Pediatric Healthcare Innovation:

Advancing Technologies to Improve Child Health

April 22, 2014
Georgia Tech Hotel and Conference Center

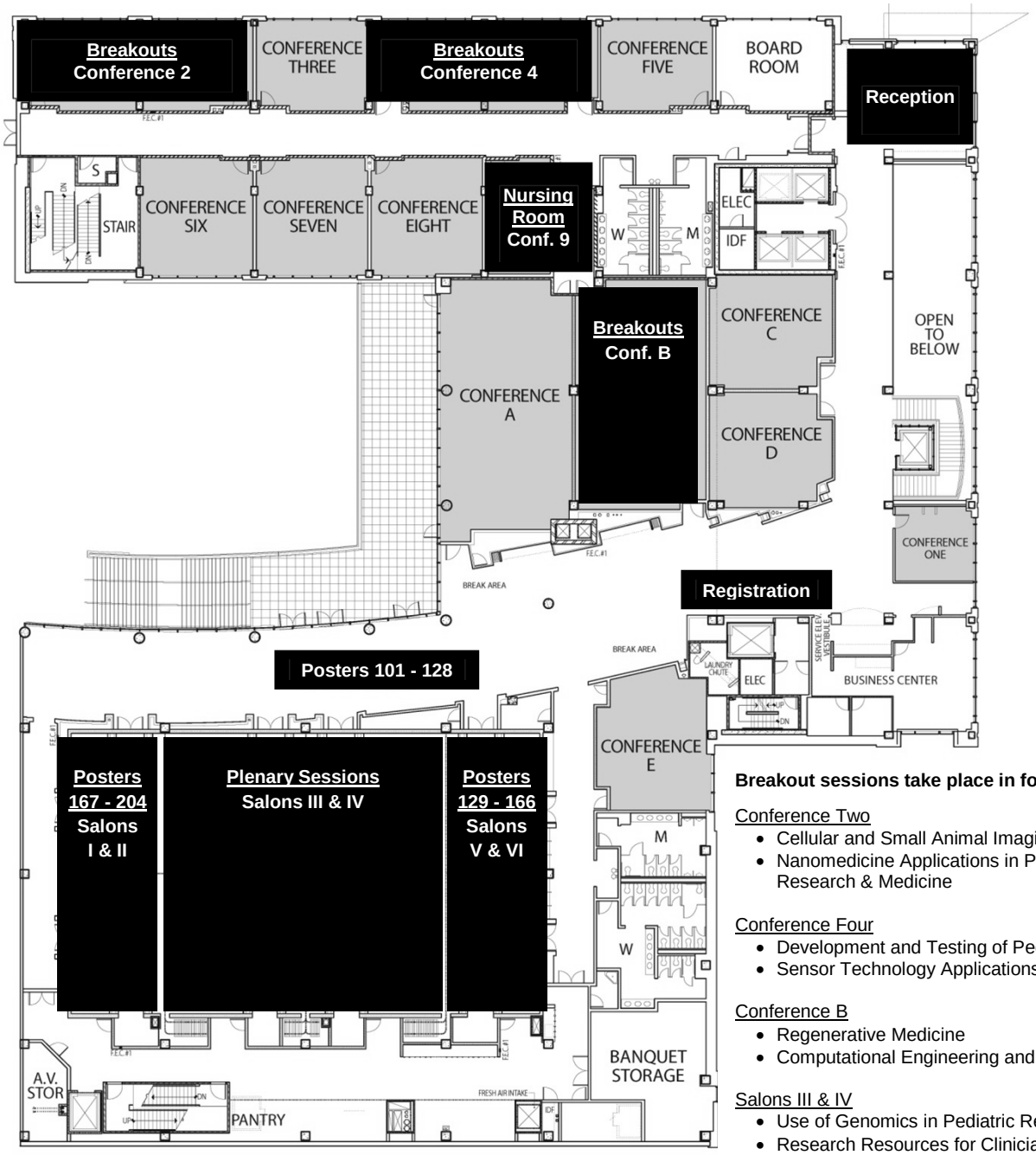
Hosted by:

Children's Healthcare of Atlanta

EMORY UNIVERSITY

Georgia Institute of Technology

Georgia Tech Hotel & Conference Center: 2nd Floor



Breakout sessions take place in four rooms:

Conference Two
- Cellular and Small Animal Imaging
- Nanomedicine Applications in Pediatric Research & Medicine

Conference Four
- Development and Testing of Pediatric Devices
- Sensor Technology Applications in Pediatrics

Conference B
- Regenerative Medicine
- Computational Engineering and Big Data

Salons III & IV
- Use of Genomics in Pediatric Research
- Research Resources for Clinician Scientists

Lunch: Lunch will be provided in the first floor restaurant.

Parking: Please pick up a free parking voucher at the registration desk. If you have a Georgia Tech parking permit, there is no charge to exit the deck after 5:00 PM.

Nursing Room: A nursing room is available in conference room nine.

Name Tags: Please leave your name tag at the registration desk before leaving!

Program Contents

How was the conference? Provide feedback on today's event at www.pedsresearch.org – link on home page.

Agenda

7:00 – 8:30	Registration and Continental Breakfast	
8:00 - 8:15	Welcome	
	Donna Hyland President and Chief Executive Officer Children's Healthcare of Atlanta Steve Cross, PhD Executive Vice President for Research Georgia Institute of Technology	Wright Caughman, MD Executive Vice President for Health Affairs, Emory University CEO, Woodruff Health Sciences Center Chairman, Emory Healthcare
8:15 - 8:30	"Pediatric Nanomedicine: Tiny Machines Give Huge Gains"	
	Gang Bao, PhD, Conference Co-Chair Robert A. Milton Chair of Biomedical Engineering College of Engineering Distinguished Professor Director, Center for Pediatric Nanomedicine Director, Nanomedicine Research Institute	
8:30 - 8:45	"Innovation and Medical Devices for Children"	
	Kevin Maher, MD, Conference Co-Chair Associate Professor of Pediatrics Emory University School of Medicine Co-Director, Center for Pediatric Innovation Director, Pediatric Cardiac Nanomedicine Children's Healthcare of Atlanta	
8:45 – 9:00	"A Rapid, Color-Based, Disposable, Patient-Operated, Point-of-Care Anemia Diagnostic Developed at Georgia Tech, Emory, and CHOA"	
	Wilbur A. Lam, MD, PhD Assistant Professor Aflac Cancer and Blood Disorders Center Department of Pediatrics Children's Healthcare of Atlanta / Emory University School of Medicine Wallace H. Coulter Department of Biomedical Engineering Georgia Institute of Technology and Emory University	

9:00 - 9:20	Rapid-Fire Poster Presentations
	Moderated by **Kevin Maher, MD** 101: "Electronic Medical Record (EMR) technology used to Improve Discharge Instructions in a Pediatric Emergency Department (ED) as a Quality Initiative" by **Bolanle Akinsola, MD**; John Cheng, MD; April Zmitrovich, MSW, MPH; Claudia Morris, MD; Naghma Khan, MD; and Shabnam Jain, MD, MPH 153: "Using Patient Data to Transform Care and Improve Outcomes for Children, Adolescents and Young Adults with Inflammatory Bowel Disease" by **Bernadette Martineau**; Cara Bergo; Britney Eyster; Christine Spainhour; Anna Roberts; and Bess T. Schoen, MD 103: "Whole-Exome Sequencing Identifies Candidate Rare Variants In Patients with Early-Onset IBD" by **Kajari Mondal, PhD**; David T. Okou, PhD; David J. Cutler, PhD; Michael E. Zwick, PhD; and Subra Kugathasan, MD 130: "Combined In Vivo and In Vitro Analyses Identify the Caspase-1 / Interleukin-1β / TRPM2 Axis as a Significant Contributor to Neutrophilic Airway Inflammation in Cystic Fibrosis" by **Osric Forrest, BSc**; Sarah Ingersoll, PhD; Marcela Preininger, BSc; Julie Laval, PhD; Milton Brown, PhD; and Rabindra Tirouvanziam, PhD 112: "Prevention of Perinatal Brain Hemorrhage with Matrix Metalloproteinase Inhibitors" by Dianer Yang, PhD; Yu-Yo Sun, PhD; Jessica Baumann, MS; and **Chia-Yi Kuan, MD, PhD**
9:20 – 9:30	Presentation of Poster Awards
9:30 - 10:00	Break & Poster Session (Prefunction and Salons I, II, V, and VI)
10:00 – 11:00	Keynote Presentation: "Cell Properties and Human Diseases"
	Subra Suresh, ScD President of Carnegie Mellon University
11:00 – 11:20	"Unraveling the Heterogeneity of Severe Asthma"
	Anne M. Fitzpatrick, PhD, APRN, CPNP Assistant Professor and Director, Asthma Clinical Research Program Emory University Department of Pediatrics
11:20 – 11:40	Rapid-Fire Core Presentations
	Moderated by **Stacy Heilman, PhD** **126: The Pediatric Flow Cytometry Core** – David Archer, PhD **118: The Pediatric Animal Physiology Core** - Mary Wagner, PhD **138: The Pediatric Biomarkers Core** – Lou Ann Brown, PhD **122: The Pediatric Immunology Core** – Larry Anderson, MD and Karnail Singh, PhD **134: Integrated Cellular Imaging Core (ICI)** – Neil Anthony, PhD and Adam Marcus, PhD **106 & 107: GA Tech Protein Engineering Core** - T. J. Cradick, PhD **111: The Transgenic Mouse and Gene Targeting Core Facility** – Tamara Caspary, PhD **102: Emory Integrated Genomics Core** - Michael Zwick, PhD **115: Cardiovascular Imaging Research Core (CIRC)** - Ritu Sachdeva, MD **140 & 141: Center for Systems Imaging & Biomedical Imaging Technology Center (CSI/BITC)** – John Oshinski, PhD

11:40 – 11:50	Please proceed to the first floor restaurant for lunch. You may choose to eat lunch in the dining room or take your lunch with you to one or both breakout sessions.	
11:50 – 1:10 Lunch & Breakout Sessions	11:50 – 12:30	Breakout Session 1 • Cellular and Small Animal Imaging in Pediatric Research (Conference Two) • Development and Testing of Pediatric Devices (Conference Four) • Regenerative Medicine (Incl. Stem Cells and Biomaterials) (Conference B) • Use of Genomics in Pediatric Research (Salons III & IV)
	12:30 – 1:10	Breakout Session 2 • Nanomedicine Applications in Pediatric Research & Medicine (Conference Two) • Sensor Technology Applications in Pediatrics (Conference Four) • Computational Engineering and Big Data for Outcomes Research and Predictive Modeling (Conference B) • Research Resources for Clinician Scientists (Salons III & IV)
1:10 – 1:15	Break	
1:15 – 2:15	Keynote Presentation: "iPSCs for Cardiovascular Diseases and Drug Discovery"	
	Joseph Wu, MD, PhD Director, Stanford Cardiovascular Institute Professor, Department of Medicine/Cardiology and Radiology	
2:15 - 2:35	Rapid-Fire Poster Presentations	
	Moderated by **Gang Bao, PhD** 143: "The Viral Restriction factor IFITM3 Promotes Hemifusion but Blocks Full Fusion of Influenza Virus" by **Tanay M. Desai, PhD**; Mariana Marin, PhD; Christopher R. Chin; George Savidis; Abraham L. Brass, MD, PhD; and Gregory B. Melikyan, PhD 108: "Generation of Human Induced Pluripotent Stem Cells for Modeling Catecholamine Induced Polymorphic Ventricular Tachycardia" by **Marcela K. Preininger, BSc**; Doan C. Nguyen, MD, PhD; Ciaran Lee, PhD; T. J. Cradick, PhD; Aarti Dalal, DO; Xuemin Chen, PhD; Paul Spearman, MD; Edward M. Balog, PhD; Peter S. Fischbach, MD; Gang Bao, PhD; Mary B. Wagner, PhD; and Chunhui Xu, PhD 109: "Molecular Beacons as a Tool to Separate Cardiomyocytes from Differentiating Pluripotent Stem Cells" by **Brian M. Wile**; Kiwon Ban, PhD; Jaemin Byun, PhD; Talib Saafir, PhD; Mary Wagner, PhD; Young-Sup Yoon, MD, PhD; and Gang Bao, PhD 116: "Effect of Exercise on Bifurcated Y-graft Fontan Total Cavopulmonary Connection" by **Jaci K. Carithers**; Maria Restrepo, BS; Chris Haggerty, PhD; Elaine Tang, B.Eng; Timothy Slesnick, MD; Kirk R. Kanter, MD; Ajit P. Yoganathan, PhD 169: "Microfluidic Platform for Acute Lymphoid Leukemia Detection" by **Gonghao Wang, BS**; Alexander Alexeev, PhD; Wilbur Lam, MD, PhD; and Todd Sulchek, PhD	
2:35 – 3:05	Break & Poster Session 2 (Prefunction and Salons I, II, V, and VI)	
3:05 – 3:20	"Cardiac Applications of Regenerative Medicine"	
	Michael E. Davis, PhD Director, Emory+Children's Center for Cardiovascular Biology Associate Professor of Cardiology and Biomedical Engineering Wallace H. Coulter Department of Biomedical Engineering Georgia Institute of Technology and Emory University	

3:20 – 3:40	"Medical Intelligence: How I Get to be Agent 007 After All"	
	Anthony C. Chang, MD, MBA, MPH Medical Director, Heart Institute Medical Director, Sharon Disney Lund Medical Intelligence and Innovation Institute Children's Hospital of Orange County	
3:40 – 4:10	Panel Discussion: Pediatric Healthcare Innovation	
	Barbara J. Stoll, MD George W. Brumley, Jr. Professor and Chair, Department of Pediatrics Emory University School of Medicine President, Emory-Children's Center Director, The Pediatric Center of Georgia Ravi V. Bellamkonda, PhD Wallace H. Coulter School Chair GRA Distinguished Scholar Wallace H. Coulter Department of Biomedical Engineering Georgia Institute of Technology & Emory School of Medicine	Jim Heitner, MBA Senior Commercialization Consultant Children's Healthcare of Atlanta Robert E. Guldberg, Ph.D. The Petit Director's Chair in Bioengineering and Bioscience Executive Director, Parker H. Petit Institute for Bioengineering and Bioscience Professor, George W. Woodruff School of Mechanical Engineering Co-Director, Center for Pediatric Innovation Georgia Institute of Technology
4:10 - 5:00	Reception (2nd Floor Break Area)	

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

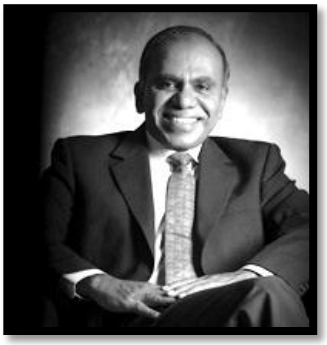
Children's designates this live activity for a maximum of 5.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Co-Chair and Speaker Biographies

Gang Bao, PhD, Co-Chair, is Robert A. Milton Chair of Biomedical Engineering and a College of Engineering Distinguished Professor in the Department of Biomedical Engineering, Georgia Institute of Technology and Emory University. He is also an Adjunct Professor of Pediatrics at Emory University. Dr. Bao is PI and Director of Center for Translational Cardiovascular Nanomedicine, a NIH/NHLBI Program of Excellence in Nanotechnology (PEN) at Georgia Tech and Emory University, Contact-PI and Director of Nanomedicine Center for Nucleoprotein Machines, a NIH Nanomedicine Development Center (NDC) at Georgia Tech, and Director of the Center for Pediatric Nanomedicine at Children's Healthcare of Atlanta and Georgia Tech. Dr. Bao received his undergraduate and Master's degrees from Shandong University in China, and his PhD from Lehigh University in the US. Dr. Bao's current research focuses on the development of nanotechnology and biomolecular engineering tools for biological and disease studies, including molecular beacons, magnetic nanoparticle probes, quantum dot bioconjugates, protein tagging/targeting methods, and engineered nucleases. These approaches have been applied to the diagnosis and treatment of cardiovascular disease and cancer, and the development of gene correction approaches for treating single-gene disorders.

Kevin Maher, MD, Co-Chair, graduated from the University of Maryland School of Medicine, and then completed a residency and chief residency in Pediatrics, also at the University of Maryland. He attended the University of Michigan for a fellowship in pediatric cardiology. In 2004, Dr. Maher joined the Sibley Heart Center Pediatric Cardiology group at Children's Healthcare of Atlanta, Emory University School of Medicine. His primary clinical responsibilities are in the pediatric cardiac intensive care unit at Children's, where he is director of the cardiac ICU. Dr. Maher's research activities include neonatal CPR, cardiac biomarkers in children, and device development. Dr. Maher works to further collaborations with Georgia Tech, aiming to bring engineers into pediatric cardiac research and device development. He is the director of the Pediatric Cardiac Nanomedicine, the Co-director of the Center for Pediatric Innovation and the associate director of the Atlantic Pediatric Device Consortium. He is an adjunct associate professor of Biomedical Engineering at Georgia Tech. Dr. Maher has been an active member the American Heart Association, serving as the Atlanta Metro AHA Board president, and is currently on the national AHA Board. Dr. Maher resides with his wife and three children in Atlanta.

Wilbur A. Lam, MD, PhD is an Assistant Professor of Pediatrics and Biomedical Engineering at Emory University and the Georgia Institute of Technology and has a unique background as a physician-scientist-engineer trained in pediatric hematology/oncology and bioengineering. Dr. Lam's interdisciplinary laboratory, located at both Emory and Georgia Tech, includes engineers, biologists, biophysicists, and clinicians. Our laboratory serves as a unique "one-stop shop" in which we develop microsystems (microfabricated devices, microfluidics, etc.) to study hematologic processes related in both health and disease and then immediately brings those technologies to the patient bedside. More specifically, the Lam lab's research interests involve the development and application of microsystems to enable research in pathologic blood cell interactions that occur in diseases such as sickle cell disease and thrombosis, as well as further translating those systems into novel diagnostic devices. Website: **http://lamlab.gatech.edu/**



Subra Suresh, Btech, MS, ScD is the ninth president of Carnegie Mellon University. Before joining Carnegie Mellon, Dr. Suresh served as director of the U.S. National Science Foundation; among his many accomplishments in that role was co-founding the Global Research Council, a forum for leaders of major science research funding agencies from around the world. He also promoted U.S. economic development through, among other initiatives, the NSF's iCorps program for technology commercialization. Dr. Suresh is a distinguished materials scientist, and his work on cellular nanomechanical processes and human disease states has shaped new fields at the intersection of engineering and biology. Dr. Suresh received his Bachelor of Technology degree from the Indian Institute of Technology, Madras, in First Class with Distinction; a master's degree from Iowa State University; and a Doctor of Science degree from MIT. Following postdoctoral research at the University of California, Berkeley, and the Lawrence Berkeley National Laboratory, he joined the faculty of engineering at Brown University in December 1983, and was promoted to full professor in July 1989. He joined MIT in 1993 as the R.P. Simmons Professor of Materials Science and Engineering and served as head of MIT's Department of Materials Science and Engineering during 2000-2006.

Anne Fitzpatrick, PhD, RN, CPNP, MSCR has a broad background in clinical and translational pediatric asthma research and her independent research program is funded by a variety of extramural grants. She currently holds two R01 awards focused on the clinical, molecular and genetic predictors of corticosteroid insensitivity and disease severity in children with asthma. Dr. Fitzpatrick also is the Principal Investigator of a U10 clinical trial infrastructure award from the NHLBI (AsthmaNet) and the Principal Investigator of the NIH/NHLBI Severe Asthma Research Program (SARP) at Emory University. She has a proven track record of recruitment for pediatric asthma studies and this outstanding recruitment has led to a number of peer-reviewed publications on asthma that were derived from her efforts. Dr. Fitzpatrick has also successfully administered all of these projects (e.g. staffing, research protections, budget) while collaborating with investigators from other institutions.

Joseph Wu, MD, PhD is Director of the Stanford Cardiovascular Institute and Professor in the Department of Medicine (Cardiology) and Department of Radiology (Molecular Imaging Program) at the Stanford University School of Medicine. Dr. Wu received his medical degree from Yale and completed his medicine residency and cardiology fellowship training followed by a PhD (molecular pharmacology) at UCLA. Dr. Wu has received several awards, including the Burroughs Wellcome Foundation Career Award in Medical Sciences (2007), Baxter Foundation Faculty Scholar Award (2008), NIH Director's New Innovator Award (2008), NIH Roadmap Transformative Award (2009), and Presidential Early Career Award for Scientists and Engineers given out by President Obama (2010). The Wu lab studies the biological mechanisms of adult stem cells, embryonic stem cells, and induced pluripotent stem cells, using a combination of next generation sequencing, tissue engineering, physiological testing, and molecular imaging technologies to better understand stem cell biology *in vitro* and *in vivo*. His clinical activities involve adult congenital heart disease and echocardiography.

Michael E. Davis, PhD holds positions as an Associate Professor in both Cardiology and Biomedical Engineering at the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. Additionally, he serves as Director of Emory+Children's Center for Cardiovascular Biology. He received his PhD in Molecular and Systems Pharmacology at Emory University in 2003 working on molecular regulation of eNOS expression by shear stress. From 2003-2006, he completed his postdoctoral fellowship at Brigham and Women's Hospital working on cardiac tissue engineering with collaborators at the Massachusetts Institute of Technology. He moved back to Emory in 2006 to join the faculty in Division of Cardiology and Biomedical Engineering Department. He was elected a Fellow of the American Heart Association in 2011 and is considered a leading expert on bioengineered and stem cell approaches to treating cardiac dysfunction.

Anthony C. Chang, MD, MBA, MPH obtained his Bachelor of Arts in Molecular Biology at Johns Hopkins University (honors) and Doctor of Medicine at Georgetown University School of Medicine. He completed his pediatric residency at National Children's Hospital Medical Center and his pediatric cardiology fellowship at Children's Hospital of Philadelphia. He has held such prestigious positions as Assistant Professor at Harvard School of Medicine, Medical Director of the Cardiac Intensive Care programs at Children's Hospitals of Los Angeles and Miami Children's Hospital, Medical Director of Pediatric Cardiac Intensive Care service, Chief of Critical Care Cardiology at Texas Children's Hospital and tenured Associate Professor at Baylor College of Medicine. He is now the Director of the Heart Institute at the Children's Hospital of Orange County and Chief of the Division of Cardiology. He has a Master's in Business Administration degree from the University of Miami and a Masters of Public Health from UCLA. He publishes and lectures widely on topics in pediatric cardiac intensive care, heart failure, sudden cardiac death, adult congenital heart disease and artificial intelligence in medicine. He leads pediatric heart teams all over the world and was one of the founding members of the Asia-Pacific Pediatric Cardiac Society (APPCS). He has been voted "Physician of Excellence" by the Orange County Medical Association and also selected as one of America's "Top Doctors", "Top Pediatricians", and "Best Cardiologists" by several organizations.

