncytial virus, human parainfluenzaviruses and measles virus (MeV) constitute a major threat for pediatric health. The polymerase (L) proteins of these nonsegmented negative strand RNA viruses (NNSV) are considered to harbor all enzymatic activities required for replication and transcription of the viral genome. Having developed an orally available nanomolar inhibitor of MeV L, it is the long-term goal of this project to transform the MeV blocker into an anti-paramyxovirus L platform through pharmacophore extraction and structure-guided scaffold design. A novel strategy for the meta-analysis of interdomain sections of MeV L was implemented to define structurally independent folding domains in search of a fragment that can be co-crystallized with the inhibitor. Based on in silico predictions of the L domain architecture, we completed a linker insertion study and identified two truly independent folding domains in L. The protein was split at this position and fragment functionality and correct folding was demonstrated in a newly established trans-complementation assay. Complementation required insertion of GCN4 affinity tags. This groundbreaking finding moves beyond the prevailing paradigm that NNSV polymerases must be synthesized as single polypeptides for RdRp activity. It furthermore demonstrates lack of a high-affinity protein-protein interface. Equivalent split constructs of RSV and Nipah L showed the same phenotype. Heterologous complementation fragments oligomerized but failed to restore RdRp activity, verifying a requirement of molecular compatibility for bioactivity. Functionally probing the L domain architecture through trans-complementation is anticipated applicable to all Mononegavirales polymerases and will be major tool to gain structural insight.

Poster 90: Does platelet activation mediate pathogenesis of malaria infection?

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The activation of platelets by malaria parasites is thought to cause pathology in malaria infection by acting as a bridge for infected red blood cells to adhere to the endothelium leading to blockage of the blood vessels in the brain, and in turn cerebral malaria. This event has most commonly been investigated in chronic malaria infection. However, depletion of platelets in mice by monoclonal antibody treatment can only protect against death in a lethal mouse malaria infection when performed within the first few days of infection. This suggests that platelets can mediate lethal inflammation in acute malaria infection, rather than act to enhance blood vessel blockage in chronic infection. Indeed we demonstrate that the removal of platelets is associated with an increase in the number of splenic T cells secreting protective IL-10, an immunoregulatory cytokine that can down-regulate anti-malarial inflammatory response. Since platelet depletion using monoclonal antibodies involves clearance of antibody-opsonized platelets, Fc triggering by the opsonized platelets and the production of IL-10 from macrophages in response, may offer an alternative explanation for the protection offered by platelet depletion in these experiments. Indeed, unlike the removal of platelets by monoclonal antibody treatment, inactivation of platelets using aspirin or Plavix[®] did not protect against the manifestations of mouse cerebral malaria. To ascertain whether platelet presence truly alters the inflammatory landscape of mouse malaria infection we have analyzed immune responses and malaria pathogenesis data from infections of mice that contain an allele for the simian diphtheria toxin receptor blocked by an upstream loxP-flanked STOP sequence crossed to mice that express Cre-recombinase under the promoter for platelet factor 4. Upon administration of diphtheria toxin, megakaryocytes and platelets are removed. The results of these experiments will be discussed.

Poster 91: Vaccine-elicited CD8+ T cells protect against respiratory syncytial virus bronchiolitis

Children's Center for Immunology and Vaccines

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Respiratory syncytial virus (RSV) is the most important pathogen for lower respiratory tract illness in infants, and there is no vaccine in use. The degree CD8+ T cells are protective versus immunopathologic in RSV infection is not fully understood, though infant data point to a protective role for T cells. We hypothesized that vaccine-elicited anti-RSV CD8+ T cells will ameliorate rather than contribute to RSV bronchiolitis. We developed a novel RSV peptide vaccine using a CD8+ T cell immunodominant epitope in BALB/c mice. Vaccination of mice with a mixture (TriVax) of RSV M282-90 peptide, a toll-like receptor agonist (polyI:C), and a costimulatory anti-CD40 antibody resulted in robust functional CD8+ CTL responses. Compared to CD8+ T cells induced by infection, a higher percentage of TriVax-induced CD8+ T cells expressed interferon-gamma. Using a mucus-inducing RSV challenge strain, we demonstrate that RSV TriVax vaccination protects against RSV infection and protects against RSV-induced airway mucus expression, mechanical airway obstruction, and cellular lung inflammation. Despite a large number of cytokine expressing and virus-specific CD8+ T cells in the lung, TriVax vaccination did not cause immunopathology. High-quality anti-viral CD8+ T cells were overwhelmingly protective in the lung, not pathologic.