Emory+Children's Pediatric Research Center Website
www.pedsresearch.org

The ECPRC website is a great resource for all the information you need about the Emory+Children's Pediatric Research Center:

Descriptions and leadership of pediatric research centers (summaries below)

Core resources available to basic and clinical scientists

Center membership

Research faculty descriptions

News and calendar for upcoming seminars and events

Pilot grant opportunities and other announcements

Aflac Cancer and Blood Disorders Center
Every advancement in curing childhood cancer and blood disorders is the result of advanced research. The Aflac Cancer and Blood Disorders Center of Children's conducts important research in the following areas: BMT, brain tumors, leukemia and lymphoma, solid tumors, cancer survivorship, hemophilia and thrombosis, sickle cell disease, gene therapy and transfusion medicine.

Center for Cardiovascular Biology
The field of pediatric cardiology has already greatly improved the survival rate of kids with heart defects and disease. Now, researchers are developing techniques and solutions that not only save these patients, but improve their quality of life. Two key research projects in the Center for Cardiovascular Biology include developing a biological pacemaker that would reduce the need for multiple surgeries as children grow; and studying a short-lived protein, that when inhibited, results in much stronger hearts in mice.

Center for Clinical Outcomes Research and Public Health
Researchers in this center focus on identifying new methods to measure and improve pediatric healthcare outcomes. Emphasis is placed upon evaluating comparative effectiveness in a variety of clinical areas including birth and neonatal outcomes, neurodevelopmental outcomes and transition of care from the teenage years into adulthood for those populations who suffer from chronic illness. There is also an important focus on wellness including health promotion and obesity prevention.

Center for Cystic Fibrosis and Airways Disease Research
CF is a devastating genetic disease that affects tens of thousands of children and young adults in the United States. Because it hampers the lungs' ability to remove mucous, cystic fibrosis leads to severe lung infections and shortens the lives of our patients. Researchers at this Center are working to develop new therapies, drugs, and tools to improve and extend the quality of lives of children with this condition.

Center for Drug Discovery
Researchers at this center will study and develop new drugs for a range of pediatric conditions, including infectious and neglected diseases, inflammatory conditions, cancers and blood disorders.

Center for Immunology and Vaccines
Infectious diseases are the leading cause of death in children worldwide. Researchers at this center are working closely with the Emory Vaccine Center and the Centers for Disease Control and Prevention to find new ways to stop the spread of infectious diseases and save the lives of children. This includes developing new vaccine and treatment options for many infectious diseases, including respiratory syncytial virus, measles, malaria and more.

Center for Neurosciences
The vision of Children's Center for Neurosciences Research is to conduct research that will ultimately improve neurological care for children. In this center, clinical physician scientists and laboratory-based researchers collaborate closely to discover and identify preventive, diagnostic and wellness strategies for children with serious neurological challenges.

Center for Pediatric Innovation
Interdisciplinary research and innovation are required to address today's grand challenges in pediatric healthcare and will help transform the practice of medicine over the next 20 years. The Center for Pediatric Innovation focuses on utilizing cutting edge technologies to advance regenerative medicine based therapies for children; develop new diagnostic and therapeutic strategies for detecting and treating pediatric diseases, and design novel pediatric medical devices to improve the care of children.

To foster the translation of medical devices for children, CPI investigators have partnered with the U.S. Food and Drug Administration to establish the **Atlanta Pediatric Device Consortium** (APDC). Historically, medical devices designed for adults have been used in children. This is less than optimal, because children differ from adults not only in terms of their size, but also in their growth, development, and immune responses. To foster the development of medical devices for children, the U.S. Food and Drug Administration funded the Atlanta Pediatric Device Consortium which is dedicated to providing an environment that fosters ideas and creativity. Innovators can bring their ideas to be reviewed, tested and developed. APDC provides assistance with engineering design, prototype development, pre-clinical and clinical studies and commercialization for novel pediatric medical devices.

Center for Pediatric Nanomedicine
This pediatric research center is the first one in the nation to be solely dedicated to the study and advancement of pediatric nanomedicine. Because nanomedicine can be applied to many pediatric diseases and conditions, nanomedicine has the potential to profoundly improve—if not completely revolutionize—the treatment, care and ultimate cure of many childhood diseases and conditions.

Center for Transplantation and Immune-mediated Disorders
When a child receives an organ transplant, his body may attack the new organ as foreign. In the same way, autoimmune diseases also cause the body to attack a part of itself as foreign. Researchers at this center are exploring new treatment options for children undergoing organ or bone marrow transplantation, and for those with autoimmune disorders.

Marcus Autism Center
The earlier autism spectrum disorders (ASD) are diagnosed, the better a patient's outcome will be. Currently, the average age of diagnosis is around 5 years old—even though a reliable diagnosis can be made by age 2. An NIH Autism Center of Excellence, Marcus Autism Center is one of the largest autism research and treatment centers in the U.S. Led by Ami Klin, Ph.D., Director of Marcus Autism Center, our research focuses on social engagement, including the use of innovative special eye-tracking equipment, to establish the earliest signs of ASD.

Children's/GA Tech Partnership
This partnership is setting up synergistic relationships between clinician scientists and investigators with engineers and computer scientists in research and development in:

- Regenerative medicine (e.g. heart valve that grows with the child);
- Nanotechnology (e.g. target defective genes for repair or replacement in single cell diseases like sickle cell anemia);
- Personalized health care delivery (e.g. technology to support management of childhood asthma, obesity and autism);
- Transformation of health care system (e.g. secure health information exchange, technology to support patient-centered medical home);
- Innovations (e.g. identify problems that frustrate clinicians and develop solutions to quickly address).

Additional research center under development:

Center for Clinical and Translational Research
This center will provide organization and leadership for clinical trials science, and act as a central point for recruiting clinical trialists in a variety of disciplines. The center will also serve as scientific home for leaders in nursing research.

Egleston Pediatric Research Center

Atlanta Clinical and Translational Science Institute (ACTSI) is an inter-institutional magnet that concentrates basic, translational, and clinical investigators, community clinicians, professional societies, and industry collaborators in dynamic clinical and translational research projects. The NIH-supported partnership is led by Emory University, along with Morehouse School of Medicine, the Georgia Institute of Technology, and Children's Healthcare of Atlanta, a consortium of medical research institutions working to improve the way clinical and translational research is conducted nationwide. National Center for Advancing Translational Sciences (NCATS) is the newest center of NIH, and is designed to spur the transformation of clinical and translational research and bring new treatments to patients quickly and efficiently.

The Pediatric Research Center (PRC) at Egleston was created to facilitate Children's Healthcare of Atlanta's vision for clinical excellence. Inpatient and outpatient units offer core support facilities (e.g. cardiology) and resources including nursing, pharmacy, laboratory, and bio nutrition. In 2013 & 2014, the PRC studied children with asthma, cardiac disease, hypertension, Crohn's Disease, Type 1 and 2 Diabetes Mellitus, kidney and hepatic disease, Sickle Cell, cystic fibrosis and MRSA. Research studies conducted follow exacting standards for delivering the interventions and collecting the requisite data. To learn more about how the PRC can support your research, please call the PRC at 404-785-0400, or email Stephanie Meisner, RN, BSN, CCRP, Clinical Research Manager, at stephanie.meisner@choa.org.

Poster Index by Author

Poster Abstracts

Cores are listed in white font and shaded in dark gray.

Rapid-fire poster presentations are shaded in light gray.

101: Electronic Medical Record (EMR) Technology Used to Improve Discharge Instructions in a Pediatric Emergency Department (ED) as a Quality Initiative

Bolanle Akinsola, MD; John Cheng, MD; April Zmitrovich, MSW, MPH; Claudia Morris, MD; Naghma Khan, MD; Shabnam Jain, MD, MPH

Background: Effective communication between the physician and patient is essential to optimize care after discharge from the ED. Written discharge care instructions (DCI) complement verbal instructions & improve communication & patient management. In 2012, Centers for Medicare & Medicaid services (CMS) proposed a quality measure (OP-19) that assesses compliance with key elements essential for high quality written DCI.

Objective: To evaluate the impact of a quality improvement (QI) intervention on improving the quality of written DCI in a pediatric ED (PED) using EMR. Design/Methods: The study was conducted at a tertiary PED with >60,000 annual visits. Based on the CMS OP-19 measure & group consensus, 8 elements were defined a priori. A QI intervention was implemented in Feb 2013 - all providers were educated on these elements. 32 physicians reviewed a random sample of 5-10 EMR charts/month (using a standardized electronic form) of patients triaged as Emergency Severity Index level 2 & 3 who were discharged home. Proportion of charts that had each element documented was compared between Pre-intervention Nov-Dec 2012 (PRE) phase and Post-intervention Mar-Oct 2013 (POST) phase using Chi-square analysis. Results: 329 charts PRE & 1434 POST were reviewed. Results are noted in table.*N: # of charts where element was noted; D: # of charts where element was applicable. The bundle measure (proportion containing all 8 elements) increased from 23% (PRE phase) to 79% (POST phase), p<0.001.Conclusions: ED DCI improved in all 8 elements following a QI intervention. It is generally accepted that a detailed transition record at ED discharge enhances the patient's ability to comply with post-discharge treatment plan. EMR provides technology to standardize DCI not applicable with use of paper charts & facilitates data extrapolation. Further studies are needed to evaluate the impact of improving DCI on ED return rates & patient satisfaction rates.

102: EMORY INTEGRATED GENOMICS CORE (EIGC)

Michael E. Zwick, PhD

The EIGC is a full-service genomics and computational facility offering Emory researchers the ability to use the latest technologies and methods of analysis in their research. We offer next-generation sequencing, high density microarray services, targeted enrichment, single nucleotide polymorphism (SNP) genotyping, and cutting-edge computational services built around our custom Galaxy server and Emory University's high performance computing and storage infrastructure. Please visit http://eigc.emory.edu/ for more information.

Posters 103 to 105 utilized the EIGC.

103: Whole-Exome Sequencing Identifies Candidate Rare Variants in Patients with Early-Onset IBD

Kajari Mondal, PhD; David T. Okou, PhD; David J. Cutler, PhD; Michael E. Zwick, PhD; Subra Kugathasan, MD

Inflammatory Bowel Disease (IBD) is a chronic, complex disorder with significant morbidity. IBD is heritable in large part and genome-wide association studies (GWAS) using common single nucleotide polymorphisms (SNPs) have identified ~163 susceptibility loci for IBD, containing at least 1441 genes of interest. The effect sizes of nearly all of these loci are small (odds ratios <1.5) and they account for only ~20% of the estimated heritability. Here we test the hypothesis that rare variants with moderate to large effect may contribute to IBD susceptibility and help explain some of the missing heritability. Early-onset forms of IBD are especially likely to be influenced by this class of genetic variation, and we predicted that the genes within the ~163 IBD associated GWAS loci and loci influencing neutrophil function would be enriched for rare variants at evolutionarily conserved sites. To test this hypothesis, we performed whole-exome sequencing (WES) on 109 individuals with very early-onset IBD. We mapped the data against the whole human genome sequence (hg19) and obtained very high quality data, with greater than 100X of average sequence coverage. WES analysis identified 83,791 replacement single nucleotide variants (SNVs), among which 17,298 were previously unobserved (not in dbSNP 137). We focused our analysis on the 1441 key genes reported within the 163 IBD associated loci and prioritized on novel nonsense and missense variants that were present at highly conserved sites and were predicted to be damaging by multiple algorithms. A total of 27 novel nonsense mutations and 132 novel missense mutants met our selection criteria. Among these was a rare novel nonsense mutation at the FUT2 locus (Q166*), a gene previously identified in a IBD GWAS. We also used another gene list consisting of 127 neutrophil pathway genes, as mutations in these genes might disrupt the neutrophil function and contribute to early-onset IBD. We found 2 novel novel nonsense mutations and 35 novel missense mutants in these 127 neutrophil pathway genes. One of the interesting mutation found was a novel nonsense mutation (Q68*) in the Mediterranean Fever (MEFV) gene, suggesting that mutations in MEFV can act as a susceptibility factor for IBD. Thus, our discovery of these novel candidate mutations not only provides an orthogonal replication of the IBD GWAS finding but also provides us with interesting candidate variants which can be followed up by various functional assays.

104: Analysis of Copy Number Variants on Chromosome 21 in Down Syndrome Associated Congenital Heart Defects

Benjamin Rambo-Martin, MS; Dhanya Ramachandran, PhD; Jennifer Mulle, MHS, PhD; Adam E. Locke, PhD; Promita Bose, MS; Lora J. Bean, PhD; Shoshona Le; Traci Rosser, PhD; Ken Dooley, MD; David J. Cutler, PhD; Soo Y. Cheong, PhD; Clifford L. Cua, MD; Cheryl L. Maslen, PhD; Roger H. Reeves, PhD; Stephanie L. Sherman, PhD; Michael E. Zwick, PhD

Atrioventricular septal defects (AVSD) are a life threatening congenital heart defect (CHD) inflicting substantial social and healthcare costs. Traditional genetic mapping strategies have revealed a limited but highly heterogeneous, set of aberrant genes responsible for AVSD, and suggest that many AVSD risk loci remain undiscovered. Children born with Down Syndrome (DS) are at a 2000-fold increased risk for AVSD over the general population, resulting in an AVSD prevalence in DS of 1 in 5. These data suggest that individuals with trisomy 21 compose a sensitized cohort with respect to AVSD, and may help reveal novel AVSD susceptibility genes. In particular, we hypothesize that copy number variants (CNVs) on chromosome 21 influence the risk of AVSD in individuals with DS, and therefore explain the elevated risk for AVSD found in the DS population. Our group and previous studies have associated large, rare CNVs across the genome with DS+AVSD. Most notably, Sailani et al., 2013, found small, high frequency CNV associations with DS+AVSD on chromosome 21 in a cohort of 108 individuals. We have performed high-density array comparative genomic hybridization of chromosome 21 in 236 cases (individuals with DS and complete AVSD) and 281 controls (individuals with DS without any CHD). To balance type 1 and type 2 errors, we analyzed CNVs that were called from normalized Log2 scores either by the ADM2 algorithm or a majority of the eight algorithms housed in the CGHweb wrapper. We successfully detected CNVs across the q-arm of chromosome 21, including 199 duplications and 1,127 deletions. Duplications and deletions were found in 22% and 50% of our cohort respectively. After performing burden tests and standard association tests with PLINK, no significant associations were detected, regardless of filtering by frequency. We did not replicate the Sailani CNVs in our larger cohort. Our preliminary analyses, in combination with published literature, suggest that the effect of a single or a few common CNVs on chromosome 21 alone do not explain the 2000-fold increased risk for AVSD in the DS population. Our data bolster arguments that there is a high level of heterogeneity found in the etiology of AVSD.

105: Contribution of Global Copy Number Variants to Down Syndrome-Associated Atrio-Ventricular Septal Defects

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Atrioventricular septal defects (AVSD), a severe congenital heart defect (CHD), occur in the general population in ~1 in 10,000 births. Nearly 20% of infants with Down Syndrome (DS) have an AVSD, representing a ca. 2000-fold increased risk compared to the euploid population. Our central hypothesis was that in the presence of an extra chromosome 21, otherwise benign copy number variants (CNVs) act to dramatically increase the risk of AVSD in individuals with DS. Here we sought to test two specific questions: (1) Do rare CNVs increase the risk of AVSD in the DS population? (2) Do common CNVs of large effect contribute to the elevated risk of AVSD in the DS population? We used the Affymetrix SNP 6.0 genotyping platform to comprehensively characterize CNVs in 459 ethnically matched individuals with DS, comprising of 211 cases (DS + complete AVSD) and 248 controls (DS – CHD). We implemented strict quality control filters to minimize false positive calls, including 3 algorithms to make the CNV calls (BEAST, GADA and GLAD). We also required each putative CNV call to contain > 20 SNPs within the interval. After excluding CNVs overlapping centromeres, we identified 550 deletions (254 in cases and 296 in controls) and 392 duplications (177 in cases and 215 in controls). Standard burden tests using PLINK revealed that cases do harbor a significantly elevated burden of large rare variants (> 100kb, < 1% frequency) ($p < 0.01$) and the case deletions intersected genes more often than those observed in controls ($p < 0.07$). Gene enrichment analysis showed a trend for enrichment for deletions impacting the ciliome pathway in cases compared to controls. No significant differences were observed for large rare duplications between cases and controls. Burden analyses of common CNVs failed to identify any significant difference between cases and controls. Our findings reject the hypothesis that the increased risk of AVSD in the DS population is caused by common variants of large effect size. Instead, our study suggests a complex multifactorial model, wherein large rare deletions that disrupt genes involved in ciliome structure and function play a significant role in elevating the risk of AVSD in a trisomic background.

106 & 107: GEORGIA TECH PROTEIN ENGINEERING CORE

T. J. Cradick, PhD

The Georgia Tech Protein Engineering Core builds tools to rapidly create precise genetic modifications. The core can provide reagents enabling specific genome editing for many applications, including making model cell lines and organisms, with custom knock-outs, or knocked-in tags or protein sequences. Nucleases have been used to edit the genomes of an ever-growing list of organisms. We are also actively involved in gene therapy projects and can provide reagents for therapeutically correcting mutations. We have successfully designed each of the major types of nucleases: Zinc Finger Nucleases (ZFN), TAL Effector Nucleases (TALEN) and CRISPR/Cas systems. The lab has developed programs for very effective nuclease design and a range of expression vectors. We have also developed bioinformatics to predict possible off-target sites and testing methods to validate and improve nuclease specificity.

Posters 108 to 110 utilized the Georgia Tech Protein Engineering Core.

108: Generation of Human Induced Pluripotent Stem Cells for Modeling Catecholamine Induced Polymorphic Ventricular Tachycardia

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a frequently lethal inherited arrhythmia syndrome resulting from abnormalities in intracellular Ca2+ regulation. Despite advances in management, CPVT remains a syndrome with an unacceptably high juvenile mortality rate. The limited efficacy of existing treatments is due largely to CPVT's genetic heterogeneity; hundreds of distinct disease-causing mutations are linked to the CPVT phenotype, each with variable responses to standard of care. Since developing a cure-all for a disease with such variable etiology is unlikely, identification of new therapies optimized for each individual's genomic signature is imperative. Here, we investigate the possibility of using induced pluripotent stem (iPS) cell technology to recapitulate the CPVT phenotype in vitro, and evaluate the efficacy of genome-editing and pharmacological therapies to restore normalcy in a patient-specific manner. A 12 year-old child with CPVT was identified clinically after his brother sustained a sudden cardiac arrest; diagnosis was confirmed by exercise stress testing, and genotyping revealed a novel point mutation in the gene encoding ryanodine receptor type 2 (RyR2). A skin biopsy was obtained from this child and from another unaffected individual, and human dermal fibroblasts were derived in vitro. The fibroblasts were reprogrammed using a polycistrionic lentiviral vector containing OSKM transcription factors (Oct4, Sox2, Klf4, and c-Myc) to generate human iPS cells. To repair the mutation via homologous recombination, CRISPRs (clustered, regularly interspaced, short palindromic repeats) were designed to induce a double-strand break at the patient's specific mutation site. Demonstrating RyR2 correction is important, as RyR2 mutations are responsible for the majority of CPVT cases. Once the mutation has been corrected at the stem cell level, we will investigate whether the repaired (mutation-free) iPS cells can be differentiated into functional cardiomyocytes with normal Ca2+ handling properties, while closely monitoring the cells for mutagenic events. Pharmacological restoration of the normal myocardial phenotype will also be optimized and explored in our model.

109: Molecular Beacons as a Tool to Separate Cardiomyocytes From Differentiating Pluripotent Stem Cells

Brian M. Wile; Kiwon Ban, PhD; Jaemin Byun, PhD; Talib Saafir, PhD; Mary Wagner, PhD; Young-Sup Yoon, MD, PhD; and Gang Bao, PhD

Regenerating heart muscle damaged by heart attacks remains a major challenge in medicine. Recent results demonstrate that scar tissue in the heart can be replaced by normal heart tissues using regenerative medicine. While these experiments are making great strides, the stem cell based approaches need to be improved in order to be translated into the clinic. To meet these challenges, we have developed a novel system in which cardiomyocytes (CMs) can be purified by cardiac specific molecular beacons (MBs). MBs are dual-labeled antisense nano-scale probes that emit a fluorescence signal when hybridized to a target mRNA. We hypothesized that MBs targeted to CM specific mRNAs can identify CMs and allow isolation and purification of CM by fluorescence-activated cell sorting (FACS). Ten MBs targeting distinct sites on either troponin T (cTNT) or α/ßmyosin heavy chain (α/ßMHC) were designed. 5 of these were synthesized by MWG Operon, characterized against synthetic targets in solution, and then delivered into various cell types. The MBs were delivered into a

range of cells similar to the cell types present in a pluripotent stem cell culture being differentiated into cardiac myocytes, including an immortalized mouse CM cell line, smooth muscle cells and fibroblasts. After beacons were nucleofected into each cell type, their efficacy at separating cardiac from non-cardiac cells was determined by FACS. After validation, the beacons were used to separate cardiac cells from differentiating cultures of human and mouse stem cells. The isolated cardiac cells were later confirmed with biochemical markers and cardiac functionality assays. 98% of the immortalized CM cells displayed fluorescent signals when transfected with cTNT or MHC beacons, but less than 10% of the non-CM cells displayed fluorescent signals detectable by FACS. The MBs with the brightest signals in the CM cells were nucleofected into both mouse and human pluripotent stem cell differentiation cultures; 41 to 49% of the cells were identified as an MB+ population. The MB+ cells yielded were found to be 97% cTNT+ by immunocytochemistry and displayed elevated cTNT expression levels in qRT-PCR. We have successfully developed a novel method for isolating specific cell types after stem cell differentiation. This technique also enables the study of a wide range of new research questions as a previously unobtainable cell population can now be purified from a differentiating culture of stem cells.

110: Microinjection of Beta-Globin Targeting Nucleases for Induced Gene Modification in K562 Cells

Renee N. Cottle; David Archer, PhD; Gang Bao, PhD

Sickle cell disease (SCD) is a major cause of global mortality and health disparities. We have been developing a gene correction approach for treating SCD by simultaneous delivery of site-specific nucleases targeting the mutant human hemoglobin β (HBB) gene and a donor template DNA into hematopoietic stem cells, with the long-term goal of replacing sickle cells with healthy red blood cells in patients. We designed and validated TAL effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPR) systems for generating DNA double stranded breaks in the HBB gene near the sickle mutation, and quantified the rate of homologous recombination (HR) in K562 cells. A major challenge in establishing the gene correction approach for treating SCD is delivery of HBB-targeting nucleases and donor templates into stem cells with high efficiency and throughput. Although transfection and electroporation can deliver DNA molecules into stem cells, they suffer from low efficiency or low cell viability respectively. Further, using viral-based methods has the risk of inducing mutagenesis in the host cells. As an alternative, we tested a microinjection-based approach for high efficient delivery of HBB-targeting nucleases and donor templates into single K562 cells, which is a hematopoietic cell line. K562 cells were microinjected with plasmids encoding an HBB-targeting TALEN pair or CRISPR/Cas9 system along with GFP donor template on a recombinant fibronectin matrix. Microinjected K562 cells having stable reporter fluorescence at 24 hours post injection were sorted as single cells using fluorescence activated cell sorting and expanded into large colonies. Single cell colonies were assessed for nuclease induced GFP integration using fluorescence microscopy and GFP PCR assay. We found that K562 cells injected with TALEN or CRISPR/Cas9 were capable of expansion into large colonies from a single cell, albeit a lower frequency compared to control cells. We observed gene targeting in cells microinjected with nucleases and donor template. The results indicate that HBB targeting CRISPR/Cas9 provides higher HR mediated gene targeting compared to TALENs. We are further investigating the effects of donor template availability on the HR frequency in K562 cells injected with different amounts of donor. The results from this study will inform strategies for increasing gene correction rate in microinjected hematopoietic stem cells.

111: THE TRANSGENIC MOUSE AND GENE TARGETING CORE FACILITY (TMF)

Tamara Caspary, PhD

The TMF is a shared resource of the Emory University School of Medicine (SOM). It was originally established in 1998. The core acts to provide both state of the art equipment and expertise for the generation and characterization of genetically altered mouse models. The core provides a full range of services, including sperm cryopreservation, transgenic production, gene targeting, and auxiliary services. Please visit http://med.emory.edu/research/core_labs/transgenic_mouse/ for more information.

Poster 112 utilized the TMF.

112: Prevention of Perinatal Brain Hemorrhage with Matrix Metalloproteinase Inhibitors

Dianer Yang, PhD; Yu-Yo Sun, PhD; Jessica Baumann, MS; and Chia-Yi Kuan, MD, PhD

OBJECTIVE: The incidence of germinal matrix-intraventricular hemorrhage (GMH-IVH) persists at 20-25% among <1500 g preterm neonates, causing neonatal mortality and functional disabilities. The current best prophylaxis of GMH-IVH is prenatal glucocorticoids (GR), but repeated exposure to GR impairs brain development, and there are no potent postnatal preventive therapy, despite the hemorrhage mainly occurs in the first 72 h after birth. To search for novel therapeutic targets of GMH-IVH in pre- and post-natal periods, we have developed a transgenic mouse model of GMH-IVH based on inducible expression of vascular endothelial growth factor (VEGF) in the germinal matrix (Yang et al., Science Transl. Med., 2013). This model captures clinical presentations of GMH-IVH and responds markedly well to prenatal GR treatment. We hypothesize that GR opposes GMH-IVH by blocking specific blood vessel-degrading proteases, which are useful targets for prophylactic intervention. RESULTS: Genetic induction of VEGF in bitransgenic Nestin-rtTA; TetO-VEGF embryos first induces a dense immature vascular network near lateral ventricles, which transformed into low- vasculature patches with hemorrhage and apoptosis near birth. Gene profiling and biochemical analysis showed strong induction of matrix metalloproteinase-9 (MMP-9), but not other vessel- busting proteases such as tissue plasminogen activator (tPA), in mutant embryos with cerebral hemorrhage. There was also significant induction of the transcriptional factor ETS1, which has two binding sites in the first 600 bp of MMP-9 promoter that were implicated in GR-mediated expression during inflammation. Prenatal GR treatment prevented GMH and blocked MMP-9 activation without attenuating angiogenesis, suggesting that MMP-9 is a critical causative factor. Consistent with this hypothesis, prenatal administration of Marimastat (a broad-spectrum MMP inhibitor) prevented cerebral hemorrhage to an extent comparable with the GR treatment in mutant embryos. CONCLUSION: Our results suggest that MMP-9 is the key neurovascular protease responsible for GMH-IVH, and that prenatal GR therapy protects cerebral blood vessels in part by blocking the ETS1-mediated MMP-9 expression. Hence, inhibition of MMP-9 before or after the birth of preterm neonates may prevent GMH-IVH.

113: Th17/IL17-Mediated Adaptive Immunity in Infection-Sensitized Hypoxic-Ischemic Brain Injury of Newborns

Yu-Yo Sun, PhD; Dianer Yang, PhD; Siddhartha Kumar Bhaumik, PhD; Jessica M. Baumann, BS; Xiaoyi Lin, MS; Diana M. Lindquist, PhD; Murali Krishna Kaja, PhD; Chia-Yi Kuan, MD, PhD

OBJECTIVE: Intrauterine infection increases brain vulnerability to hypoxic-ischemic (HI) insults in infants, but the mechanisms linking (remote) maternal infection to brain damage are unclear and potent therapies of this condition lacking. We hypothesize that infection-sensitized HI induces early onset of Th17 lymphocytes, which enter brains to prime microglia for greater responses to secondary HI insults. This hypothesis predicts that blocking the differentiation or CNS-entry of Th17 cells (e.g. by FTY720, a sphingosine 1-phosphate [S1P] receptor antagonists used for treating Multiple Sclerosis) will oppose infection-sensitized HI injury in neonates. RESULTS: We determined that cord blood mononuclear cells from late preterm infants with histological chorioamnionitis had increased IL-23R transcripts, a Th17-lymphocyte marker, and reduced S1PR1 mRNA, which was recapitulated by the LPS-sensitized HI model in rodents (low-dose LPS, IP injected 4 h before the Rice-Vannucci HI model). The LPS/HI insult caused rapid reduction of CD43 expression in the ipsilateral choroid plexus (CP), and many CD43+ T-cells began to migrate across the CP into subcortical white-matter. Because CD43 expression repels T cell homing, our data suggest a novel mechanism for T-cell recruitment in infection/HI- injured newborn brains. FTY720 treatment markedly reduced CD43+ T-cells in the brain, and mitigated NF-kB signaling, microglia activation, and expression of Th17/Th1-cytokines, but not Th2 cell markers. The FTY720 therapy conferred dose-responding reduction of brain atrophy. Similar effects were found by application of SR1001 (an inhibitor of Th17 cell differentiation). Interestingly, FTY720 lacked direct inhibition of microglia in both in-vivo and in-vitro models, and failed to resist pure-HI brain injury. These results suggest that FTY720 opposes infection- sensitized HI brain injury by disruption of Th17-IL17 pathway rather than neuroprotection per se or direct inhibition of microglia. CONCLUSION: The CD43 expression in CP forms a barrier to T-cell recruitment in the brain. Infection-sensitized HI insult triggers early development of adaptive immunity and attenuates CD43 expression in the CP, allowing Th17 cell entry and amplification of microglial responses. Agents that block Th17 cell differentiation or mobility, such as FTY720, are promising therapy of infection-sensitized HI brain injury in neonates.

114: Plasma Biomarkers of Neonatal Encephalopathy: Osteopontin (OPN) and Scavenger Receptor BI (SR-BI)

Yikun Li, PhD; Dianer Yang, PhD; Nicholas Seyfried, PhD; Chia-Yi Kuan, MD, PhD

OBJECTIVE: A major challenge in neonatal neurocritical care is the lack of reliable laboratory markers of brain damage. The current method of measuring multiple plasma cytokines is less specific and often difficult to interpret the results. To search for definitive biomarkers of neonatal encephalopathy, we used quantitative proteomics to compare the plasma protein composition in mouse pups following hypoxia-ischemia (HI), LPS-sensitized HI, or low-dose LPS-exposure. By subtracting the protein composition from untouched controls, we aim to identify biomarkers of neonatal brain damage (altered after both HI- and LPS/HI-injury), markers of immune responses (altered after LPS-exposure), and unique plasma biomarkers of LPS/HI-induced brain damage. RESULTS: The plasma of experimented mice (10-day-old) was collected at 24 h post-treatment and run on SDS-PAGE (n=3 each group). The divided gel slices were digested by trypsin, eluted, and processed for reverse-phase liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) analysis and bioinformatical identification. The protein abundance was compared using log2 ratio fit of Gaussian distribution. The expression of candidate proteins in the plasma after treatments was verified by immunoblot. This analysis uncovered 29 up-regulated proteins following HI- or LPS/HI-injury (common markers of brain damage), 61 uniquely up-regulated proteins in LPS/HI-injury (potential markers of infection-sensitized HI), and 102 up-regulated proteins after LPS-exposure that is insufficient to cause brain damage, but not in LPS/HI-injury (markers of immune responses). POTENTIAL BIOMARKERS: While comprehensive validation of the candidate proteins is in progress, our current data suggest that osteopontin (OPN) is a sensitive plasma biomarker of HI brain injury, both with and without infection sensitization. This idea is consistent with the report of elevated OPN expression in HI-injured brains, which may be secreted into the blood. Further, up-regulation of the plasma scavenger receptor B1 (SR-BI) protein appears a sensitive indicator of immune responses. The plasma SR-BI may come from the platelet- or endothelium-derived microparticles following exposure to the bacterial endotoxins. On-going experiments include correlation to the severity of brain damage, temporal analysis of the value in early diagnosis, and ultimately validation of these biomarkers in clinical subjects.

115: CARDIOVASCULAR IMAGING RESEARCH CORE (CIRC)

Ritu Sachdeva, MD

The CIRC provides non-invasive cardiovascular imaging support for investigators involved in clinical research involving infants, children and adolescents. The CIRC has dedicated space, equipment and experienced staff to provide high quality cardiovascular imaging services as well as post-processing of previously acquired images using specialized software. These services include performance of a routine complete or limited congenital or non-congenital two-dimensional echocardiography, color and spectral Doppler imaging; advanced echocardiographic imaging including three-dimensional echocardiography, tissue Doppler imaging, strain and strain rate imaging; stress echocardiography and cardiac magnetic resonance imaging. CIRC has also launched a program for assessment of vascular health in pediatric patients that includes non-invasive assessment of endothelial function using brachial artery flow-mediated dilation, measurement of arterial stiffness using applanation tonometry and assessment of structural arterial changes using carotid imaging. Please visit www.pedsresearch.org for more information.

Posters 116 and 117 utilized the CIRC.

116: Effect of Exercise on Bifurcated Y-graft Fontan Total Cavopulmonary Connection

Jaci K. Carithers; Maria Restrepo, BS; Chris Haggerty, PhD; Elaine Tang, B.Eng; Timothy Slesnick, MD; Kirk R. Kanter, MD; Ajit P. Yoganathan, PhD

Background: The Fontan total cavopulmonary connection (TCPC) procedure is used to palliate single ventricle congenital heart defects, and while it has improved patient outcome, there are long-term morbidities such as pulmonary arteriovenous malformations (PAVM) formation and decreased exercise capacity. The bifurcated Y-graft is a novel modification to the TCPC, where the inferior systemic venous return is split between the left pulmonary artery and the right pulmonary artery. One of the main advantages is that even distribution of the flow is thought to avoid the development of PAVM. Preliminary analysis on these patients demonstrates encouraging results, but it is necessary to evaluate the performance of these grafts under exercise conditions. This study aims

to evaluate the hemodynamic performance of patient-specific Y-grafts under resting and exercise conditions using computational fluid dynamics (CFD) to further support the effectiveness of the Y-graft in comparison to the original TCPC. Materials and Methods: Patient-specific anatomies and flows were reconstructed from cardiac magnetic resonance (CMR) images. CFD modeling was performed for each patient case using three inferior vena cava (IVC) flow conditions: resting (original IVC flow), moderate exercise (2X IVC flow) and rigorous exercise (3X). The connection's hemodynamic performance was assessed by: i) evaluating the energetic performance (in the form of power loss) and ii) computing the IVC flow split (hepatic flow distribution [HFD]) to both lungs. Results and Discussion: 30 patients have received a Y-graft Fontan connection at Children's Healthcare of Atlanta. Currently the hemodynamic results evaluated for n=7 cases have shown that exercise hemodynamic results (in the form of power loss) in the Y-graft are improving with respect to the traditional TCPC: the average increase in power loss for moderate and rigorous exercise in the Y-graft was 2.8 times and 6.2 times resting, respectively, whereas the average increase in power loss for moderate and rigorous exercise in the TCPC was 10.5 times and 38.9 times resting, respectively (Whitehead, 2007). Initial HFD results show that each case has maintained relative symmetry of flow during moderate and rigorous exercise simulations. These preliminary results show that the Y-graft has comparable performance to the existing Fontan procedure, but may be an improvement due to the robustness of the HFD under exercise.

117: Four-Dimensional Phase Contrast Imaging In Congenital Heart Disease

Sassan Hashemi, MD; Denver Sallee, MD; W. James Parks, MD; Timothy Slesnick, MD

Background Cardiac magnetic resonance imaging (CMR) has evolved over the last thirty years, and a central component is use of phase contrast (PC) imaging to quantify blood flow magnitude, direction, and velocity. Initial work was limited to two-dimensional PC imaging. Technological advances now allow four-dimensional (4D) quantification, with simultaneous measurement of velocity vectors in all three directions throughout the cardiac cycle. We sought to describe our early experience with this technology. Methods For each data set, the imaging parameters and data quality were compared. 4D PC data was analyzed to demonstrate the complex flow. Angle of eccentricity of aortic outflow was compared to the degree of ascending aortic dilation. For patients who have undergone a Fontan procedure, analysis of superior versus inferior systemic venous flow contributions to branch pulmonary artery blood supply was calculated. Results Since August 2013, 15 patients have undergone 4D PC CMR imaging at Children's Healthcare of Atlanta. In regard to aortic valve and ascending aorta, 5 patients had a bicuspid aortic valve (BAV), five had complicated anatomy or prior interventions and were not included in the analysis. Five patients had a tricuspid aortic valve (TAV) with normal ascending aorta. At the sinotubular ridge, the angle of eccentricity was significantly larger in the BAV group (n=5, mean=24.1º ± 2.7) compared to the TAV group (n=5, mean=8.7º ± 5) ($p<0.0003$). Linear regression analysis revealed a strong correlation between angle of eccentricity at the level of sinotubular junction and ascending aorta Z-score ($r=0.81$, $p=0.004$). Contrarily, the degree of ascending aorta dilation could not be predicted based on peak aortic flow velocity ($r=0.32$, $p=0.37$). We performed 4D PC imaging on 2 patients with Fontan palliation. Particle tracing analysis showed asymmetric IVC flow to the branch pulmonary arteries in one of the patients. Conclusion 4D flow analysis enabled delineation and quantification of flow eccentricity and its correlation with progressive ascending aortic dilation in BAV patients, a feature which conventional 2D PC imaging cannot demonstrate. It also revealed asymmetry of branch pulmonary blood supply in a patient with Fontan palliation through particle tracing. Future works with larger patient cohorts are needed to fully utilize the potential of 4D PC CMR.

118: THE PEDIATRIC ANIMAL PHYSIOLOGY CORE

Mary Wagner, PhD

The Animal Physiology Core provides pediatric researchers with services and equipment to develop and characterize animal models relevant to investigating pediatric diseases. We provide acute and survival surgery for rats and mice, as well as USDA regulated animals such as rabbits, guinea pigs and piglets. Options include providing the investigator with the surgical equipment for their own use or our trained surgical staff can perform the surgical procedures. We also offer high resolution small animal ultrasound examinations towards characterizing cardiac function and liver and kidney blood flow. Studies using the new Visualsonics Vevo 2100 High Frequency Ultrasound system can either be conducted for you by our trained staff or investigators can reserve the equipment and utilize their own laboratory personnel. Core staff currently are trained to do ultrasound examinations for cardiac function, liver and kidney blood flow. We will work with investigators to optimize their experiments. Please visit www.pedsresearch.org for more information.

Posters 119 to 121 utilized The Pediatric Animal Physiology Core.

119: Dysfunctional Calcium Handling in a Juvenile Rat Model of Right Heart Failure

Olivia Minkhorst, BS; Bo Wang, BS; Brian H. Crawford, PhD; Ming Shen, BS; Gitanjali Baroi, BS; Rong Jiang, MD, PhD; Mary B. Wagner, PhD

Little is known about how the immature heart responds to abnormal hemodynamic load. The number of young patients with right ventricular (RV) dysfunction is increasing due to improvements in cardiac surgery. We investigated the time course of RV dysfunction in a young rat model of RV pressure overload caused by pulmonary artery banding (PAB) and determined abnormal calcium handling underlies this dysfunction. Methods: PAB was performed in young (5-6 weeks) rats by the Animal Physiology Core and rats were followed weekly by echocardiography (Visualsonics 2100). After 8 weeks, hearts were excised and mounted on a Langendorff perfusion system for measurement of RV pressure or used for isolated cell studies. Cell shortening and calcium (IonOptix) were measured in single cells. Calcium leak from the sarcoplasmic reticulum (SR) was measured by tetracaine. Results: Evidence of RV dysfunction was noted as early as 2 weeks post banding by echocardiographic measures of RV wall thickness and tricuspid annular plane systolic excursion (TAPSE). At 8 weeks post banding, TAPSE was significantly smaller in the PAB group indicating RV dysfunction (3.16±0.10, n=8 vs. 2.06±0.25, n=8, $p<0.05$). Contractile reserve of RV function measured in isolated hearts was decreased in PAB group. Developed pressure increased with increasing doses of dobutamine in sham hearts (36.4±5.8 mmHg, control vs. 48.7±3.6 mmHg, 1 uM dobutamine, n=5, $p<0.05$) but did not change in PAB hearts (39.3±4.4 mmHg, control vs. 42.9±4.3 mmHg, 1 uM dobutamine, n=5, p=ns). In isolated RV myocytes, amplitude of sarcomere shortening was similar between PAB and sham rats whereas calcium transient amplitude was significantly greater in PAB compared to sham cells (2075±195 a.u. fluorescence, n=12 vs.1235±283 a.u. n=28, $p<0.05$) which suggests decreased sensitivity to calcium in PAB. We also found increased calcium leak from the SR in PAB cells compared to sham (0.18±0.02 a.u. fluorescence, n=12 vs.0.12±0.03 a.u. n=28, $p<0.05$). Levels of calcium handling proteins SERCA and PLB were decreased which may contribute to this dysfunction. Conclusions: Pulmonary banding in juvenile rat results in RV dysfunction early following banding. Decreased contractile reserve is likely due to abnormal calcium handling, including decreased calcium sensitivity and leaky calcium stores. Understanding how the young heart responds to pressure overload may suggest new therapies for children with pediatric heart disease.

120: Early Cardiac Dysfunction in Mice with Chronic Kidney Disease (CKD) is Detectable with Ventricular Strain Analysis

Pamela D. Winterberg, MD; Rong Jiang, MD, PhD; Sonal Harbaran; Mary B. Wagner, PhD

Background: Cardiovascular disease is the leading cause of mortality for children with chronic kidney disease (CKD). Mouse models of CKD have previously reported rates of left ventricular hypertrophy (LVH) but little is known about cardiac function in this model. Conventional echocardiography measures lack the sensitivity to detect subtle alterations in cardiac function during CKD. Speckle-tracking based strain analysis has recently been described as a highly sensitive, non-invasive measure of cardiac function in mouse models of cardiovascular disease. We aimed to determine whether ventricular strain analysis could detect changes in cardiac function in a mouse model of CKD. Methods: CKD was induced in male 129X1/SvJ mice through five-sixths nephrectomy (5/6Nx) in a two-stage surgery. Age-matched mice that underwent unilateral partial nephrectomy resulting in overall two-sixths renal mass reduction (2/6Nx) or no surgeries (NS) served as controls. Renal function was assessed by measuring blood urea nitrogen (BUN), plasma cystatin c (CysC), and urinary albumin to creatinine ratio (ACR). Cardiac function was assessed via transthoracic echocardiography under 1% isoflurane anesthesia using a digital ultrasound console (Vevo2100, VisualSonics, Toronto, Canada) at 8 weeks post-surgery. Anesthesia was titrated to maintain heart rate >400 bpm during image recording. Speckle-tracking based strain analysis was performed offline using parasternal long-axis B-Mode images. Results: Mice undergoing 5/6Nx had significantly higher BUN and CysC than the 2/6Nx and NS age-matched controls. CKD mice displayed concentric LVH with significantly increased thickness of the anterior and posterior left ventricular walls. Traditional measures of cardiac function including ejection fraction and fractional shortening were not significantly different among the groups. However, longitudinal left ventricular strain was significantly altered in the CKD mice (19.0%, s.d. 4.08) compared to 2/6Nx (27.4%, s.d. 4.90) and NC (30.0%, s.d. 2.28) mice (One-way ANOVA, $p<0.0001$). Conclusions: Speckle-tracking based strain analysis is more sensitive than the traditional measures of ejection fraction and fractional shortening in detecting early cardiac dysfunction in a mouse model of CKD.