Poster 92: Microarray analysis of the human antibody response to Cryptosporidium glycopeptides

Children's Center for Immunology and Vaccines

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Cryptosporidium parvum is a protozoan parasite that infects the epithelial cells of the small intestine causing diarrheal illness that can be especially severe in the immunocompromised and children under 2 years of age. Drug treatment is very limited and no vaccines exist. Several *C. parvum* glycosylated membrane proteins/antigens including various mucin-like proteins are reported to inhibit binding or be associated with protection. In the present study, synthetic glycopeptide arrays were used to screen sera from cryptosporidium-infected individuals. We probed for the presence of IgM and IgG antibodies present in the sera that bind to different glycopeptides. While binding was observed on a number of microarrays using positive sera, the most distinct binding occurred with glycopeptides expressing the Tn antigen (GalNAc₆-Ser/Thr-R). The Tn antigen is a precursor in higher animals for elongated glycans, and not normally found in vertebrate glycoproteins, but its presence in lower organisms and parasites has not been well explored. Sera from cryptosporidium-infected individuals bound to certain multivalent Tn antigen epitopes presented on glycopeptides, suggesting that the parasite expressed glycoepitopes or glycopeptides that contain the Tn antigen and induce immune responses upon infection. Since a known immunodominant antigen previously demonstrated binding to lectins that recognize the Tn antigen, we synthesized glycopeptides with different Tn valency to determine how these groups may affect the sera binding. We found that in some individuals binding was decreased, while in others glycosylation resulted in up to 5-fold increase in reactivity. Molecular differences in glycosylated peptides (e.g. substituting Ser for Thr) as well as the site of glycosylation also had a pronounced effect on individual reactivity. In summary, differences in glycosylation and Tn expression could significantly affect the binding of sera antibodies to the immunodominant 17kDa antigen.

Poster 93: The expression profile and regulation of EphB receptors and Ephrin B ligands in mouse and human immune cells.

Children's Center for Immunology and Vaccines

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Eph receptors and their Ephrin ligands represent the largest family of receptor tyrosine kinases. The Eph family of molecules is divided into the EphA and EphB which bind respectively to EphrinA and EphrinB ligands. Beyond their well-defined role in developmental processes and cancer, little is known about their role during immune response. Ephrin ligands have been shown to be present on the surface of CD4⁺T cells but there are currently no reports of Eph receptors on dendritic cells, the main immune cells activating CD4⁺T cells. Using quantitative RT-qPCR, we explore mRNA expression of EphB receptor kinases in mouse splenic and bone marrow-derived myeloid dendritic cells (BMDC) in response to the bacterial TLR ligands (LPS and CpG1668) or to EphrinB ligands in the presence of INF γ . We have also visualized protein expression of these molecules using immunohistochemistry. Our preliminary data shows that EphB1, EphB2, EphB3 and EphB6 are expressed in naive splenic dendritic cells while EphB2, EphB3, EphB4 and EphB6 are present in BMDC. EphB2 and EphB3 are highly upregulated in BMDC treated with EphrinB, LPS, and CpG1668 in the presence or absence of INF γ . We have also assessed the expression profile of EphB and EphrinB families molecules in peripheral blood mononuclear cells (PBMC) purified from the blood of healthy human volunteers and exposed to the malaria parasite *Plasmodium falciparum*. The malaria parasite significantly activates transcription of mRNA for EphrinB1 and EphrinB2 in PBMC. Our results are the first to show up-regulation of these molecules in immune cells responding to malaria, and currently we are investigating the role this family of molecules plays in anti-malarial immune responses.