121: Mice With Chronic Kidney Disease Display Premature Immune Senescence

Pamela D. Winterberg, MD; Sonal Harbaran; Allan D. Kirk, MD, PhD

Background: Accumulation of effector memory T cells and T cell senescence have been described in elderly humans and animals. These changes have been implicated in many age-associated disease processes. Our group recently reported that children with chronic kidney disease (CKD) also show signs of premature immune senescence. Mice are typically studied without long-standing CKD. We aimed to determine whether CKD alters the T cell repertoire in mice, and thus could be a variable worthy of consideration in murine models of transplant biology. Methods: CKD was induced in 129X1/SvJ mice through five-sixths nephrectomy (5/6Nx) in a two-stage surgery. Age-matched mice that underwent unilateral partial nephrectomy resulting in overall two-sixths renal mass reduction (2/6Nx) or no surgeries (NS) served as controls. Renal function was assessed by measuring blood urea nitrogen (BUN), plasma cystatin c (CysC), and urinary albumin to creatinine ratio (ACR). T-cell memory subtypes were assessed via multicolor flow cytometry of blood and spleen 8 weeks following CKD induction. Activation markers CD25, CD69, and CD27 and senescence markers PD1 and KLRG1 were assessed. T cell memory subsets were determined by expression of CD44, CD62L, and CCR7. Results: Mice undergoing 5/6Nx had significantly higher BUN, CysC and urinary ACR than the 2/6Nx and NS age-matched controls. Total peripheral white blood cell count was not significantly different among the groups, but the 5/6Nx mice had significantly lower percentage of lymphocytes and absolute number of CD3+ T cells compared to both control groups. The frequency of peripheral blood CD4+ and CD8+ T cells as well as the CD4+:CD8+ ratio did not vary significantly among the groups. Mice with CKD had significantly higher frequency of both CD4+ and CD8+ splenic T cells expressing PD1 and KLRG1. The PD1- and KLRG1-positive cells were primarily CD62L-CCR7-CD44high effector memory T cells. Conclusions: Mice with CKD display signs of premature immune senescence with lymphopenia, reduced number of peripheral T cells, and increased expression of the senescence-associated markers PD-1 and KLRG1 on splenic T cells. These data suggest that CKD can promote significant alterations in the immune repertoire independent of age or environmental antigen exposure. The impact of these alterations on alloimmunity is under investigation.

122: THE PEDIATRIC IMMUNOLOGY CORE

Larry Anderson, MD and Karnail Singh, PhD

The goal of the Immunology Core is to provide the instrumentation and expertise to allow investigators to apply immunological-based assays to their research. Available applications include enzyme-linked immunosorbent spot (ELISPOT) assays; Luminex multiplex bead arrays; enzyme-linked immunosorbent assays (ELISA); intracellular straining by flow cytometry including consultation, design, and performance of the assay; real-time PCR, including primer design; and isolation of peripheral blood mononuclear cells (PBMCs) and/or other specimen processing for clinical trials. Please visit www.pedsresearch.org for more information.

Posters 123 to 125 utilized The Pediatric Immunology Core.

123: Human Rhinovirus Species-Associated Cytokine/Chemokine Response to Infection of Airway Epithelial Cells and Exposed to Peripheral Blood Mononuclear Cells

Devi Rajan, PhD; Courtney E. McCracken, PhD; Hannah B. Kopleman; Dean D. Erdman, PhD; Larry J. Anderson, MD

Human rhinoviruses (HRV) cause over 300 million episodes of the common cold each year. Infections with HRV are commonly associated with exacerbations of asthma (~50% of exacerbations) and are likely to be major contributors to these exacerbations. The important role that HRVs play in asthma exacerbations suggests they can be used to explore the pathogenesis of these exacerbations and recognize host-specific or virus-specific factors that contribute to disease. In previous studies, using a two-chamber trans-well tissue culture in vitro system, we noted differences in immune responses between HRV 14, a species B virus, and HRV 16, a species A virus. Species A HRVs are more often associated with serious HRV disease. To look for species differences in responses that might explain differences in manifestations of disease, we evaluated 3 other species A viruses, HRV 25, 31 and 36 and 3 other species B viruses, HRV 4, 35 and 48 by exposing human PBMCs to Calu-3 cells infected with these viruses in our in vitro model. HRVs from both species increased levels of (significant increase compared to mock-infected cells) of IL-15, IP-10, IFN-α, HGF, IL-28A, ENA-78, and MCP-1. Species B viruses induced higher levels of MIP-1α and MIP-1β in PBMCs than species A viruses and ENA-78 levels were significantly increased in

species B infected cells without addition of PBMCs. Thus, our results indicate that cells infected with different strains of HRV and exposed to PBMCs induce various levels of host inflammatory and immune response and some of these differences may be linked to the HRV species and explain species differences in disease with infection.

124: Prophylaxis with a Respiratory Syncytial Virus (RSV) Anti-G Protein Monoclonal Antibody Effect on Adaptive Immune Response to RSV rA2-line19F Infection in BALB/c Mice

Seyhan Boyoglu-Barnuma; Tatiana Chirkova, PhD; Sean O. Todd; Thomas R. Barnum; Kelsey A. Gaston; Patricia Jorquera; Lia M. Haynes.; Ralph A. Tripp; Martin L. Moore, PhD; Larry J. Anderson, MD

Respiratory syncytial virus (RSV) is the single most important cause of serious lower respiratory tract infections in young children, yet no highly effective treatment or vaccine is available. In the present study, we investigated the effect of prophylactic treatment with the intact and F(ab')2 forms of an anti-G protein monoclonal antibody (mAb), 131-2G, on the humoral and cellular adaptive immune response to RSV rA2-line19F challenge in BALB/c mice. The F(ab')2 form of 131-2G does not decrease virus replication but intact 131-2G does. Prophylaxis with either form of 131-2G induced higher IFN-γ and lower IL-4 expression in T cells and higher neutralizing and IgG2a antibodies and lower IgG2b and IgG1 antibody titers compared to untreated, rA2-line19F infected mice. This effect was most evident on or after day 75 p.i. These data suggest that the RSV G protein has substantial impact on the both humoral and cellular adaptive immune response.

125: Critical Role of Airway Epithelial CX3CR1 in RSV Infection

Tatiana Chirkova, PhD; Songbai Lin, PhD; Kelsey Gaston; Seyhan Boyoglu-Barnum, PhD; Tom Oomens, PhD; Assem Ziady, PhD; Larry J. Anderson, MD, PhD

Respiratory syncytial virus (RSV) is a major cause of severe pneumonia and bronchiolitis in infants and young children and short- and long-term morbidity in subjects with compromising medical conditions. One of the RSV surface glycoproteins involved in binding to the cell surface, the G protein, contains a conserved CX3C chemokine motif, and binding of G to CX3CR1 has been hypothesized to facilitate RSV infection. To evaluate the role of CX3CR1 in RSV pathogenesis in human airway epithelium, we studied RSV infection in primary human airway epithelial cells (HAEC) which were obtained from lung tissue explants from patients with or without cystic fibrosis, and had different levels of CX3CR1 expression. We show that in lung tissue derived HAEC only ciliated cells expressed CX3CR1 on their apical surface. Cultures that had higher surface expression of CX3CR1 were more susceptible to RSV infection. Blocking CX3CR1 with antibody or using RSV with mutated CX3C motif significantly decreased RSV infection. HAEC derived from cystic fibrosis patient produced distinctive cytokine/chemokine pattern in response to RSV infection, including IL-1RA, IL-6, IL-8, IL-15, IP-10, MCP-1, RANTES and fractalkine. Analysis of cytokine production kinetics showed that RSV CX3C-CX3CR1 interaction promoted pro-inflammatory responses of cystic fibrosis AEC (RANTES, IL-6, IL-8, fraktalkine) while down-regulated production of IL-15, IL1-RA and MCP-1. These findings suggest that expression of CX3CR1 on the apical surface of human primary HAEC facilitates RSV replication and virus G protein CX3C-CX3CR1 interaction is important for the pathogenesis of RSV infection in airway epithelium.

126: THE PEDIATRIC FLOW CYTOMETRY CORE

David Archer, PhD

The mission of the Flow Cytometry Core located on the main Emory campus is to provide instrumentation and technical expertise to support pediatric research using flow cytometric and other cell analysis and separation technologies. Some flow cytometric applications that can be analyzed in the flow cytometry facility include immunophenotyping, cell cycle, ploidy, mitochondrial potential, apoptosis, PhosFlow, live/dead, stem cell analysis, cell proliferation, and oxidative burst. Please visit www.pedsresearch.org for more information.

Posters 127 to 133 utilized The Pediatric Flow Cytometry Core. *Posters 109, 110, 113, 124, 125, and 137 also used this core.*

127: A Novel In-Vitro Sickling Assay Combined with Imaging Flow Cytometry Allows Dynamic Measurement of pO2, RBC Sickling and Automatic Quantification of the Percentage of Sickled Cells

Chengjing Zhou; Prasanthi Chappa; Fang Tan; David Archer, PhD

Introduction: Polymerization of deoxygenated hemoglobin and the subsequent formation of sickled red blood cell morphology is central to the pathophysiology of sickle cell disease. Current in-vitro sickling assays are usually performed under static conditions where cells are completely deoxygenated. While the maximum percentage sickled cells can be observed, the current methods do not effectively monitor the dynamic process of RBC sickling during deoxygenation. Methods and Results: Peripheral blood from control (expressing normal human hemoglobin; AA) and homozygous sickle mice (expressing human beta-sickle globin; SS) were used in this study. The sickling assay was performed in a HemOx instrument with modifications to allow for the sampling of a small aliquot of the suspension. While generating the O2 equilibrium curve, consecutive aliquots of 50 µl of sample were collected at known pO2 values. The samples were immediately transferred into deoxygenated 2% glutaradehyde/PBS. Cells were fixed at RT for 30 min to 1 hr, washed and analyzed with imaging flow cytometry. Our results showed that sampling of small aliquots does not change the O2 equilibrium curve. To automate the quantification of percent sickling, we generated an algorithm on the ImageStreamX Mark II using cytometric and morphometric parameters. The combination of Circularity, Shape ratio and area provided the optimal discriminators for sickled and un-sickled cells. The results show that the sickling vs. pO2 curve generated with this algorithm was highly consistent with the curve generated by manual counting under microscopy. Conclusion: We have developed a novel in-vitro method of sickling assay that allows assessment of dynamic process of RBC sickling and automated quantification of the percentage of sickled cells. We expect that utilization of this assay will help better understand the process of RBC sickling and rapidly quantify the high volume of samples.

128: The Role of Purinergic Receptors in HIV-1 Entry and Fusion

Mariana Marin; Yuhong Du; Emily Kim; Haian Fu; Gregory Melikian, PhD

Recently, in collaboration with the Emory Chemical Biology Discovery Center (ECBDC) we have conducted a pilot screen for HIV-1 fusion inhibitors and found that purinergic receptor antagonists strongly diminish the virus fusion. Interestingly, the purinergic receptors (P2XR) have previously been implicated in productive HIV-1 entry into macrophages. We demonstrate here that these receptors are necessary for HIV-1 fusion with target cells. Inhibition of purinergic receptors resulted in a dose-dependent reduction of HIV-1 fusion, independent of the coreceptor tropism. Inhibition was specific for HIV-1 since the entry of an unrelated virus, VSV, was not affected by the tested P2XR inhibitors. We also observed that P2X1 but not P2X7 receptors are necessary for HIV-1 entry. Our working hypothesis is that, through coreceptor-mediated signaling, HIV-1 induces ATP release from target cells, which in turn opens the P2XR channels, elevates the cytosolic calcium, and redistributes phosphatidylserine (PS) from the inner to outer leaflet of the plasma membrane. We hypothesize that PS acts as a cofactor for HIV-1 entry that facilitates the virus uptake and/or fusion steps. Experiments presented here test key aspects of this hypothesis. Our results are consistent with the idea that cells secrete ATP in response to the HIV-1 binding and that ATP opens purinergic calcium channels and thereby promote externalization of PS. Further validation of the working hypothesis may reveal a novel role for cellular signaling and PS in supporting the HIV-1 fusion with target cells and suggest new strategies to fight infection.

129: The YW Motif in HIV-1 gp41 Cytoplasmic Tail is Required for Transportation Through FIP1C Pathway and Efficient Env Incorporation in A Cell Type Dependent Manner

Mingli Qi, PhD; Xuemin Chen, MD; Junghwa Choi, Xiaoyun Wen, PhD; Jason Hammonds, PhD; Lingmei Ding; Paul Spearman, MD

Incorporation of Envelope glycoprotein occurs at late stage of HIV-1 life cycle during viral assembly and budding, which is essential for the virus to be fully infectious. However, the detailed cellular pathway and factors utilized in this process are largely unknown. We demonstrated recently that cellular proteins, Rab11a-FIP1C and Rab14 are required for the Env cytoplasmic tail (CT) dependent traffic and incorporation onto HIV-1 particles. In current study, we further explored the potential interaction between Rab11a –FIP1C and HIV-1 Env by mapping a serial of Env gp41 CT mutants and found that the YW motif at position 795 is required for HIV-1 Env incorporation and Rab11a-FIP1C mediated traffic in viral producing cells. More interestingly, YW mutant exhibits a cell type dependent manner for Env incorporation: in permissive cells like 293T, YW mutant incorporates same level of gp120 and gp41 as wild type virus; in semi-permissive cells, such as HeLa and MT-4, YW mutant incorporates 3-4 times lower level

of Env as wild type virus; while in non-permissive cells like T cells and macrophage, Env incorporation of YW mutant severely impaired and reduced more than 10 fold comparing to wild type Env. Strikingly, the YW Env incorporation shows no sensitivity to FIP1C depletion in producing cells while the wild type Env does, and the reverting mutant from H9 T cell culture for YW mutant regains sensitivity to FIP1C depletion. Collectively, we hypothesize that FIP1C mediated specific Env sorting and trafficking determines the cell type dependent Env incorporation.

130: Combined In Vivo and In Vitro Analyses Identify the Caspase-1 / Interleukin-1β / TRPM2 Axis as a Significant Contributor to Neutrophilic Airway Inflammation in Cystic Fibrosis

Osric Forrest, BSc; Sarah Ingersoll, PhD; Marcela Preininger, BSc; Julie Laval, PhD; Milton Brown, PhD; Rabindra Tirouvanziam, PhD

Background: Severe inflammation with polymorphonuclear neutrophils (PMNs) is a dominant feature of cystic fibrosis (CF) airway disease. Caspase-1 is a key enzyme of the inflammasome pathway in epithelial cells and leukocytes, leading to generation of the pro-inflammatory mediator interleukin-1β (IL- 1β) secretion. Here, we hypothesized that PMNs activate the inflammasome pathway upon recruitment to CF airways, thus creating a pro-inflammatory loop. Methods: We tested this hypothesis by: (i) direct analysis of in vivo airway fluid and plasma samples as well as airway and blood PMNs isolated from patients; (ii) in vitro conditioning of blood PMNs in a novel model developed in our group, in which PMNs are made to migrate through an air-interface small airway epithelial culture into CF airway fluid added apically, which recapitulates key steps in the CF inflammatory process. Results: Comparative analysis of CF plasma and airway fluid revealed highly increased IL-1β levels in the latter. Consistently, CF airway PMNs showed highly increased caspase-1 activity compared to CF blood PMNs, which held true during both steady-state and acute pulmonary exacerbations. PMNs recruited into CF airway fluid in our in vitro model showed similar upregulation of caspase-1 activity to that observed in vivo. The pro-inflammatory calcium channel TRPM2 has been recently linked to caspase-1 activation, and conventional triggers of TRMP2 activity, oxidants and nucleotides, are highly enriched in CF airway fluid. Here, we show that increased surface TRPM2 expression correlates with the induction of caspase-1 activation in CF airway PMNs in vivo. This correlation is striking in our model, where transmigrated PMNs concomitantly upregulate TRPM2 levels and caspase-1 activity over time. Conclusions: Our data suggest that TRPM2 expression and caspase 1 activity are intimately linked during the pathological activation of CF airway PMNs and that targeting TRPM2 and / or the inflammasome pathway may be effective therapeutic methods to counter the chronic inflammatory process in CF.

131: Exocytosis of Toxic Primary Granules by Human Neutrophils is Associated with High Surface TRPM2 Expression and Pinocytosis

Sarah A. Ingersoll, PhD; Osric Forrest, BS; James Bowen, BS; Milton Brown, PhD; and Rabindra Tirouvanziam, PhD

Polymorphonuclear neutrophils (PMNs) play a key role in host defense against microbial infection. PMN responses culminate in the mobilization of highly toxic intracellular primary granules directed toward the phagosome (during phagocytosis), nucleus (during NETosis), or plasma membrane (exocytosis). Mechanisms regulating the fate of PMN primary granules remain unclear. Here, we studied the dynamics of PMN primary granule exocytosis in two relevant sets of conditions: 1- in vivo migration of blood PMNs into chronically infected airways of patients with cystic fibrosis; 2- in vitro treatment of blood PMNs with latrunculin B and fMLF. Using flow and image cytometry, we show a striking resemblance between these two sets of conditions, with a close association between primary granule exocytosis (based on surface CD63 expression) and increased surface expression of the inflammatory calcium channel TRPM2. In addition, high primary granule exocytosis associates with major membrane rearrangements, as evidenced by the loss of surface phagocytic receptors (e.g., CD16 and CD35) and high pinocytosis (based on Lucifer Yellow uptake), a process previously linked to TRPM2 activation. All the while, exocytosing PMNs maintain their nuclear integrity. Thus, high primary granule exocytosis, surface TRPM2 upregulation and high pinocytosis are a concerted set of events indicative of a functional program in activated PMNs that is distinct from phagocytosis and NETosis.

132: Stiffness and Size Dependent Separation of Cells in a Microfluidic Device

Todd Sulchek, PhD; Gonghao Wang; Wilbur Lam, MD, PhD; Alexander Alexeev, PhD

Abnormal cell mechanical stiffness can point to the development of various diseases including pediatric cancers and infections. We report a new high-throughput technique for continuous cell separation utilizing variation in cell stiffness and variations in cell size. We use a microfluidic channel that is decorated by periodic diagonal ridges to force cells of different stiffness values to follow different trajectories. The ridges within the microfluidic flow channel compress and deform the cells in rapid succession to translate each cell perpendicular to the channel axis in proportion to its stiffness. We report the experimental demonstration of separation as well as computational validation of the mechanism of separation. Atomic force microscopy (AFM) was used to independently measure cell stiffness. By flowing cells through the microfluidic device, we can quickly and efficiently separate mixtures into subpopulations of stiff cells and soft cells. We then summarize how we expect this technology may produce new biomedical diagnostic capabilities.

133: ROCK1 and LIM Kinase Modulate Retrovirus Particle Release and Cell-Cell Transmission

Xiaoyun Wen, MD, PhD; Lingmei Ding, MS; Jaang-Jiun Wang, PhD; Mingli Qi, PhD; Jason Hammonds, PhD; Hin Chu, PhD; Xuemin Chen, MD; Eric Hunter, PhD; Paul Spearman, MD

The assembly and release of retroviruses from the host cells requires dynamic interactions between viral structural proteins and a variety of cellular factors. It has been long speculated that the actin cytoskeleton is involved in retrovirus production, and actin and actin-related proteins are highly represented in HIV-1 virions. However, the specific role of actin in retrovirus assembly and release remains unknown. Here we identified LIM Kinase-1 (LIMK1) as a cellular factor regulating HIV-1 and Mason-Pfizer monkey virus (M-PMV) particle release. Depletion of LIMK1 reduced not only particle output but also virus cell-to-cell transmission, and was rescued by replenishment of LIMK1. Depletion of the upstream LIMK1 regulator ROCK1 inhibited particle release, as did a competitive peptide inhibitor of LIMK1 activity that prevented cofilin phosphorylation. Disruption of either ROCK1 or LIMK1 led to enhanced particle accumulation on the plasma membrane as revealed by total internal reflection fluorescence microscopy. Electron microscopy demonstrated a block to particle release, with clusters of fully mature particles on the surface of the cells. Our studies support a model in which ROCK1 and LIMK1-regulated phosphorylation of cofilin and subsequent local modulation of dynamic actin turnover plays a role in retrovirus release from host cells and in cell-to-cell transmission events.

134: INTEGRATED CELLULAR IMAGING CORE (ICI)

Neil Anthony, PhD and Adam Marcus, PhD

The new ICI core provides access to cutting-edge cellular imaging technologies and technical expertise to support pediatric research. ICI is a partnership facilitated by the Emory School of Medicine and includes the Emory+Children's Pediatric Research Center Cellular Imaging Core along with other cellular imaging sites on campus including Winship Cancer Institute, Emory NINDS Neuroscience Core Facilities (ENNCF), and the Department of Physiology. The scientific direction of the ICI effort is being led by Adam Marcus, PhD, and Alexa Mattheyses, PhD. Their efforts will help ensure all cellular microscopy efforts at Emory generate maximum quality data with the highest scientific impact possible. They will be leading educational events and seminars to facilitate scientific exchanges. Please visit www.pedsresearch.org for more information.

Posters 135 to 137 utilized ICI.

135: Transcriptional Regulation at IGF2 Promoters and Mechanistic Insights on Induction of IGF2 Downstream of YAP in Shh Medulloblastomas

Abhinav Dey, PhD; Mélanie Robitaille, PhD; Marc Remke, MD; Damien Faury, PhD; Caroline Maier, BS; Anshu Malhotra, PhD; Nada Jabado, MD, PhD; Michael Taylor, MD, PhD; Stéphane Angers, PhD; Anna Kenney, PhD

In mouse models for Shh-medulloblastomas, IGF2 is required for tumor formation, growth, and metastases. We showed that YAP over-expression induces IGF2 expression as a part of YAP's radiation-resistance program in mouse Shh-medulloblastomas and in cerebellar granule neuron precursors (CGNPs), proposed cells-of-origin for

the Shh subclass of medulloblastoma. IGF2 and its regulatory program may represent a therapeutic target in medulloblastoma, but the mechanism of IGF2 induction downstream of YAP is not well understood. The anomalous loss of IGF2 imprinting in the human fetal brain is intriguing and exemplifies the complexity of the IGF2 gene's regulation. Although CTCF mediates allele-specific expression at the IGF2/H19-imprinted locus in both mice and humans, subsequent evidence suggests that CTCF binding at the IGF2/H19 imprinting control region is insufficient to regulate IGF2/H19 expression in human tissues. This makes a compelling case in favor of studying the transcriptional regulation at the different IGF2 promoters in order to delineate the mechanism of IGF2 induction downstream of YAP. We have employed biotinylated-DNA 'fishing' combined with proteomics to delineate the transcriptosomes at the IGF2 promoters in medulloblastoma cells, and directly validated them using medulloblastoma cell-derived material. The results of transcriptosome analyses revealed factors, Yb1 and Myef2, associated with IGF2 promoter Pr3 in PZP53 cells (derived from a Ptc+/-/p53-/-mouse medulloblastoma) and SmoA1 tumor tissue. Myef2 was consistent in its association with IGF2 promoter Pr3 in mouse P5 cerebella, as in case of PZP53 cell line and SmoA1 tumor tissue. Of note, we observed increased levels of Myef2 and Yb1 in Shh-treated CGNPs. Our results indicate that association of Yb1 at IGF2 promoter Pr3 could be mediating the induction of IGF2 downstream of YAP and the radiation-induced expression of IGF2 could be linked to DNA repair mechanisms of Yb1.

136: Yes-Associated Protein: A Master Metabolic Regulator in Medulloblastoma

Anshu Malhotra, PhD; Abhinav Dey, PhD; Rachel Rotenberry, BS; Chad Potts, BS; SunPhil Choi, PhD; David A Ford, PhD; Zaher Nahle, PhD; Anna Marie Kenney, PhD

Downstream of mitogenic Sonic hedgehog signaling, Yes-Associated Protein (YAP) can drive proliferation in Cerebellar Granule Neural Progenitor cells, and its ectopic expression promotes highly aggressive Shh-driven medulloblastoma growth and radio-resistance (Fernandez et al., 2009). More recently we have found that YAP can regulate Fatty Acid Synthesis (FAS) enzymes in CGNPs, independent of Sonic Hedgehog (Shh). Deregulating the metabolic machinery for aberrant energy utilization is one of the hallmarks of a proliferating cancer cell. To gain further insight into lipid regulation in Shh medulloblastomas, we carried out lipid mass spectrometry, and we found that Shh mouse medulloblastomas feature high levels of cholesteryl ester accumulation. Cholesteryl ester synthesis from free cholesterol is catalyzed by the enzyme Sterol O-acyltransferase 1 (SOAT1). To determine whether YAP regulates SOAT and other metabolic enzymes, we performed a co-immunoprecipitaton of YAP followed by mass spectrometry and analysed the results with Ingenuity Pathway Analysis (IPA). We found that predicted direct and indirect targets of YAP comprised multiple metabolic pathways, including cholesteryl esterification and FAS, consistent with our experimental results. The present study has attempted to dissect the mechanism by which YAP regulates SOAT expression and activity and also confirm the IPA-predicted metabolic targets of YAP. The result of disrupting these pathways through YAP ablation and pharmacological means, on CGNP and medulloblastoma cell proliferation, is also presented. The study investigates YAP-regulated metabolic pathways as potential targets for novel medulloblastoma therapies that may reduce or eliminate the requirement for high dose radiation.

137: Cholesteryl Esters Metabolism in Sonic Hedgehog Mouse Medulloblastomas

Victor Maximov, PhD; Chad R. Potts; Sun-Phil Choi; Zaher Nahlé; Joachim Fuellekrug; David A. Ford, PhD; Anna M. Kenney, PhD

Medulloblastomas (MBs) are the most common solid malignant pediatric brain tumor. These tumors arise in the developing cerebellum as a result of aberrant activity of critical developmental pathways such as the WNT, Notch, and Sonic hedgehog (Shh) signaling pathways, and they can be divided into 4 subtypes with unique gene expression patterns, genomic abnormalities, and histological traits. The SHH subclass of MB can be modeled in mice by driving elevated Shh pathway activation in the neonatal cerebellum. Altered metabolic pathway regulation is characteristic of cancers. Indeed, we have previously demonstrated that exaggerated de novo lipid synthesis and accumulation of neutral lipids is a hallmark of highly proliferative, aggressive mouse Shh-driven medulloblastomas. To determine the intra-tumoral lipid composition, we carried out a mass spectrometry analysis, comparing Shh MB to adjacent non-tumor cerebellum. Here we show that Shh mouse MB feature high levels of cholesteryl esters (CE), the form in which free cholesterol is stored and transported outside of cells. CE accumulation is driven by the activity of Sterol O-acyltransferase 1 (SOAT1). SOAT protein levels are increased in these tumors, as are those of the fatty acid transporters CD36 and FATP4. Primary cerebral granular neuronal progenitor cell cultures induced by Shh have an increased level of SOAT protein, suggesting these cultures are a good model for investigation of lipid metabolism pathway downstream of activated Shh signaling. Inhibition of

SOAT causes death in mouse and human medulloblastoma cell lines derived from Shh tumors, suggesting that accumulation of intracellular free cholesterol is cytotoxic to the tumor cells. These findings reveal the possibility that modulating the activity of enzymes in the cholesteryl ester pathway could be of future therapeutic benefit.

138: THE PEDIATRIC BIOMARKERS CORE

Lou Ann Brown, PhD

The Biomarkers Core provides state of the art equipment and up-to-date technology to provide high quality analysis of biological samples in the fastest turnaround time possible to support pediatric research. This core provides equipment and technical expertise to assay samples using methods that combine the features of gas-liquid chromatography and mass spectrometry. The core has an Agilent gas chromatography/mass spectrometer and a Waters High Performance Liquid Chromatography with fluorescence detector. Please visit www.pedsresearch.org for more information.

Poster 139 utilized The Pediatric Biomarkers Core.

139: Placental Fatty Acid Ethyl Esters Identification of Maternal Alcohol Use during Pregnancies Complicated by Prematurity

Theresa W. Gauthier, MD; Sowmya S. Mohan, MD; Anne M. Fitzpatrick, PhD; Lou Ann Brown, PhD

Objectives: To 1) determine the prevalence of maternal alcohol use after premature delivery and 2) investigate whether placental fatty acid ethyl esters (FAEEs) could identify these pregnancies. We hypothesized that maternal alcohol use occurs in a significant proportion of premature deliveries, and placental FAEEs are elevated in alcohol-exposed pregnancies. Study Design: This prospective observational study evaluated 86 placentas from 80 women after premature delivery. Subjects were interviewed for alcohol intake using an extensive standardized questionnaire and placental FAEEs were quantified via GC/MS. Receiver Operator Curves (ROC) were generated to evaluate placental FAEEs' ability to predict maternal drinking during pregnancy. Results: During pregnancy, 31% of the subjects admitted to drinking alcohol. Multiple placental FAEEs were significantly elevated with alcohol exposure, including Palmitate, Stearate, Linoleate and Arachidonate. The combinations of Oleic + Linoleate + Linolenate (OLL), OLL + Stearate, and OLL + Stearate + Palmitate were significantly higher in the placenta with multiple patterns of maternal drinking. ROC analyses demonstrated that these FAEEs combinations significantly predicted premature pregnancies not exposed to maternal drinking with negative predictive values ranging from 74% to 98%. Placental OLL + Stearate had the highest area under the curve (82%), sensitivity of 86%, specificity of 66%, positive predictive value of 17% and negative predictive value of 95% for drinking in the 2nd trimester. Conclusions: Approximately one third of premature pregnancies were alcohol-exposed. Placental FAEEs were elevated with maternal alcohol use and demonstrated high negative predictive values. Placental FAEEs hold great promise to accurately identify the non-alcohol-exposed premature newborn.

140 &141: CENTER FOR SYSTEMS IMAGING AND BIOMEDICAL IMAGING TECHNOLOGY CENTER (CSI/BITC)

John Oshinski, PhD

CSI is a cross-disciplinary scientific, administrative, and educational home for imaging science at Emory University. The center is housed in 17,000 square foot newly-renovated facility on the 2nd floor of the Wesley Woods Health Center Building. The goals of the center are to: support the advancement of scientific research focused on the development of imaging biomarkers; provide core services for animal and human imaging studies; and build cross-cutting educational symposia and training programs. The mission of BITC is to conduct cutting-edge research in biomedical imaging, to provide support for researchers in and around the Emory community, and to provide training and dissemination of knowledge related to our expertise. With a Siemens Magnetom Trio TIM® 3T whole body MRI scanner dedicated for research and a high field Bruker BioSpec® 94/20 animal scanner, our research emphasizes biomedical magnetic resonance at high magnetic fields. Please visit http://corelabs.emory.edu/csi and http://bitc.bme.emory.edu for more information.

Poster 142 utilized CSI/BITC.

142: A Quantitative Analysis of Cerebrospinal Fluid (CSF) Flow in Pediatrics with Type I Chiari Malformation

Samir Sarda, BS; Joshua J. Chern, MD, PhD; Nilesh K. Desai, MD; John N. Oshinski, PhD

Background: In the pediatric population, selecting patients with Type I Chiari Malformation (CM-1) for decompression surgery remains a challenge. The primary criteria for diagnosing CM-1 include tonsillar herniation and, if not asymptomatic, presentation with suboccipital headaches, difficulty swallowing, and/or nausea, among others. The extent of tonsillar descent does not correspond to the severity of clinical symptoms or prognosis. Therefore, recommending surgery depends solely on qualitative measures such as whether the patient has hydrocephalus, syringomyelia or other co-morbidities. Objective: We sought to determine whether abnormal CSF flow is associated with the clinical symptoms of Chiari patients in order to establish an objective test for surgical patient selection. Methods: The study cohort consisted of 38 pediatric subjects who had been referred to a single neurosurgeon (J.C.1) between August 1st, 2012 and November 31st, 2013 for CM-1 due to tonsillar ectopia. Each subject underwent a clinical MRI that included a set of phase contrast magnetic resonance (PCMR) scans to quantify CSF flow. The PCMR studies included two axial slices at the level of C6 and the foramen magnum, and one mid-sagittal slice. CSF flow parameters such as phase difference, or the time delay between max cranial or caudal flow values in the anterior and posterior spinal segments, as well as peak cranial and caudal velocities, were determined. Subjects were divided into Chiari headache and syringomyelia subgroups for analysis. Results: 55% of subjects were diagnosed with Chiari headaches and 45% with syringomyelia. We found that the phase difference between max caudal flow values at the level of the foramen magnum is significantly larger in subjects without Chiari headaches. Additionally, the absence of a syrinx is associated with significantly higher cranial peak velocities. Conclusions: The results of this CSF study suggest a more simultaneous anterior-posterior caudal flow pattern in the Chiari headache population. Additional PCMR scans in pediatric controls will likely determine whether smaller phase differences in caudal flow contribute to Chiari headaches and whether lower cranial peak velocities in patients can serve as a marker for abnormal CSF flow patterns in children with syringomyelia and Chiari Malformation.

143: The Viral Restriction Factor IFITM3 Promotes Hemifusion But Blocks Full Fusion of Influenza Virus

Tanay M. Desai, PhD; Mariana Marin, PhD; Christopher R. Chin; George Savidis; Abraham L. Brass, MD, PhD; Gregory B. Melikyan, PhD

Interferon-induced transmembrane proteins (IFITMs) are up-regulated as part of a cell's defense against viral challenges. These small proteins inhibit entry of diverse viruses, such as influenza A (IAV), West Nile and dengue virus. The mechanism by which IFITMs block viral entry is not understood. Recent reports suggest that IFITMs inhibits viral hemifusion (merger of proximal leaflets of the viral and cellular membranes), presumably by disrupting cholesterol trafficking and causing aberrant cholesterol accumulation in late endosomes. Here we employed time-resolved single IAV imaging to identify fusion step(s) affected by IFITM3 ectopically expressed in human lung epithelial cells. These experiments revealed that, contrary to previous reports, lipid mixing between IAV and endosomes was, in fact, promoted upon IFITM3 expression. In contrast, virus-cell fusion assays monitoring the release of the viral content showed marked inhibition of fusion pore formation by IFITM3. This effect was not due to excessive cholesterol accumulation in endosomes or reduced endosomal acidity in IFITM3-expressing cells. Furthermore, conditions that induced the accumulation of cholesterol in late endosomes/lysosomes did not restrict IAV fusion. To conclude, IFITM3 blocks IAV fusion by disfavoring the formation of fusion pores, and this phenomenon is independent of cholesterol levels. We propose that IFITM3 can block viral fusion at a post-hemifusion stage either directly, by inserting into and stabilizing the cytosolic leaflet of endosomal membranes, or indirectly, by altering the lipid composition and thus disfavoring the formation of fusion pores. This work was partially supported by the NIH R01 GM054787 (to GBM) and 1R01AI091786 (to ALB) grants.

144: Evaluating the Classification Potential of Eye-Tracking Measures Based On Perception of Social and Physical Contingencies in Toddlers with ASD

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BACKGROUND: Two-year-olds with ASD show increased orientation to physical contingencies, in the form of audiovisual synchrony (AVS), relative to social contingencies, which are preferentially attended to by typically developing (TD) peers. Furthermore, ASD toddlers were as sensitive to AVS as their TD controls. However, when social contingencies were introduced, TD toddlers differed in their viewing pattern compared to ASD toddlers. The goal of this study is to understand how physical and social contingencies bias attention in ASD and TD toddlers and evaluate the potential of eye-tracking measures as biomarkers for discriminating between ASD and TD toddlers. METHODS: TD (N=22) and ASD (N=30) toddlers (Mean±S.D: 23.3±7.3 months) participated in a preferential looking paradigm, with audiovisual stimuli varied in social context to calibrate the biasing effect of social context and AVS on visual attention. To extend generalization to naturalistic settings, a second cohort of TD (N=23) and ASD (N=44) toddlers (23.5±6.1 months) were presented videos with a caregiver and a moving toy synchronized with the caregiver's speech. Eye-tracking measures of visual fixation were collected and used to derive classifiers which were evaluated using Receiver Operating Characteristics (ROC) with cross-validation. RESULTS: When infants were presented with split-screen stimuli with caregiver faces and circles synchronized to the caregiver's speech, percentage of total fixation time spent on faces was significantly higher (P<.001) for TD controls (79.8±21.2%) relative to ASD peers (56.2±30.3%). Using this measure to classify TD and ASD toddlers yielded an ROC with sensitivity 71%, specificity 72%, and AUC = 0.78. When presented with naturalistic stimuli, percentage of total fixation time spent on objects was significantly higher (P<.001) for ASD toddlers (34.1±23.9%) compared to TD peers (17.9 ±19.3%); this measure yielded an ROC with sensitivity 79%, specificity 79%, and AUC = 0.86. CONCLUSIONS: Visual scanning patterns of toddlers with ASD are biased by the presence of social and physical contingencies. In naturalistic settings, physical contingencies draws ASD toddlers' attention away from social context, suggesting a mechanism of derailment of normative developmental processes of learning. SPONSORS: National Institute of Mental Health (R01 MH83712), the Simons Foundation (94924), the Marcus Foundation, Georgia Research Alliance, and the Whitehead Foundation.

145: Kingella Kingae RTX Toxin Gene Detection in Osteoarticular Infections of Children

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Osteoarticular infections pose significant risk to health and mobility of young children and it is currently recognized as a significant problem in pediatric health. Diagnosis of the causative agent makes it possible to optimize treatment. Clinical microbiological culture has been traditionally used to detect pathogens with molecular diagnostic testing being increasingly used as an adjunct to cultural methods. Some pathogens are difficult to cultivate and prior antibiotic treatment may compromise the ability to culture and isolate the pathogens. We used Taqman probe based real time PCR assays to detect Kingella kingae which is difficult to culture in vitro. Using several available nucleotide sequences, we designed a primer pair and Taqman probe to detect RTX toxin A gene locus and additionally used previously published RTX toxin gene locus B based assay. We applied these RTX A and RTX B real time PCR assays to joint fluid specimens from 33 children with suspected septic arthritis. Three of 33 specimens were positive by Taqman real time PCR assays targeting both RTX A and RTX B gene loci and displayed similar levels of critical threshold cycle detection sensitivities. Kingella kingae being fastidious bacteria failed to be cultured from any of these three real time PCR positive specimens. Studies to further characterize the Kingella kingae genomic sequence are in progress. The medical records of these children are being reviewed for the clinical features, treatment and course of their infection. This report illustrates the value of adjunct molecular testing to identify pathogens in children with septic arthritis.

146: In Situ Kinetic Analysis of HIV Envelope Glycoprotein Interaction with Host Cells

Ke Bai, PhD; Mariana Marin, PhD; Gregory Melikian, PhD; Cheng Zhu, PhD

HIV is one of the most serious and deadly diseases in human history. T cells are the main targets of HIV in the blood, especially the helper T cells that express CD4. The first step of HIV infecting T cell is through the binding of the viral envelope glycoprotein (Env) gp120 subunit to its primary receptor CD4. This leads to the conformational change of gp120 to expose the binding site for its co-receptor CCR5 or CXCR4 on the T cell membrane, which eventually mediates fusion between the viral and cell membrane. Although the specific interaction between CD4

and co-receptors with gp120 has been broadly studied, the direct physical binding kinetics between them remain unclear. To fill this gap we measured the two-dimensional (2D), or in situ kinetics of the gp120–CD4 bimolecular and gp120–CD4–CXCR4 trimolecular interactions between HIV virus liked particles (VLPs) and CD4-expressing 3T3 cell line with or without co-expression of CXCR4. We used the micropipette adhesion frequency assay, which evaluate the kinetic on-and off-rates from the dependence of adhesion probability on contact duration, and the biomembrane force probe (BFP) force-clamp assay, which measure the force-dependent single bond lifetimes of these interactions. The trimolecular interaction has higher 2D affinity than the bimolecular interaction (24.8 vs. 15.1 10-4μm4). Both gp120–CD4 and gp120–CD4–CXCR4 exhibit catch bonds whose lifetime increases despite increasing force, with the gp120–CD4–CXCR4 trimolecular bond lasting longer at optimal force than gp120–CD4 bimolecular bond (1.5±0.23s at 6pN vs. 0.93±0.42s at 4.25pN). These data provide the first in situ kinetic measurements of HIV Env protein to its receptor and co-receptor on living cells.

147: 60 Seconds or Less: Interoperable Cell Phone Multimedia Messaging for Pediatric Health Promotion

Michael Bartenfeld, MA; Georgina Peacock, MD, MPH; Shoukat Qari, DVM, PhD; Mark Wooster, PhD; Cesar Bandera, PhD; Peter Schmitt, PhD; Jie Mai, MSBA

Promoting timely, accessible science-based messages to clinicians and public health practitioners is a challenging endeavor. The National Center on Birth Defects and Developmental Disabilities (NCBDDD) within the Centers for Disease Control and Prevention (CDC) has various methods for promoting key messages from emerging research or public health activities, and a partnership with Cell Podium, a New Jersey-based mobile multimedia technology developer, has leveraged innovative technology to reach end-users in a medium these individuals already use and will easily understand. With CDC support, including collaboration with the Office of Public Health Preparedness and Response, Cell Podium has developed a mobile multimedia messaging platform by which practitioners can create messaging campaigns; users can subscribe and receive short video messages with video clips, images, text, and audio conveying a key message—all in sixty seconds or less. NCBDDD worked with Cell Podium to pilot this technology by deploying a messaging campaign that ties timely public health research to clinical and public health practice for populations with special healthcare needs. The pilot video message urged care providers of children with special health care needs to ensure these children and their providers receive the seasonal flu vaccine. This pilot demonstrated the efficacy of the messaging platform to communicate a non-emergency health education message and the ability to reach individuals regardless of mobile carrier, phone type or internet connectivity, and exposed the principal challenge of this type of message distribution, which was campaign promotion and subsequent user subscription required by anti-spam legislation. This technology appears to have broad potential for public health organizations, professional medical associations or other groups looking to easily and effectively broadcast a visually-rich message to a targeted group of people.

148: Longitudinal Characterization of Gut Microbiota in Children with Inflammatory Bowel Disease

Madeline Bertha, BA; Tatyana Hofmekler, MD; Archana Kumar, BA; Jarod Prince, BS; Cary Sauer, MD; Subra Kugathasan, MD

The human microbiome is comprised of more than 100 trillion cells, or roughly 10 x the number of human cells. Over the past decade significant advances in technology have enabled an improved characterization of the vast array of organisms in the intestinal microbiome, yet an understanding of the effect of the microbiome on health and disease status is just beginning. Numerous cross-sectional studies have established that individuals diagnosed with inflammatory bowel disease (IBD) have intestinal microbiomes that are significantly altered from their healthy counterparts (decreased proportion of Firmicutes and Bacteroidetes and increased proportion of protetobacteria), suggesting that the microbiome of diseased individuals is intricately involved with the disease pathogenesis. However, little is known about how the intestinal microbiota changes over the course of the disease process. We propose a novel pilot study to explore the longitudinal relationship between the fecal microbial flora in patients with IBD and its relationship to intestinal inflammation by obtaining repeated stool samples over the course of one year. Since the commencement of our IRB-approved prospective study in June 2013, we have collected 96 stool samples from 22 children (17 Crohn's disease, 5 ulcerative colitis) with active IBD. We plan to characterize the fecal microbiota through 16S rRNA profiling and sequencing using the Illumina MiSeq platform. We will then analyze the fecal microbial profile of each sample and its relationship to fecal calprotectin (a measure of intestinal inflammation) by using enzyme-linked immunosorbent assay (ELISA). We will control for diet, maintenance therapy, prednisone use, antibiotic use, medications and disease phenotype. Preliminary results will be presented at the 2014 Pediatric Research Retreat. This is the first study to longitudinally explore the microbial changes in IBD patients over the course of their illness. The potential impact of this analysis is far-reaching, as it will not only

provide more awareness into the pathogenesis of IBD, but also support future avenues to explore new therapeutic opportunities.

149: Type I Interferon Mediated Anti-Viral Programs Exert Opposing Effects on Quantity and Quality of West Nile Virus specific CD8 T Cells by Regulating Antigen Levels

Siddhartha K Bhaumik, PhD; Albanus Moguche, MS; Sunil Thomas, PhD; Murali-Krishna Kaja, PhD

Activation of innate immune system is an essential prerequisite for induction of adaptive immunity. Type-I interferons are one of the component of early innate cytokines produced in response to viral infection that exert pleotropic effects on immune system, including direct antiviral effects as well as modulation of adaptive immunity. West Nile Virus (WNV) is an emerging infectious disease that was first discovered in 1937, and in recent years has spread beyond its traditional boundaries, causing illness in birds, horses, and humans in Europe and now the United States. Several of the circulating WNV species develop potent IFN-I evasive strategies. How IFN-I influence adaptive immunity in the case of WNV infection is unclear. Here we used murine footpad inoculation model of WNV to address the role of type-I interferons on virus-specific CD8 response. By titrating the viral inoculum, we found that at a certain low dose, viral inoculum is capable of inducing innate signals indicative of type-I IFN induction but fail to exhibit detectable viral replication or induction of adaptive CD8 T-cell response. The same low dose inoculum, however, lead to productive viral replication and a massive expansion of the virus specific CD8 T cells when the host was deficient in type-I interferon signaling mediated innate anti-viral programs. The expanding WNV-specific CD8 T cells in IFN-I signaling deficient host show signs of prolonged antigenic stimulation, functional exhaustion and exaggerated contraction. These defects were not due to lack of direct IFN-I signals, but due to the lack of IFN-I mediated antiviral effects. These results, together, suggest that type-I interferon mediated anti-viral programs exert dramatic influence on CD8 t cell expansion by modulating antigen levels which have consequences on quantity, quality and memory differentiation programs of the CD8 T cells. These results have implications for understanding how innate and adaptive immune systems are affected by host-viral interface.