Poster 94: Molecular determinants for synergies between paramyxovirus and Streptococcus pneumoniae infections

Children's Center for Immunology and Vaccines

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It is well documented that respiratory viruses of the myxovirus families predispose for secondary bacterial infections in particular by *Streptococcus pneumoniae*, a gram-positive pathogen that causes infections of the respiratory tract, bacterial pneumonia and meningitis. However, the underlying molecular mechanism remains poorly understood. It has been suggested that presence of the RSV glycoprotein triggers increased *S. pneumoniae* adherence through direct interactions. To test this hypothesis, we have established novel qualitative and quantitative binding assays that assess the effect of a panel of paramyxovirus-derived envelope glycoproteins on bacterial attachment. Assays were normalized for equal expression levels of the different viral glycoproteins examined. Remarkably, only the presence of NDV-HN resulted in increased bacterial adherence. To assess whether this is based on exposure of cryptic bacterial receptors through NDV-HN neuraminidase activity or direct binding of *S. pneumoniae* to NDV-HN, HN variants deficient in neuraminidase activity were generated and cells pre-treated with external, purified neuraminidase. Either approach consistently pointed towards removal of cellular sialic acid moieties as the basis for enhanced *S. pneumoniae* adhesion, which is corroborated by studies that have examined the effect of influenza virus on bacterial colonization. The correlation between glycosylation pattern and bacterial adherence was investigated in glycan arrays. Notably, a repetitive disaccharide was sufficient for bacterial adherence. The contribution of this disaccharide motif in the context of glycosylated lipids and/or glycoproteins to bacterial disease is currently under investigation.

Poster 95: Low level of Natural Ribonucleotide Pools in Human Macrophages Versus Lymphocytes lead to the Discovery of Modified Ribonucleosides with Anti-HIV-1 Activity

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Background: Macrophages (MΦ) are a significant viral reservoir, and understanding mechanisms responsible for these data is critical to design novel therapies aimed at eradication of virus from these sanctuaries. We sought to determine 1) levels of endogenous dNTP/rNTPs in MΦ *versus* lymphocytes with a goal of understanding how these competing nucleotides could impact incorporation of anti-HIV nucleoside reverse transcriptase inhibitors (NRTI) into the growing viral DNA strand, and 2) determine if differences in dNTP/rNTP pools in MΦ could confer potency of ribonucleoside inhibitors in MΦ *versus* lymphocytes.

Methods: MΦ and lymphocytes were isolated from buffy coats. dNTP /rNTP levels were quantified with LC-MS/MS. Biochemical simulation studies were performed in a cell free system using HIV-1 RT. For antiviral potency studies, virus was quantified using HIV-1 p24 ELISA. EC₅₀ was determined using the Chou method. Toxicity was assessed using the MTT assay.

Results: MΦ harbored 22-320 fold lower dNTP concentrations *versus* lymphocytes, and MΦs display a significantly greater ratio of rNTP:dNTP *versus* lymphocytes. Biochemical simulation of HIV-1 reverse transcription revealed that rNTPs are efficiently incorporated into DNA in the MΦ, but not the lymphocyte simulated environment. Two ribonucleoside inhibitors demonstrated potent inhibition of viral replication (EC₅₀ of 19.8 ± 7.2 μM and 5.5 ± 4.4 μM), and were not toxic (IC₅₀ > 100 μM) in Vero, CEM, and primary human lymphocytes).