150: Structural Differences Between Neonatal and Adult Clots: Implications on Treatment of Post-Cardiopulmonary Bypass Bleeding

Ashley C. Brown, PhD; Riley Hannan; Janet D. Fernandez, CCRC; Thomas H. Barker, PhD; Nina Guzzetta, MD

Introduction: Quantitative and qualitative differences exist between the hemostatic systems of neonates and adults, among them the presence of ‘fetal’ fibrinogen, a qualitatively dysfunctional form of fibrinogen that exits until one year of age. The functional consequences of ‘fetal’ fibrinogen on hemostasis in neonates have not been well characterized. Here, we first compare baseline structure of neonatal and adult clots. We then examine the sequential changes in neonatal clot structure in a small sample of neonates undergoing cardiac surgery and cardiopulmonary bypass (CPB). Methods: After IRB approval, 16 neonates scheduled for elective cardiac surgery and CPB at CHOA were enrolled. Baseline blood samples were obtained from six neonates, pooled and used to purify neonatal fibrinogen. With purified neonatal and adult fibrinogen, we constructed clots with identical fibrinogen concentrations. Next, blood samples from 10 neonates were used to examine the effects of CPB on clot structure. Samples were collected before and after CPB and following the transfusion of cryoprecipitate (i.e. adult fibrinogen component). We used confocal microscopy to examine clot structure and measured volume fraction (VF) to determine clot porosity. Results: At equivalent fibrinogen concentrations, neonatal clot structure is significantly different from adult. In clots formed from purified fibrinogen, adult fibrinogen formed robust, dense clots with higher VFs than clots formed with neonatal fibrinogen, which formed wispy, thin clots with a small number of thick fibers (adult VF=0.23±0.05 vs. neonate VF=0.12±0.04). In post-bypass samples, neonatal clots were more porous and VFs decreased compared to baseline (baseline VF=0.17±0.08, post-CPB VF=0.14±0.07). Post-transfusion of adult fibrinogen, neonatal clots had an equivalent VF to baseline (VF=0.17±0.07), but had an altered structure comprised of predominantly wispy, thin fibers. This occurred despite an equivalent fibrinogen concentration. Conclusions: Our results confirm that significant differences exist in clot structure between neonates and adults. The ‘fetal’ fibrinogen present in neonates creates an altered clot structure. Even after transfusion of adult fibrinogen, clots more closely resemble neonatal clots suggesting that neonatal and adult fibrinogen may not completely integrate during fibrin formation. Our results have important implications in the treatment of bleeding in neonates after major surgery.

151: Design of a Microfluidic Assay for Von Willebrand Disease Screening

Lauren D.C. Casa, MSME; Shannon L. Meeks, MD; David. N. Ku, MD, PhD

Von Willebrand disease (VWD) is the most common inherited bleeding disorder in children, with an estimated 1 to 3 individuals per 1000 at risk for VWD and at least 100 per million individuals suffering from symptomatic disease. Symptoms include nose bleeding, bruising, prolonged bleeding from trivial wounds, oral cavity bleeding, and excessive menstrual bleeding. The disease can have multiple mechanisms, including quantitative decreases in von Willebrand factor (VWF) concentration and qualitative changes in VWF function. Most essentially, VWD impairs the binding of platelets to VWF during platelet plug formation. Platelet-VWF binding is the dominant hemostatic pathway under high shear rate flow conditions. Despite the prevalence of VWD, it remains difficult to classify and recognize due to its many subtypes and wide range of symptom severity. No existing test adequately screens for VWD under relevant shear and biochemical conditions. To more accurately and efficiently screen for VWD, we have developed a whole blood, microfluidic assay that models high shear (>3000 s-1), VWF-dependent platelet plug formation. The device requires less than 2 mL of whole blood per test, making it practical for multiple simultaneous tests and for routine screening in the clinic. Other design considerations include channel geometry, spatial and temporal flow variations, and manufacturability. The device provides real-time monitoring of platelet thrombus growth using an optical detection system calibrated using confocal microscopy. A detailed analysis platelet thrombus growth is generated, including lag time, growth rate, and occlusion time. In the future, such a device may improve the identification of patients with a range of VWD pathologies with high sensitivity and specificity.

152: BMP-2-Mediated Repair of Segmental Bone Defects in a Juvenile Rat Model

Albert Cheng; Laxminarayanan Krishnan, PhD; Lisa Tran, MD; Joseph Williams, MD; Robert E. Guldberg, PhD

The repair of large bone defects is one of the most challenging problems faced by orthopaedic surgeons today. Current treatments involve bone grafts and/or delivery of osteoinductive proteins such as bone morphogenetic protein 2 (BMP-2). However, the use of BMPs, especially at the high doses used clinically, has been associated with increased inflammation, ectopic bone formation, and osteolysis. Despite these risks, BMPs are used in pediatric patients to repair large bone defects resulting from injury, tumor resection, or congenital deformity. The lack of any data on appropriate BMP dosing for the pediatric population heightens these concerns. The overall goal of this project is to establish a pre-clinical small animal model using juvenile rats to characterize bone regeneration in the pediatric population. Our group has previously established a critically-sized segmental bone defect model in adult rats and determined the minimum healing BMP-2 dose for delivery in a collagen sponge, which is the current clinical standard. Therefore, the objective of this study was to extend our model to juvenile rats and evaluate differences in the BMP-2-mediated healing response. We hypothesized that compared to adult animals, juvenile animals would be able heal at a lower BMP-2 dose but also exhibit an increased inflammatory response at higher BMP-2 doses. At an early 2 week time point, radiographs showed no obvious differences in mineralization between juvenile and adult rats for a 5 μg BMP-2 dose delivered in the clinical standard collagen scaffold. However, RT-PCR revealed differences in gene expression, suggesting that differences may be observed as healing progresses. The juvenile animal exhibited increased expression of inflammatory genes such as CCR7 and interferon-γ. Interestingly, this did not seem to inhibit recruitment of osteoprogenitor cells and induction of osteoblastic differentiation as stromal cell-derived factor 1 (SDF-1), BMP-2, and osteocalcin were all upregulated in the defect tissue of the juvenile animal. Forthcoming data will seek to better define gene expression trends at additional timepoints, evaluate the ability of juvenile rats to regenerate bone at a sub-healing BMP-2 dose, and determine if there are functional differences in the new bone formed. Our efforts to better characterize the BMP-2 healing response in a juvenile pre-clinical animal model may lead to improved regenerative strategies for bone repair in pediatric patients.

153: Using Patient Data to Transform Care and Improve Outcomes for Children, Adolescents and Young Adults with Inflammatory Bowel Disease

Bernadette Martineau; Cara Bergo; Britney Eyster; Christine Spainhour; Anna Roberts; Bess T. Schoen, MD

Background: Despite therapeutic advances in treatment of pediatric inflammatory bowel disease (IBD), there has been limited improvement in outcomes. Objective: The aim of this study is to use patient data to transform care and improve outcomes for children, adolescents and young adults with IBD. Methods: The ImproveCareNow (ICN) Collaborative was formed in 2007 at 9 pediatric gastroenterology practices. Practices received training in QI

developed care algorithms, enrolled patients into a registry, and began testing small changes in systems of chronic illness care. The classification of growth and nutritional status according to established definitions were recorded at each patient encounter, and monthly run charts were created to track performance improvement. Remission rates for Crohn's and Ulcerative Colitis (UC) patients were followed. In May 2012, the percentage of UC patients in remission at Children's Healthcare of Atlanta at Emory (CHOA-Emory) was found to be significantly lower than the Collaborative and therefore a failure mode analysis was completed on UC patients not in remission. Results: At CHOA-Emory, overall remission rates increased from 52% to 74% since joining ICN. The percentage of Crohn's patients in remission increased from 42% to 76%. The percentage of UC patients in remission increased from 45% to 65%. The percentage of patients with satisfactory nutrition increased from 86% to 90% since a nutritionist was added to the healthcare team. Finally, the percentage of patients with satisfactory growth increased from 80% to 94%. Conclusions: With the help of run charts and QI tools from ICN, CHOA-Emory has been able to discover weaknesses and improve our IBD care. The result of this work has been significant improvement in remission rates, nutrition and growth in our patient population.

154: Mining Association Rules for Neurobehavioral and Motor Disorders in Pediatric Cerebral Palsy

Chih-Wen Cheng; Thomas Burns, PsyD; Aiswaria Nair; May D. Wang, PhD

Cerebral Palsy (CP) is a nonprogressive group of disorders of motor and posture caused by brain injury that may occur during the prenatal, perinatal and/or postnatal period. The prevalence of CP has remained stable over time and is estimated to occur in four out of 1,000 births equally between males and females. The underlying etiologies of CP vary; however, a global assault on the brain development is generally implicated. General symptoms of CP vary depending on type, severity, and limb involvement. Additionally, many medical morbidities can co-occur with CP, such as seizures. Given such a nature of CP and related motor impairments, psychological assessment can be a difficult task. Although literature has suggested factors (e.g., low birth weight) that may contribute to cognitive and motor difficulties, there has been a paucity of research trying to statistically predict what percentages of patients will incur cognitive, motor, and behavioral problems as a result of CP. This study, through medical history and neuropsychological instrument scores of children diagnosed with CP, uses association rule mining (ARM) to determine meaningful relationships among age, birth weight, and cognitive, motor, and behavioral disorders. In ARM, each rule is in a form of implication X==>Y with two measures: Support=A% and Confidence=B%. We are not aware of any published study investigating the ARM method in assessment of neurobehavioral and motor disorders, especially in pediatric CP. Data of demographic information and medical history includes age, history of seizure, shunt placement due to hydrocephalus (Shunt), current antiepileptic drugs use, and birth weight were taken from a sample of 155 patients that were seen in the clinic of CHOA. Four neuropsychological instruments were also administered to assess different neuropsychological disorders, including intellectual ability, visual motor ability, emotional disorder, and depression. As a result, our mined rules can predict both normal and abnormal neuropsychological disorders. We discovered 22 rules that can predict abnormalities, which deserve more attention. For example, history of seizure, use of AEDs, and shunt placement are all good predictors of lower IQ, and history of seizure predicts the best. Our mined association rules provide useful quantitative knowledge for assessment of patients who have comorbid diagnoses and risks for neurobehavioral concerns, motor deficits, and lower overall cognitive potential.

155: Development of Clinical E-Media Data Library and Online Resource Sharing Capability for the Marcus Autism Center, Children's Healthcare of Atlanta

Courtney L. Crooks, PhD, LP; Keith Kline, PhD; Cheryl A. Rhodes, MS, LMFT, LPC; Emily Rubin, MS, CCC-SLP; Felissa Goldstein, MD, FAPA; Apoorva P. Verlekar

The Marcus Autism Center (MAC), Children's Healthcare of Atlanta (CHOA), Cisco, and Georgia Tech Research Institute (GTRI) have partnered to develop a state-of-the-art telemedicine suite to serve families in Georgia and neighboring states. In addition to autism screening and continuing care, the newly designed and implemented system will support education and training of providers and caregivers, and enhanced video-teleconferencing capabilities. Observations of formative design studies and clinical telemedicine/training sessions have revealed the need for an efficient means of organizing, storing, and sharing documents and recorded videos between sites, providers, and caregivers. Providers currently use fax and email to send educational documents during clinical sessions, which is cumbersome and prohibitive. Also, while video recording capability is possible via the new telemedicine system and associated data center, video searching or sharing is not currently supported. An innovative, "e-based" provider/caregiver repository system and toolset is currently being developed for storage, sharing and optimized use of a keyword searchable library of electronic education and training materials and video.

These resources will be accessible by a virtual user workspace through which “patient” and “provider-facing” materials can be accessed, organized, searched, and shared. The proposed system will be capable of generating PHI-secure emails to support communication between patients, families and providers, with embedded resources including information about CHOA-supported county and city services. The proposed system will be designed with the intent of optimizing clinic-based work process flow as well as individual access to care, and will support additional functions that optimize research based evaluation and improvement. Currently, there is no subsystem of this nature in use or available to MAC or CHOA. The launch of this Data Repository and Resource Rx (DRRX) will, as a result, greatly enhance clinical capability, reduce workload, improve provider-to-patient interface, and enhance user satisfaction with clinical services while adding a state-of-the-art component to the burgeoning CHOA telemedicine program.

156: Using a Wizard of Oz Approach to Study the Effect of EHRs on Clinical Workflow

Marla Daves, MD, MSHI; Ashley Ferguson; Frank Durso, PhD; Robert Grundmeier, MD; Ann Mertens, PhD

Background: The implementation of electronic health records (EHRs) promise improvements in the quality and safety of healthcare by providing easy access to information, providing clinical decision support at the point of care, and by allowing the automated tracking of outcomes and care. However, these systems are often felt to be intrusive and time consuming to users. Understanding user cognition in complex systems is central to ensuring system usability and implementation success. In this study, we used methods from cognitive science research to study healthcare provider interaction with the EHR. Methods: We performed structured interviews with 16 hematology/oncology providers in an ambulatory clinic. Each subject was given 2 patient scenarios representing common visit types in the outpatient pediatric hematology/oncology clinic. During one scenario, we used a “wizard of Oz” approach to learn the user’s ideal workflow in a “perfect system.” In the other, we performed cognitive walkthrough in the clinic’s EHR training environment. The interviews were video recorded and transcribed. The order of tasks in each scenario was modeled using Microsoft Visio software. Results: In the scenarios performed in the current EHR’s training environment, the order of task completion was determined largely by the build of the system. In the ideal scenarios, providers did not consistently follow this order. For example, they were more likely to review the patient’s historical information prior to reviewing the current visit data. In addition, the ideal systems described by the providers elucidated four areas of need: better visualization tools providing comprehensive summaries of patient histories and data, improved data entry at the point of care, efficient communication tools between care providers, and the addition of patient involvement in the EHR system. Subject matter experts reviewed the workflows to identify deviations in task completion. Conclusions: Cognitive task analysis is an effective way of identifying gaps in the build of an EHR. It was useful in understanding ways in which the EHR causes deviations from providers’ cognitive models of a patient encounter. In addition, we identified further areas of need in the EHR. In future studies, we will perform observations with time studies to see if the EHR scenarios adequately represented the true clinic workflow and to quantify how deviations may affect clinic efficiency.

157: Using the Engineering and Science of Healthcare Delivery to Improve the Experience of Care and Reduce Cost at Sibley Heart Center Cardiology (SHCC)

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Background: SHCC seeks to improve the experience of care and reduce non-contact wait times, while maximizing efficiency and resource utilization. SHCC and Georgia Tech’s SimTigrate Design Lab have partnered to apply engineering and architectural tools to the science of healthcare delivery. We will standardize methods for data collection and create a simulated model of care. This model will permit rapid testing of various staffing models and will assess the impact of clinic layouts on care coordination. The team has completed Phase I of a four-phase project that will include: problem identification, modelling the current state, solution identification and ongoing evaluation. The resulting “Sibley Model of Care” will be tested and validated for wider application. Objectives: The Phase I objectives include current-state modeling, project scope refinement and problem focus area identification. The impact of process deviations, resource utilization, clinic layout and scheduling on workflow efficiencies will be evaluated. Methods: Clinical processes were defined and timed by observers at three outpatient pediatric cardiology clinics. SPSS was used to analyze time distribution at each care step. Process modeling software (MedBPM) was used to map current clinical processes and deviations. Space Syntax analysis was performed to measure visibility within the clinics. Results: Total visit times ranged from 40 minutes to 200 minutes. No significant differences were observed in process times based on age, visit type, or new vs. established patients. Patients spent an average of 29% of their visit waiting for services; in some cases wait time exceeded 2 hours.

High variability in care steps and workflow was observed. Increased access to rooms with windows modified room utilization. Conclusions: The clinical process itself, rather than patient attributes, created long wait times. The longest waits were spent in a single room, which created additional bottlenecks. Communication between clinical teams, low line of sight, variable space usage, and resource availability contributed to inefficiencies. A discrete event model will be created in Phase II to simulate and test strategic distribution of waiting across multiple care steps. Opportunities to strengthen leadership, standardize processes and empower staff will be explored to improve workflow predictability and consistency. Visibility, walking distance and access to natural light will be further evaluated.

158: An Ecosystem for Objectively Monitoring and Improving Medication Adherence in Adolescent Transplant Recipients

Shriprasad Deshpande, MBBS, MS; Christina Choi, PhD; Maysam Ghovanloo, PhD

Medication non-compliance, in patients with chronic illnesses, is associated increased healthcare cost, complications, and disease progression. Estimated prevalence of non-compliance in U.S. is 33%, causing $100 billion in excess hospitalizations costs alone. Improved medication adherence will be vital in the overall outcomes in these patients. Presently, there is no objective way to track medication adherence. There is a need for a portable, wearable, and acceptable health platform that can remind patients of their medication regimen, track medication compliance, and monitor the users' overall health status. We are developing a system in the form of neckwear that will automatically track medication ingestion using the well-established radio frequency identification (RFID) technology in very high frequency (13.56MHz) band. The device will be activated by swallow and the use of coated, tagged pills will ensure 100% accuracy in medication ingestion detection. During a medication ingestion event, pertinent information will be collected from a pre-programmed RFID tag, time-stamped, and wirelessly transmitted to a smartphone or PC to build an objective user-specific compliance history. Since the WEAMS system conducts real time ingestion-based adherence monitoring, it can provide physicians with accurate information compared to current surrogates. This is particularly important for patients with chronic conditions or transplants. Throughout the development of the proposed system, performance, including usability/acceptability and costs/benefits will be evaluated through focus groups, questionnaires, and in real life scenarios of the target population. Initial data on the prototypes developed by us, achieved accuracy of 79.9% in a pilot study performed with healthy subjects. For RFID verification, a "phantom neck" model with a motor controlled pill conveyor is in development to mimic the motion and speed of swallowing. In order to assess design preferences, an IRB-approved study will be conducted at the CHOA with organ transplant recipients. We have developed several mockup designs for the device. We will present these iterations to subjects to collect feedback to be used to guide a user-centered design of a fully functional WEAMS system. This study will assess the willingness of participants to accept and use this potential technology. A survey questionnaire has been developed to assess the same and the study will start enrollment over the next month.

159: Analyzing Critical Incidents Within the Electronic Health Record

Ashley N. Ferguson, BS; Francis T. Durso, PhD; Marla Daves, MD, MSHI

Without the proper research into clinic workflows and providers' thought processes, Electronic Health Records (EHR) are often time consuming and unintuitive. This study focused on determining incidents where the EHR impacted patient safety, clinic efficiency, or caused a near miss or failure. By determining where these incidents frequently occur in the EHR implementations could be made to prevent similar incidents. These modifications could decrease errors and increase clinic efficiency, thus, increasing patient safety and satisfaction. Thirteen healthcare providers in a pediatric oncology/hematology outpatient clinic at Children's Healthcare of Atlanta were given a structured interview based on Klein et al.'s critical decision method (1989) to elicit these incidents. A total of eighteen incidents were elicited from the providers. The majority of these incidents effected clinic efficiency, often making the patient wait longer in clinic due to incorrectly ordered labs or the provider spending more time on patient instructions or chemotherapy orders. A few of these incidents directly impacted patient safety, such as giving a patient an incorrect dose of a medication due to missing information in the system and lab results being interpretable due to incorrect orders or incorrect timing of labs. Almost all of the incidents could have impacted patient safety if the provider had not caught them in time. Half of the incidents concerned problems with ordering labs. A third of these involved problems with the system defaulting to order the labs in the "future" instead of ordering them as "normal" for the current visit. This resulted in significant delays in performing labs and even one patient having to receive a second bone marrow biopsy. Many of the lab-related incidents also involved the provider ordering a lab in an incorrect location within the EHR. As a result, the technicians were unable to see the orders or

perform the lab tests. The providers were also asked how they believed the EHR contributed to these events and how the events could be prevented in the future. Further analyses of these incidents could influence the EHR system increasing both satisfaction and safety. Klein, G. A., Calderwood, R., & MacGregor, D., 1989. Critical decision method for eliciting knowledge. IEEE Transactions on Systems, Man, and Cybernetics, 19, 462-472.

160: Impact of Race, Socioeconomic Status, and Cognitive Level on Early Diagnosis of ASD

Samuel Fernandez-Carriba, PhD; Celine Saulnier, PhD; Jonathan Berman, BS; Baindu Davis, BS; Gerianna Kneeland, BS; Ami Klin, PhD

Whereas the prevalence of Autism Spectrum Disorder (ASD) is reportedly lower in racial and ethnic minorities in the US (Mandell et al., 2009), a positive association between ASD and socioeconomic status has been described in all ethnic groups, but no association when ASD presents with cognitive delays (Durkin et al. 2010). The aim of this study was to explore the possible interaction between ASD and race, socioeconomic status, and level of functioning in young children newly diagnosed with ASD. 131 toddlers between the ages of 10 and 30 months were recruited. 100 participants were white (52 ASD; 26 with Developmental Delays; 22 Typically Developing; 25 females) and 31 participants were black (17 ASD; 12 with DD; 2 TYP; 7 females). Diagnostic evaluations included the Autism Diagnostic Observation Schedule, Toddler Module, the Vineland Adaptive Behavior Scales, Second Edition, and the Mullen Scales of Early Learning. Race was computed by self-identification, and socioeconomic status by level of maternal education (college degree or more, and less than college degree). Mullen derived IQ scores were grouped as higher or lower than 70. Chi-Square analyses revealed no significant effects of race by diagnosis. They did reveal however a significant effect for maternal education by diagnosis, with 46% of mothers of children with ASD having a college degree or higher compared to only 31% of the DD sample [$p<.01$]. When separating the groups by IQ level, the age of those with verbal and nonverbal IQ scores higher than 70 receiving a diagnosis of ASD was significantly lower if their mothers' education was a college degree or higher, according to independent sample t-tests [$p<.05$]. Conversely, maternal education did not predict any differences in age of diagnosis for children with ASD when their verbal or nonverbal IQ scores were below 70. Further analyses with children with DD and typically developing children did not reveal any significant effect of maternal education on age of evaluation for those who had IQ scores higher or lower than 70. These results are consistent with Durkin et al.'s (2010) previous findings. Higher socioeconomic status (maternal education) predicts earlier diagnosis of ASD in white and black children with higher cognitive functioning, but not in those children with lower cognitive functioning. Maternal education was not associated either with a younger age at the time of the evaluation for typically developing children and those with DD.

161: What are the Areas in Need for Improving Access to Pediatric Primary Care?

Monica Gentili, PhD; Nicoleta Serban, PhD; Julie Swann, PhD

In this research, we make inferences on the geographic access to pediatric primary care across 14 states in the U.S., assuming a healthcare system operating under the current implementation of the Affordable Care Act (ACA). Our measurement models for geographic access are based on optimization models that match patients with providers considering a series of user and provider system constraints. On the provider side, an example of constraint is the maximum caseload of providers with different levels of training, e.g., physician and nurse practitioners. On the user side, an example of constraint is the reduced acceptability of patients with Medicaid insurance and it state-level extension, the Children's Health Insurance Program (CHIP). For the latter, we will set the provider participation in these two programs according to the implementation of ACA. We will use these models to derive multiple dimensions of geographic access estimated at the census tract level. We will compare these measures for two population groups, children insured by Medicaid and/or CHIP and other children on private insurance or health insurance exchange, and across the 14 states. We focus on both local and global geographic variations.

162: Longitudinal Profiling of Prosodic Variation in Maternal Speech for Infants at Risk of Autism

Shweta Ghai, PhD; Yael Stern, BS; Ami Klin, PhD; Gordon Ramsay, PhD

Introduction: Impairments in social communication, often characterized by atypical prosody, are one of the core features in autism. In our previous research, we showed that around the same time when infants at risk of autism exhibit elevated and more variable fundamental frequency contours, the number of vocal interactions between caregiver and child decreases, which triggers a later decline in caregiver's vocalizations. We do not yet know if

early styles of prosodic interaction perseverate or atrophy in mothers of infants with ASD, nor if they impact the development of social communication between mother and child. The goal of this study is to compare developmental profiles for intonation for mothers of infants at low and high risk of autism over the first year of life. We test the hypothesis that weakening of prosodic function in caregiver and infant may be caused by, and further reinforce, the early derailment of social communication in ASD. Methods: Day-long home recordings of 4 low-risk and 4 high-risk infants were made once every month with a digital audio recorder until the child was 12 months old. Infant-directed and adult-directed speech samples from each child's mother were extracted from the recordings by hand labeling. The fundamental frequency contour was estimated on a frame-by-frame basis for all segmented speech files. Functional Data Analysis was used to derive profiles showing prosodic variation in maternal speech over the first year of development. Clinical assessments of children were carried out at 24 months to determine outcome. Results: Two high-risk infants were diagnosed with broader autism phenotype and two had non-autistic language delays. All low-risk infants were typically developing. Preliminary analyses showed that fundamental frequency contours for infant-directed speech in mothers of high-risk infants were elevated and more variable relative to low-risk controls. Conclusions: Atypical prosodic variation in infant-directed speech of caregivers may affect social communication in infants, and both cause and be caused by atypical patterns of social interaction in children at risk of ASD. Impact: This study demonstrates the role of caregiver's prosodic interaction in shaping social communication skills in children with ASD and, in turn, may help to increase yields from early intervention services for treating autism. This work is supported by NIMH (P50 MH100029), Simons Foundation, Marcus Foundation, and Whitehead Foundation.

163: Thrombosis in Pediatric ECMO

Susan M. Hastings, BS; Scott Wagoner, MBA, RRT; Shriprasad Deshpande, MD; L. Andrew Lyon, PhD; Kevin O. Maher, MD; David N. Ku, MD, PhD

ECMO is a form of extracorporeal life support for patients requiring long-term cardiopulmonary support. The majority of the ECMO patients are pediatric. The therapy is plague with many complications, and one of the biggest challenges in managing ECMO patients is determining the proper balance among clotting, anticoagulation, and hemorrage. Clotting in the circuit endangers the survival of the patient and generally inhibits progress and recovery. Prior to this study, ECMO clot characterization is scant and the driving mechanisms poorly understood. Here we identify the location of ECMO clotting and its relation to local hemodynamics. In this study, used ECMO circuits from pediatric patients (N=9) were obtained from Children's Hospital of Atlanta at Egleston. After removal from the patient, the circuits were drained of blood and filled with saline. Circuits were taken to the Ku Lab at Georgia Tech and examined carefully for visible clots. Found clots were preserved in formalin and histological analysis was done with Cartstairs' stain. A computation fluid dynamics model done in COMSOL Multiphysics® was used to analyze shear rate at areas of interest. Clots were found at the junction of the tubing and connectors in the circuit, and were axisymmetrically adherent (40/42, 95%, $p<<0.05$). Although the tubing comprises over 90% of the exposed area in the extracorporeal circuit, no clots were found adherent along the free tubing surface. Clots were also found in the oxgenator, but these clots were not adherent to the membrane surface. The computational analysis showed that the junction formed by the tubing and connector creates areas of low shear ($<100s^{-1}$). The histological analysis revealed fibrin-rich clots with trapped red blood cells and very few platelets, which is consistent with the low shear assessment. Our findings imply that driving mechanism of ECMO clots is fibrin-related and are correlated to low shear. Our sample also suggests that thrombosis occurs in 100% of ECMO circuits, which has not been previously reported. A better understanding of the driving forces of ECMO clotting may allow for targeted prevention methods and optimal patient outcomes.

164: Clinical Outcome and Prediction of Final Diagnosis in Pediatric Inflammatory Bowel Disease Unclassified (IBDU) Patients

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Approximately 10% of patients with IBD are diagnosed with IBD unclassified (IBDU). Due to diagnostic ambivalence these patients may experience delayed standard treatment for UC and CD. IBDU may be associated with higher relapses, poor surgical outcomes and higher risk of cancer. Prospective studies examining pediatric IBDU patients are lacking. Aim: To test the hypothesis that pediatric patients diagnosed with IBDU comprise a distinct clinical entity compared with UC and CD. Data were obtained from the RISK study, an ongoing, prospective observational research study started in 2008 that includes 28 centers in North America. Children under

17 years with newly diagnosed IBD were enrolled from 2008 to 2011. A site investigator established a diagnosis of IBDU in the setting of colon-only IBD, without small bowel involvement, and accompanied by endoscopic and histological features that did not allow a firm diagnosis of CD or UC. Of the 1400 patients enrolled, 134 (10%) were labeled IBDU at baseline and followed for a mean of two years. During the follow up, patients either remained as IBDU or were reclassified as CD or UC. Baseline characteristics were compared to determine differences predictive of final diagnoses. Multiple logistic regressions were used to identify risk factors associated with a final diagnosis of UC or CD. Of the 134 IBDU patients, 26 (24.1%) had a subsequent diagnosis of CD, 39 (36.1%) UC, and 69 (51.5%) remained IBDU. In children with IBDU, PGA improved most with early therapy of steroids and immunomodulators/biologics. During follow up, patients that remained IBDU or were diagnosed with CD had higher levels of ASCA compared with UC patients. Both CD and UC patients had higher ANCA levels compared with IBDU patients. More CD and UC patients had NOD2 variants compared with IBDU. Logistic regression models indicated elevated ANCA and CBir levels as risk factors associated with CD (AUC=0.743), whereas elevated ANCA and low ASCA levels were associated with UC (AUC=0.732). In a well-characterized cohort of 134 children with IBDU at diagnosis, half remained IBDU at 2 years. Those who remained IBDU had mild to moderate PGA at diagnosis. Factors that predict change to CD include ASCA, ANCA, NOD2, CBir; factors that predict change to UC include ANCA and low ASCA. Those remaining IBDU tend to be sero-negative and lack genetic markers suggesting a different pathogenesis plays a role in persistent IBDU.

165: Evaluation of a Technology Supported Manual for the Treatment of Pediatric Feeding Disorders

Kathryn S Holman, PhD; Leanne West, MS; Brian Wells, BS; Heyword Adams, BS; Kristen K. Criado, PhD; William G. Sharp, PhD

Objective: Between 3% and 10% of children develop chronic feeding issues exceeding ordinary developmental variation and associated with a number of serious medical and developmental outcomes including growth retardation, malnutrition, invasive medical procedures (e.g., placement of a feeding tube), or death. Therapeutic behavioral intervention is the only treatment with well-documented empirical support; however, treatment primarily occurs at specialized programs. Unfortunately, few programs exist, and treatment often requires 6-8 weeks of daily intensive services at a cost of nearly $60,000/child to eliminate disruptive behaviors that preclude food acceptance. These barriers limit access to treatment and highlight the need for alternative methods to disseminate behavioral feeding intervention. This project involves the development and evaluation of the first manual-based, mobile-platform decision support tool for behavioral feeding intervention. This application-based technology represents an enormous therapeutic breakthrough in the treatment of pediatric feeding disorders, holding the potential for large scale application. Methods: The mobile application was built using a three tiered approach. Phase 1: We developed a treatment manual using a paper-based decision matrix and data collection system during a double-blind, randomized control trial involving 16 children with chronic food refusal. Data on operationally defined behaviors guided movement through the matrix. Phase 2: We translated the current data collection system into a touch-screen application in partnership with Landmarc Research Center at Georgia Tech. Phase 3: We will evaluate the application using a waitlist control design. Results: Phase 1: Findings indicated the manual-based feeding intervention was associated with significant improvements ($p < .05$) on all dependent variables. The magnitude of the observed effects was "large". Phase 2: Development of the touch-screen application was completed and confirmation of appropriate navigation through the matrix was established. Phase 3: Evaluation of the mobile platform is ongoing. Conclusions: This is the only manual-based, behavioral feeding intervention in pediatric populations. Our preliminary findings suggest that this technology has the potential to fill an important gap in the field, including 1) increasing efficiency, 2) enhancing involvement of parents in treatment, and 3) supporting dissemination across settings and therapists.

166: The Impact of Family-Centered Rounds on Nursing Workload and Family Information Needs

Sadaf Kazi; Qing Li, MSHS; Pinar Keskinocak, PhD; Atul Vats

Background: Family-Centered Rounds (FCR) are a venue for engaging families in medical decision-making and patient care, particularly in the pediatric setting. Although it has been previously demonstrated that FCR increase the satisfaction of patients' families, it is unknown whether FCR have an effect on nursing workload and also what information families hope to gain from FCR. We hypothesize that FCR decrease nursing workload, help bridge the gap between information desired by and given to patients' families, and improve the quality of nurse-family relationship. Methods: Families of patients in the Pediatric Intensive Care Unit (PICU) and the Cardiac Step-down Unit (CSU) at Children's Healthcare of Atlanta (Egleston campus), were administered a modified version of the Critical Care Family Needs Inventory (CCFNI) to investigate their information needs and how well these needs

were met. Nurses completed a modified NASA-Task Load Index (NASA-TLX) to quantify the workload associated with providing plan-of-care (POC) information to families. Nurses also logged details about interruptions they faced from patients' families. Results: 1) Perceived performance was statistically lower for nurses whose assigned families did not attend rounds (N=244 nurses, PICU lower by 2.49 and CSU lower by 4.28, $\alpha<0.05$). Perceived performance was also significantly lower for the CSU night shift (-3.16 pts, $\alpha<0.05$). 2) Top two types of interruptions for PICU nurses whose families attended rounds, were POC updates (12.3%) and medical information (31.5%, N=122 nurses). Families who attended rounds in the CSU interrupted nurses for non-medical supplies (26.4%) and other information (29.4%). Of the CSU families who attended FCR, 94% tended to interrupt their assigned nurse; this effect was not seen in the PICU. 3). In both the PICU and CSU (N=50 families), information desired by the families are currently being met by FCR. Conclusions: FCR is linked to improvement in nurses' performance, improvement in the family-nurse relationship, and satisfaction of families' information needs. Some possible negative effects of FCR may be giving families too much information and the increase in interruptions of nurses by the families to ask for further explanation. These two points may be mitigated by understanding the families' information needs and anticipating an increase in family interruptions after rounds.

167: Activating RIG-I Pathway at the Time of Vaccination Enhances Germinal Center Reaction, Follicular T Helper Cell Response and Confers Protective Immunity Against Pandemic Influenza

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Vaccines work by eliciting T and B cell mediated adaptive immunity. Optimal induction of adaptive immunity is critically dependent on innate immune activation at the time of vaccination. Although live attenuated vaccines can efficiently activate innate immune system via pattern recognition receptors, there is a need towards developing subunit/ protein antigen-based vaccines capable of inducing protective immunity against several human pathogens. Efficient use of these vaccines requires combining their administration along with strategies that can activate innate immune system. Molecular adjuvants that activate innate system via TLR mediated pathways have been extensively explored with some success. Retinoic acid-inducible protein I (RIG-I)-like receptors (RLR) are a recently discovered class of cytosolic pattern recognition receptors that sense viral RNA and trigger an antiviral immune response by inducing type-I interferon production. 5' triphosphate double stranded RNA (5'ppp-dsRNA) is a synthetic ligand for RIG-I. Here, we investigated the use of 5'ppp-dsRNA as vaccine adjuvant in murine models. We found that 5'ppp-dsRNA administration along with protein antigen could enhance antigen-specific CD4 T cell expansion, their Th1 cytokine effector functions and differentiation in to follicular helper cells along with augmented germinal center formation and antibody mediated memory. These responses induced by RLR activation at the time of vaccination were superior to TLR4 and TLR7 adjuvants as well as alum. Incorporation of similar strategies of RLR activation along with monovalent pandemic influenza vaccine resulted long lasting influenza-specific memory B cells, bone marrow homing plasma cells and serum antibodies that were qualitatively better than the one induced by unadjuvanted vaccine. In addition, 5'ppp-dsRNA adjuvanted vaccine conferred highly efficient protective immunity against pandemic influenza virus challenge. The adjuvant effects of 5'PPP-RNA ligand required type-I interferons and IPS-1, an adapter protein downstream of RIG-I signaling; but were independent of signaling through MyD88, TLRs 4, 7 and 3. More importantly, we found that RLR activation provided an excellent dose-sparing effect even at 100 times lesser doses than the conventional vaccine doses used in these models. These studies have implications for designing better vaccines not only against pandemic influenza but several other protein antigens.

168: Population-Based Analysis of Hydroxyurea Use and Emergency Department and Inpatient Hospital Utilization in Children with Sickle Cell Disease (SCD)

Rodney Theodore, MPH; Yuritzi Jones; Carlton Dampier, MD; James Bost, PhD; Peter Lane, MD

Background: Clinical trials have demonstrated the efficacy of hydroxyurea (HU) in reducing episodes of pain and acute chest syndrome, the leading causes of ED visits and inpatient (IP) hospitalization in children with Hb SS and Sβ°thalassemia ≥ 5 yr old. Objectives: We sought to determine whether trends in HU use over a 3-year period (2010-2012) were associated with trends in ED and IP utilization in children with Hb SS/Sβ°thal. For comparison, we also examined ED and IP utilization in Hb SC and S β+thal, genotypes of SCD for which HU is rarely used. Methods: The clinical database of the SCD Program at CHOA was used to identify all 5-16 yr olds with SCD who received comprehensive care at CHOA during 2010-2012. SCD genotype, county of residence, treatment with HU and/or chronic transfusions (CT), and all ED and IP utilization were determined. Subjects on CT and those outside the 28-county Greater Metro Atlanta Area (GMAA) were excluded. ED and IP utilization was analyzed by comparison of mean+/- SD; subset analysis was performed for 3 subgroups (5-8; 9-12; and 13-16 yrs). Outliers for

high ED and IP utilization were defined as ≥6 ED visits and ≥3 IP admissions/yr. Data were analyzed for significance by Chi-square. The extent to which the data were population-based was determined from the Georgia Hospital Association database with includes DRG-level data for all inpatient hospitalizations in Georgia. Results: Hospitalizations at CHOA accounted for 96.1% of all SCD admissions for children within the GMAA. From 2010 to 2012, use of HU among 5-16 yr olds with SS/Sβ°thal increased 36.8%, with the greatest increase (63.1%) among the 5-8 yr subgroup. ED utilization decreased 23.5% (from 1.92 +/- 2.14 to 1.47 +/- 1.89 visits/subject/yr; p <.01), with the greatest decrease among 5-8 yr olds. IP admissions decreased 27.7% (from 1.01 +/- 1.46 to 0.73 +/- 1.22 admissions/subject/yr; p <.01). Outliers for high ED utilization decreased from 6.6 to 3.2% of subjects (p .02) with the greatest decrease in the 5-8 yr subgroup. IP utilization outliers also decreased from 16.4 to 8.2% (p <.01). No significant differences in ED or IP utilization or in utilization outliers were observed among subjects with SC/S β+thal. Conclusions: Increased use of hydroxyurea was associated with a significant decrease in ED and IP utilization in a large population-based analysis of children and adolescents with SS/Sβ°thal.

169: Microfluidic Platform for Acute Lymphoid Leukemia Detection

Gonghao Wang, BS; Alexander Alexeev, PhD; Wilbur Lam, PhD, MD; Todd Sulchek, PhD

Acute lymphoid leukemia (ALL) is the most common form of leukemia in children: 3 out of 4 cases of childhood leukemia are ALL with the peak incidence occurring age 3-7 years. It is one of the deadliest diseases for children and correct diagnoses are crucial for effective treatment, because the specific chemotherapeutic protocols differ in children and adults and the symptoms progresses quickly if not treated immediately. Current ALL detection is mainly achieved by cell count through routine blood test. Other forms of detection include physical exam, biopsy and X-ray. However, there are no widely recommended blood tests or other screening exams for most children to look for leukemia before it starts to cause symptoms. As a result, a new detection method for ALL will benefit children who are known to be at increased risk of leukemia. We have invented a microfluidic platform that separate blood cells by their biophysical characteristics. The ALL affects the white blood cells by increasing cell mechanical stiffness and altering the cell viscoelasticity. Our cell separation method exploits the differences in mechanical stiffness and viscoelasticity to separate cells. The microfluidic device employs periodic diagonal ridge constrictions to repeated “probe” cell stiffness and viscoelasticity when cells are streamed through. The gap between the ridges and the bottom channel wall is smaller than the cell diameter, thus the cells streamed through the channel are periodically compressed by the ridges. The difference in mechanical resistance to compression of cells with different stiffness and viscoelasticity give rise to a stiffness-dependent force associated with cell passage through constrictions formed by the consecutive channel ridges. The compression in combination with secondary flows in the ridged microfluidic channel translates each cell perpendicular to the channel axis in proportion to its stiffness and viscoelasticity. Leukemia cell line (HL60) and white blood cell lines (K562) are employed as models for our preliminary study. We demonstrated that our device can separate these two cell lines with 70% purity for Leukemia cells. The method is label-free, high-throughput, and has high enrichment factor. In addition, the devices are low-cost (direct material cost less than $1) and can be batch manufactured. The device is effective in classify leukemia types and therefore has great potential for early screening ALL for children.

170: Deriving and Evaluating Amygdalo-Prefrontal Connections in Humans and Monkeys Using Diffusion Tractography

Longchuan Li, PhD; Xiaoping Hu, PhD; Jocelyne Bachevalier, PhD; Warren Jones, PhD; Sarah Shultz, PhD; Ami Klin, PhD

Background: The amygdaloid (Amyg) complex and its connectivity with prefrontal cortical areas comprises a major component of the ‘social brain’ network and is critical for modeling the pathophysiology of Autism Spectrum Disorders (ASD)1. Although extensive studies on Amyg-prefrontal connections have been performed in monkeys using invasive tracers2,3, research on the related connectivity in humans is largely lacking. Such knowledge is important, as it is a prerequisite for understanding the neural networks in ASD. Objectives: (1) To derive the Amyg projections to the prefrontal cortex in monkeys using diffusion tractography and compare the results with the tracing evidence from the same species; and (2) To examine the corresponding connections in humans using diffusion tractography to determine whether cortical projections from the Amyg follow the same rule as those in monkeys. Methods: Ten rhesus monkeys and ten humans were included in the study. MRI data were obtained using two 3T Trio Tim scanners. The parameters can be found in [4]. We manually drew Amyg seed masks and prefrontal target masks bilaterally in each subject. Fiber-tracking algorithms in FSL were used to trace the connections between the Amyg and the prefrontal cortex. After each subject’s Amyg-prefrontal tracts were derived, they were normalized and mapped to volume and surface templates for visualization and comparisons. Results: Tracing

studies in monkeys showed that the heaviest Amyg projections terminated in medial and orbital regions including areas 24, 25, 32, 14, 13 and 122,3. The heaviest prefrontal projections to the Amyg include areas 25, 24, 12o and 133. When comparing our tractography-derived connections in monkeys with tracer literature, we found a high correspondence in the connectivity patterns between the Amyg and the prefrontal cortex2,3. We then compared the connectivity between the prefrontal cortex and the Amyg across the species. Connectivity patterns in humans generally showed high resemblance to those in monkeys. We do, however, observe relatively stronger connections between prefrontal areas 12m, 12r and the Amyg in humans than in monkeys when comparing these relative strength to that in the medial prefrontal cortex. Interestingly, a hemispheric asymmetry was noted in both species, with stronger left Amyg-medial prefrontal cortex than to the right, similar as those observed in a tracer study3.