Conclusions: These data imply that HIV-1 preferentially incorporates rNTPs during viral replication in MΦ. Based on this discovery we identified two non-toxic ribonucleoside inhibitors that demonstrate selective anti-HIV potency. These data demonstrate that the biochemical landscape of HIV-1 replication in MΦ is distinct from that of lymphocytes, and that ribonucleoside chain terminators represent a new class of anti-HIV-1 agents that inhibit viral replication in MΦ.

Poster 96: Potent Dual Activity of Purine Dioxolane ProTides against HIV-1 and HBV

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BACKGROUND: Purine nucleoside analogs represent an established class of clinically useful antiviral agents. (-)-β-D-2,6-Diaminopurine dioxolane (DAPD, AMDX, Amdoxovir) is a purine nucleoside analogue in phase 2 clinical development for HIV-1 with modest hepatitis B virus (HBV) activity *in vitro*. Synthesized DAPD analogues included modifications at the C6 position of the purine ring and conversion to the corresponding ProTides to increase intracellular delivery and improve antiviral activity against both viruses. METHODS: The synthesized nucleoside analogs and ProTides were evaluated for anti-HIV activity in primary human lymphocytes (PBM) infected using HIV-1/LAI and anti-HBV activity using the HepG2 HBV system. Cellular toxicity was assessed in human hepatocytes (HepG2), PBM, Vero, and CEM cells. Cellular pharmacology was assessed in both PBM and HepG2 cells by LC-MS/MS. RESULTS: Anti-HIV-1 activity of certain C6 modified purine ProTides in PBM cells were up to 250-fold more potent than DAPD and displayed up to 70-fold more potency than the DAPD deaminated metabolite, DXG. Some of the compounds were low nM inhibitors of HIV. No apparent cytotoxicity was observed for all dioxolane analogs tested in HepG2, PBM, Vero, and CEM cells. In both cell systems, the levels of the active metabolite DXG-TP were > 100-fold higher for C6 modified ProTides than the levels achieved with the parent nucleoside analogs. CONCLUSIONS: The ProTide approach alone and in combination with modification at the C6 position of the purine ring resulted in a significant enhancement of the anti-HIV and -HBV activity compared to the parent nucleoside analogues. The increased potency with no increased toxicity can be attributed to increased formation of intracellular active nucleoside triphosphate. Additional preclinical studies are warranted to advance these potent novel nucleosides to the clinic.

Poster 97: Identification of host proteins required for HIV-1 and M-PMV virus assembly and budding through a novel RNAi screening method

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The assembly and budding of retroviruses from the host cells requires interactions between the viral structural proteins, viral genome and cellular factors. Different genera of retroviruses utilize distinct assembly pathways. Lentiviruses such as Human immunodeficiency virus type 1 (HIV-1) assemble the internal structures of their particles concurrently with envelopment at the plasma membrane. In contrast, betaretroviruses such as Mason-Pfizer monkey virus (M-PMV) assemble immature capsids in the cytoplasm. M-PMV capsids then translocate to the plasma membrane for envelopment and budding. Although a number of cellular factors involved in retrovirus assembly have been identified, we hypothesize that retroviruses utilize a number of cellular trafficking factors to expedite their assembly and budding that have not yet been defined. Here we performed a RNAi screening using a siRNA library that targets 140 host membrane trafficking genes to identify host factors required by HIV-1 and M-PMV virus assembly and budding. Assembly was carefully assessed using a microplate-based fluorescent measurement of reverse transcriptase activity in cellular supernatants. We identified that RhoA/ROCK1/LIM Kinase-1/Cofilin1 pathway is involved in HIV-1 and M-PMV virus assembly and budding. LIM kinase-1 (LIMK1) is a serine protein kinase involved in the regulation of actin polymerization. RhoA is able to phosphorylate and activate ROCK1, and LIMK1 is phosphorylated by ROCK1. LIMK1 in turn phosphorylates and inactivates the actin depolymerising factor Cofilin 1 (CFL1), which results in an increase in the cellular filamentous actin. We found that depletion of ROCK1 or LIMK1 diminished both HIV-1 and M-PMV virus assembly/budding, whereas depletion of CFL1 greatly enhanced both HIV-1 and M-PMV virus assembly/budding. Our findings suggest that retroviruses have developed strategies to remodel the peripheral actin cytoskeleton in order to facilitate their assembly and budding. Further investigation on how the retroviruses interact with the RhoA/ROCK1/LIM Kinase-1/Cofilin1 pathway will help to develop novel antiviral therapies targeting this critical step in the viral life cycle.

Poster 98: Innovative high-throughput screen protocol to identify host-directed inhibitors of myxovirus replication

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Traditional antiviral drugs target pathogen components, creating a basis for the rapid emergence of viral resistance. To counteract viral escape and develop next-generation antivirals with a broadened pathogen target range, we pursue a host-directed antiviral strategy. To identify inhibitor candidates that can inhibit orthomyxovirus (influenza virus) and paramyxovirus (respiratory syncytial virus, human parainfluenzaviruses, measles virus) replication, we designed a novel high-throughput screening protocol based on co-infection of cells with two distinctly traceable myxovirus representatives. Towards this goal, a novel measles virus recombinant expressing renilla luciferase and an influenza A/WSN (H1N1)-based renilla firefly luciferase reporter were generated. Initial characterization demonstrated robust expression of either reporter after successful co-infection of cells with both pathogens. After scale-up of this dual luciferase detection system to a 96-well plate format, we observed good reproducibility, desirable signal to background ratios, and overall high suitability of the assay for automated hit discovery (i.e., $Z' \geq 0.61$). Thus, in a single-well setting this dual pathogen assay system has the capacity to identify orthomyxovirus-specific, paramyxovirus-specific, and broadly myxovirus-active, most likely host-directed inhibitor candidates. This provides a valid basis for the automated discovery of innovative next-generation antivirals through high-throughput screening of small-molecule compound libraries after further scale-up to a 384-well plate format.

Poster 99: Traditional Risk Factors Overshadow HIV-Related Factors in Predicting Vitamin D Deficiency in HIV-Infected Children and Young Adults

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Introduction: Vitamin D deficiency is common in HIV-infected children and adults. In adults, both traditional and HIV-related risk factors play a role in determining vitamin D status. In HIV-infected youth, less is known about factors associated with vitamin D status. This study sought to determine factors contributing to vitamin D status and deficiency in HIV-infected youth.

Methods: HIV-infected subjects (1-25 years old) from the Grady HIV Clinic were prospectively enrolled, along with an age-, sex-, and race-matched healthy control group. HIV clinical and laboratory data were collected for the HIV-infected group, while traditional risk factor data, including vitamin D intake, sun exposure, skin type, physical activity level, body mass index (BMI) and fasting lipids were collected for both groups. 25-hydroxyvitamin D (25(OH)D) was measured in duplicate with ELISA.

Results: 200 HIV+ subjects and 50 healthy controls were enrolled. Groups were similar in age, race, sex, and BMI (HIV+: mean (SD) age =17.2 (4.6) years; 95% black; 53% male). HIV+ group had a median time since HIV diagnosis of 12 years (64% perinatally-infected), median CD4 (CD4%) of 424 cells/mm³ (26%), 67% on antiretroviral therapy (26% on efavirenz); 50% HIV-1 RNA <80 copies/mL. There was no difference in mean 25(OH)D between groups; 77% HIV+ and 76% controls had vitamin D deficiency (25(OH)D <20 ng/mL). Fitzpatrick skin type was the only variable associated with vitamin D status and vitamin D deficiency in both groups. No HIV-related variables were associated with 25(OH)D previously found to be associated in adults.

Conclusion: Vitamin D deficiency is common among HIV-infected youth. HIV factors do not appear to play the same role in determining vitamin D status as they do in HIV-infected adults. Further studies in this young population are urgently needed, especially supplementation trials, as data generated from HIV-infected adults cannot be automatically extrapolated to the pediatric population.

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