171: Development of a Computer Interface for Surgical Planning of Congenital Heart Diseases

Mark Luffel; Maria Restrepo; Elaine Tang; Lucia Mirabella, PhD; Timothy Slesnick, MD; Kirk Kanter, MD; Ajit Yoganathan, PhD; Jarek Rossignac, PhD

Children born with congenital heart defects require complex palliative surgeries that improve patient survival; however, there are still long term problems that affect these patients. Virtual surgical planning allows tailoring the surgery to the patient specific anatomy, and this can yield better outcomes for this patient population, and for that reason we have developed the software program SURGEM III. With this, clinicians can explore surgical options virtually, and perform a comparative evaluation of these options. Currently it supports three repairs:1) intraventricular repair for patients with double-outlet right ventricle (DORV); 2) Total cavopulmonary completion (TCPC) for the Fontan procedure; and 3) stent implantation for vessel stenosis. The surgical planning tool allows the user to upload patient-specific anatomy that can be reconstructed from several imaging techniques. In each application, the tool provides outputs that are useful for the clinical team in surgical planning. In DORV surgery planning the user can place a virtual baffle into the right ventricle (RV) to redirect blood flow through the ventricular septal defect into the aorta. The planning goals for a DORV surgery are: to ensure that both the LV and RV retain sufficient volume, and to identify the shape of baffle needed for a given patient's surgery. SURGEM provides the information necessary to suffice these two. Similarly, in the TCPC planning, the tool allows the user to connect the inferior vena cava to the pulmonary arteries to bypass a defective ventricle. The design parameters we control are the location and angle of the graft's attachments. Lastly, stent placement procedures can be planned by placing different stent sizes and compare the hemodynamic performance. SURGEM allows clinicians to generate and evaluate geometries for surgical options and generates 3D surfaces that provide the boundaries for blood flow simulations in the heart and nearby vessels. This can then be sent to a computational fluid dynamic solver that can be used to understand the hemodynamic performance. The tool has already been used in 4 DORV, more than 10 Fontan and 5 vessel stenosis cases.

172: A Mobile Device to Enable Access to Pediatric Therapy Apps for School-Age Children with Upper-Body Motor Impairments

J. MacCalla, PhD; Ayanna Howard, PhD

Background: Due to the pervasiveness of tablet devices and their ease-of-use, the emergence of tablet-based applications (apps) for providing rehabilitation and therapeutic interventions for children with disabilities is fast growing. The resulting dilemma though is that with the introduction of the tablet device itself, there is an entire demographic of children with disabilities that become excluded - such as those with neurological movement disorders that include cerebral palsy, traumatic brain injury, spina bifida, and muscular dystrophy. These children are kept from interacting with touch-based tablet computers due to difficulties in 'touching' a specific small region with appropriate intensity and timing (i.e. effecting press and swipe gestures). Methods: Based on the emerging appeal of tablets, there has been a slow influx of switch-accessible apps being created for children with upper-body motor limitations, but most are focused on AAC apps. Thus, in order to fully engage children, especially younger children, with disabilities into the world of tablet-based apps, we have developed a plush switch device that is designed to engage children that have difficulties affecting the common pinch and swipe gestures required for touch-based interaction. The mobile device is designed based on the functionality of the slammer switch (a single-switch input device) into an n-selection wireless input device. The device provides wireless access to the tablet via Bluetooth, implanted within a kid-friendly design made to increase durability and interactivity for children with limited fine motor control. Pressure-based sensors embedded within the plush housing can be grouped together in various configurations, either acting together as one switch or acting independently for increasing functionality. This provides the ability to generate a number of unique commands using the wireless device, which enables conversion of any consistent and voluntary movement from any body part into various tablet-based gestures. Results: A pilot

study evaluating the functionality of the device has shown the viability of usage with children with upper-body motor impairments. Preliminary results with three children with cerebral palsy (male: 2; female: 1; mean(age)=9.6, stdv(age)=1.5) show a response rate when interacting with a cause-and-effect app of 27.4 seconds and an accuracy of 64% as compared with a baseline of 28.2 seconds and an accuracy of 57% when using touch.

173: Wireless Wearable Moisture Sensor RFID System for Treating Incontinence

Blake R. Marshall; Gregory D. Durgin, PhD; Andrew J. Kirsch, MD

The Wireless Wearable Moisture Sensor (WiWeMS) is an inexpensive radio frequency identification (RFID) system to quantitatively measure moisture and wirelessly send the data to a small reader 3 to 5 meters away. Children of all ages and adults with enuresis struggle with incontinence. The WiWeMS monitoring system helps to solve this problem without using a battery or external antennas as other solutions have used in the past by using backscatter radio. The final diaper inlays will use an integrated circuit (IC) to reduce the cost down to $0.16 or less and can be used for various applications such as hospital surveillance, home nocturnal void testing, and daily monitoring in a classroom setting.

174: Higher Obesity Rates Amongst U.S.-Born Hispanic Children When Compared to Their Foreign-Born Counterparts: Is Acculturation the Explanation?

Brenda Mendizabal, MD, MS; Matthew Oster, MD, MPH; Alexandra C. Ehrlich, MPH

Childhood obesity disproportionally affects Hispanic children compared to white children. Many risk factors have been considered regarding the cause of this disparity. The National Health and Nutrition Examination Survey (NHANES) has been able to provide information about the health and nutritional status of children in the U.S, particularly looking at both U.S. born and foreign-born Hispanics. To date, there has been no clear evidence that Hispanic children born in the U.S. are at greater risk for obesity and cardiovascular disease compared to foreign-born Hispanics. Using the National Health and Nutrition Survey (NHANES), we found that U.S born Hispanics have higher rates of obesity compared to foreign-born Hispanics. This holds true even when adjusting for age, sex, socioeconomic status (poverty-to-income ratio), and race/ethnicity. Specifically, amongst Mexican American children, there are still higher rates of obesity among those second generation U.S. born children, compared to the first generation, foreign-born children. Linear regression analysis shows higher BMI z-scores in U.S. born Hispanics, with a p-value of 0.005. Using logic regression analysis, U.S. born Hispanics with BMI z-scores >2 had an OR 2.4 and p-value < 0.001. The Mexican American subset born in the U.S. shows similar results with an OR 1.8 and p-value <0.0056 among those with BMI z-scores >2. With even more striking evidence, when looking at U.S. born Hispanics with BMI z-scores >1, the OR is 1.6 and the p-value is < 0.0007. The Mexican American subgroup born in the U.S. similarly have an OR 4.3 and p-value <0.0134 for those with BMI z-scores >1. There are higher rates of obesity in U.S born Hispanics compared to foreign-born Hispanics, adjusting for age, sex, socioeconomic status, and race/ethnicity. Further research is required to determine whether acculturation is truly the reason for this disparity, or if other factors are involved.

175: Whole Exome Sequencing Identifies ABCB4 as Modifier Gene in Biliary Atresia

Anya Mezina, BA; Khanjan Gandhi, MS; Aniko Sabo, PhD; Madhuri Hegde, PhD; Saul Karpen, MD, PhD

The role of genetic factors in determining clinical outcomes in biliary atresia (BA) after Kasai hepatoportoenterostomy (HPE) is unknown. We performed a pilot study of whole exome sequencing (WES) in 20 BA patients from the NIDDK-supported ChiLDREN dataset to identify variants in genes that stratify between disparate outcome groups: 10 who underwent early transplant prior to age 2 (ET) compared to 10 who survived beyond age 4 with native liver (SNL) and normal platelet count (>150,000). WES identified the ABCB4 phospholipid floppase gene as a candidate gene with disproportionately more non-synonymous (NS) variants in the ET compared to SNL group. ABCB4 mutations are implicated in liver diseases such as Low Phospholipid-Associated Cholelithiasis (LPAC) and may provide a pathophysiological link to worsening cholangiopathy in BA. We hypothesized that deleterious variants in ABCB4 would modulate phenotypic severity and sought to validate this finding in a larger cohort of ET and SNL ChiLDREN subjects. Methods: Sanger DNA sequencing was performed for the 27 coding exons and promoter region of the ABCB4 gene for subjects stratified as SNL (n=97) or ET (n=98). Variants were compared to reference NM_018849.2. Results: ABCB4 sequencing identified 1 splice site, 9 Synonymous and 9 NS variants. The polymorphism, p.A934T, described in LPAC patients, was present in 4 subjects in the ET group and none in the SNL group. All 4 individuals were of African American (AA) race (20 AA in

ET group and 13 AA in SNL group). P.A934T is differentially represented in US racial subgroups, with an AA heterozygote frequency of 2.45%, compared with <0.01% among European Americans. Armitage trend test demonstrated p.A934T was significantly associated with ET outcome when examining all races (p=0.04). Other variants reported in LPAC patients (p.T34M, p.T175A, p.R590Q, p.R652G, p.R788Q, p.E1058K) were similarly distributed among ET and SNL groups. Discussion: This is the first WES study to discover genetic determinants of clinical outcomes in BA and identified ABCB4 as a biologically plausible candidate gene modifier. Heterozygosity for p.A934T is overrepresented among AA subjects with BA requiring early transplantation post-HPE. This finding underscores the utility of WES and subsequent validation studies of one candidate gene in a large, well-phenotyped cohort of racially diverse subjects with BA. Support: NIH (TL1TR000456, U01DK062456, U01DK062470) & Bauer, Spain & Alpard Foundations

176: Development of Live Attenuated Respiratory Syncytial Virus Vaccine Candidates with Improved Immunogenicity and Stability

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Respiratory syncytial virus (RSV) is the most common viral causative agent of respiratory tract infections in infants and young children. Live-attenuated RSV vaccines are the most clinically advanced in children, but current candidates are physically and genetically unstable, and have suboptimal immunogenicity. We are using a RSV reverse genetics system to engineer RSV live-attenuated vaccine candidates to overcome these limitations. We identified a mutation in the RSV fusion (F) gene that enhances virus thermal stability. The F-stable RSV mutant maintains infectious titers at 4°C and 37°C longer than wild-type (wt) RSV. The F-stable mutant also exhibits higher immunogenicity than wt RSV, as measured by neutralizing antibodies induced in mice. Additionally, we are utilizing codon usage bias engineering (CUBE) to down-regulate RSV virulence genes. In CUBE, many synonymous mutations are introduced into the virus to alter codon usage to rare codons, thereby decreasing viral protein translation efficiency. As many silent mutations across a gene additively contribute to CUBE, the risk of reversion (genetic instability) is exceedingly low. We used CUBE to target the RSV NS1 and NS2 genes in combination, as well as the RSV G gene. The CUBE NS1/NS2 RSV vaccine candidate (RSV-dNSh) exhibited significant attenuation in vitro and in mice. Mice vaccinated with RSV-dNSh were completely protected from challenge with wt RSV and had higher neutralizing antibody levels than mice immunized with wt RSV. Thus, we have for the first time generated a RSV vaccine strain that is both attenuated and more immunogenic compared to wt.

177: Asthma Academy: Comparing Educational Technologies for Medication Adherence and Attitudes

Aiswaria Nair; Karen Freedle, MD; Saumya Venkatesan; Chih-Wen Cheng; May D. Wang, PhD

Asthma is a leading chronic disorder among children and adolescents given that on an average, in about 5 of every 30 children are likely to be susceptible to asthma. While transitioning into adulthood, while some children outgrow asthma, there are others who fall prey to extreme spells of asthmatic attacks. The fads and fallacies of teenagers about their asthmatic conditions and its treatment are often not recognized or addressed in clinical consultations. The very fact that asthma, in itself, can be conquered is unknown to a vast majority of patients. There are many reasons why adolescents are reluctant to take their asthma medication, particularly some including preventive therapy and peer pressure. Multiple studies conducted by several health institutes highlight the importance of technological intervention in healthcare education. Adolescents explicitly require human-computer interaction interfcaes which can effectively address the several opportunities and challenges faced by them--especially with respect to engagement with healthcare systems. It is very significant to design health information technologies which target the adolescent population mainly because several health disorders here affect their transition into adulthood. Our application is an interactive education assistant which aims at delivering healthcare education in the most interactive yet effective way. We target adolescents and provide Asthma specific educational content via a six-fold lesson technique in a local environment. The children are subjected to a questionnaire towards the end of every video which assesses what they grasp through the lesson. Thus, having a platform which rewards kids for their regulated activity helps them build skills which could equip them to self-monitor the disease. The Interactive Education Assistant aims to usher in a user centric design perspective and provide a platform which combines knowledge and healthcare threaded in a simple yet effective manner via animated videos. This idea has been developed by Georgia Institute of Technology in conjunction with Children's Healthcare of Atlanta (CHOA). We are aiming to test the efficiency of this application by performing Group based First Click Tests and Heuristic analyses by deploying it to a group of 20-25 adolescents along with complementary medically prescribed tests which shall

evaluate their performance against a backdrop of regular check-ups and assessments over a period of about six-seven weeks.

178: Immediate Postoperative Catheter Intervention Across Suture Lines

George T. Nicholson, MD; Dennis W. Kim, MD, PhD; Robert N. Vincent, MD; Christopher J. Petit, MD

Background: Early postoperative cardiac catheter intervention is regarded as high-risk, particularly when a dilation intervention across a fresh suture line is performed. There are little data available demonstrating the safety of such interventions. The purpose of this study was to examine the outcomes of catheter dilation interventions upon surgical anastomotic sites in the immediate postoperative period. Methods: All catheter dilation interventions performed within 30 days after congenital heart surgery between August 2005 and November 2013 were retrospectively reviewed. Values reported as median and interquartile range (IQR). Our primary endpoint was procedural success, which was defined as an increase in vessel diameter of >75% of the adjacent normal vessel or 50% increase over pre-dilation diameter. Results: Fifty-three patients, median age 0.15 years (IQR 0.03 – 0.51 years), weight 4.1 kg (IQR 3.1 – 6.4 kg), underwent 62 interventional procedures on median postoperative day 7 (IQR 3 – 13 days). At time of intervention, 10 patients were receiving extracorporeal cardiopulmonary support. Among the 62 dilation interventions at surgical anastomotic areas, were 30 stent and 32 balloon angioplasty procedures. There were 3 major complications including: procedural mortality due to tear during angioplasty (n=1), umbilical arterial perforation (n=1), and intimal tear requiring covered stent placement (n=1). There were 12 deaths (22%) prior to hospital discharge. One year postoperative survival was 68% (36 patients). For stenting procedures, the median ratio of stent diameter to initial stenosis diameter was 2.62 (IQR 2.27 – 3.73). For angioplasty procedures, the median ratio of balloon diameter to initial stenosis diameter was 2.27 (IQR 1.84 – 2.94). Conclusions: Though caution is paramount, early postoperative catheter dilation intervention across fresh suture lines can be performed safely in small, critically ill children.

179: Facile and Efficient Surface Labeling for Single-Virus Tracking

Yoon-Hyeun Oum, PhD; Gregory Melikian, PhD

Imaging single virus entry and fusion in live cells is a powerful technique that is capable of providing critical insights into early steps of infection. We have traditionally labeled enveloped viruses by incorporating chimeric viral proteins tagged with GFP or its derivatives. Because of the large size of GFP-based tags, new technologies enabling non-invasive and stable labeling of enveloped viruses with small dye molecules are needed to ensure successful single virus imaging. Here, we introduce a simple, efficient, and generalizable labeling method that minimally perturbs the viral functions. We employed a metabolic oligosaccharide engineering technique which allows the biosynthetic incorporation of unnatural sugar (N-azidoacetyl sialic acid, SiaNAz) into viral envelope glycoproteins. Subsequent “bioorthogonal click chemistry” enables conjugation of various fluorescent dyes with sugars residing on viral envelope glycoproteins. The labeled-viral-surface protein serves as a fiduciary marker for imaging single virus entry and release of viral content (a GFP-based marker) into the cytoplasm. The viral envelope-conjugated dyes showed more than 80% colocalization with a viral content maker, thus providing much improved labeling strategy, compared to genetic labeling previously employed by us and others. This new labeling strategy will enable more reliable detection of viral fusion and early post-fusion events of virus entry.

180: Genomic Characterization of Inflammatory Response and Prediction of Clinical Outcome After Infant Cardiac Surgery

John H. Phan, PhD; William T. Mahle, MD; Po-Yen Wu; Kevin Maher, MD; May D. Wang, PhD

Immediately following newborn heart surgery, there is a profound inflammatory response related to exposure of the blood to foreign materials during cardiopulmonary bypass (CPB). Post-operative expression of pro-inflammatory cytokines (i.e., IL-6 and IL-8) have proven to be correlated with cardiac intensive care unit (CICU) length of stay (LOS). In addition, for high risk infants, the exaggerated systemic inflammatory response significantly increases the risk of neurologic damage measurable by MRI in the form of white matter injury (WMI). This leads to lifelong cognitive deficits. A full understanding of the genomic mechanism for inflammatory response may help (1) identify high risk patients and modify surgical procedures on a personalized basis in order to improve overall clinical outcome; and (2) develop therapeutic strategies targeting specific cytokines to alter clinical outcomes. Thus, we have initiated one of the first studies to characterize the underlying genetic mediators following newborn heart surgery in order to identify potential genomic biomarkers. Using an initial cohort of 56 subjects (for which serum

samples, clinical data, and neuroimaging data are available), we quantified pro-inflammatory cytokines in pre- and post-operative serum blood samples from infants who have undergone cardiac surgery. We confirmed that some pre-inflammatory cytokines, such as IL-8, were significantly correlated with CICU LOS. We then sequenced the exome to identify single nucleotide polymorphisms (SNPs) and other gene polymorphisms in the same pre-operative serum samples. In the final phase of this work, we plan to determine whether SNPs and other gene polymorphisms can independently predict CICU LOS or new WMI, assessed by neuroimaging. At the conclusion of this study, after a thorough functional interpretation of genomic biomarkers, we hope to gain a better understanding of the genomic mechanism for inflammatory response in subjects that undergo cardiac surgery in infancy.

181: Increased Antibody Responses to Porphyromonas Gingivalis in Children with Anti Cyclic Citrullinated Peptide Antibody-Positive Juvenile Idiopathic Arthritis

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Background: Rheumatoid arthritis (RA) is an inflammatory arthritis typically presenting in women in their fifties. Most individuals with RA have antibodies such as anti-cyclic citrullinated peptide antibodies (CCP). In addition, cigarette smoking and periodontal disease (PD) secondary to Porphyromonas gingivalis are risk factors for RA. Some children with juvenile idiopathic arthritis (JIA) phenotypically resemble adults with seropositive RA, by the presence of anti-CCP antibodies. Our objective was to investigate the association between anti-CCP antibodies and anti-P. gingivalis antibodies, as well as the association between anti-CCP antibodies and symptoms of PD, in children with CCP-positive (CCP+) JIA vs. children with CCP-negative (CCP-) JIA. Methods: Study participants included 77 children with CCP+JIA and 130 children with CCP-JIA. Antibodies to P. gingivalis, P. intermedia, and F. nucleatum outer membrane antigen were measured using ELISA in 71 children with CCP+JIA and 74 children with CCP-JIA. Oral health history and smoke exposure history were collected using a parent questionnaire from 37 children with CCP+JIA and 127 CCP-JIA. T-tests were used to compare means between the two groups; Chi-Square or Fisher's tests were used to compare categorical variables. Results: Children with CCP+JIA were more likely to be female (89% vs. 64%), older at the time of diagnosis (10.3 vs. 6 years), and either African American (29.9% vs. 11%) or Hispanic (17% vs. 9.2%) compared to children with CCP-JIA. Anti-P. gingivalis IgG antibody titers were significantly higher in the CCP+JIA cohort than in the CCP-JIA cohort (9.04 vs. 5.69; $p < 0.003$). There was no association between CCP+JIA and smoke exposure in the prenatal period or in the 6 months prior to JIA symptom onset. Several symptoms of poor oral hygiene were higher among children with CCP+JIA: red/swollen gums (35% vs. 20%, $p < 0.08$), tender bleeding gums (41% vs. 24%, $p< 0.06$), pain on chewing (38% vs. 18%, $p < 0.03$), and never/rarely flossing (49% vs. 32%, $p <0.08$). When oral health comparisons were limited to Non-Hispanic white subjects, red/swollen gums ($p <0.003$) and tender bleeding gums ($p <0.002$) were even more prevalent in children with CCP+JIA compared to children with CCP-JIA. Conclusion: Children with CCP+JIA have higher titers of antibodies to P. gingivalis compared to children with CCP-JIA and appear to have symptoms of poor oral health. Smoke exposure and CCP+JIA showed no association.

182: Modeling Pediatric Cardiac Diseases Using Induced Pluripotent Stem Cells

Cardiomyocyte Stem Cell Laboratory, Center for Pediatric Nanomedicine and Center for Cardiovascular Biology, Emory+Children's Pediatric Research Center

In collaboration with researchers at Emory University, Georgia Institute of Technology, and Children's Healthcare of Atlanta, we are developing stem cell models to study pediatric cardiac diseases. Currently, we are focusing on two inherited cardiac diseases: Duchenne muscular dystrophy (DMD) and catecholamine induced polymorphic ventricular tachycardia (CPVT). DMD is the most common and devastating form of muscular dystrophies in children. Muscle weakness is the earliest and most noticeable clinical feature; however, heart problems have now become the leading cause of death in DMD patients. CPVT can lead to life-threatening arrhythmias that are often induced by physical or emotional stress in pediatric patients. There is an urgent need to develop targeted therapies to treat the cardiac abnormalities in DMD and CPVT patients. To this end, we are trying to establish human cell models that can recapitulate diseased cardiac phenotypes using induced pluripotent stem (iPS) cells. Human iPS cells can be derived from patient skin biopsies, and subsequently coaxed to become heart cells. We plan to use these iPS cell-derived heart cells to investigate the mechanisms contributing to cardiomyopathy and arrhythmias, and to investigate the efficacy of potential therapies.

183: Toward an Automated System for Objective Measurement of Problem Behaviors

Aftab Khan, PhD; Andrea Reavis; Nathan Call, PhD, BCBA-D; Thomas Ploetz, PhD; Agata Rozga, PhD

Background: Many individuals with developmental disabilities engage in self-injurious, aggressive, and disruptive/destructive behaviors. Accurate data on the frequency of these behaviors is critical to assessing response to treatment and its generalization to everyday settings. Current methods for gathering data are subjective and either don't capture precise frequency of behavior (parent-report checklists) or are too time- and resource-intensive to deploy at longer time scales and in naturalistic settings (direct observation). Objective: We aim to develop a wearable system to collect automated, objective measures of the frequency and intensity of problem behaviors. We capitalize on the fact that these behaviors are typically linked to intensive and characteristic movements by the individual. Our approach uses low-cost sensors (wrist- and ankle-worn accelerometers) and computational tools (machine learning techniques, namely semi-supervised statistical modeling approaches for sequential sensor data) to automatically detect problem behaviors; to classify them as self-injurious, aggressive, or disruptive; and to measure their intensity. Methods: Data was collected at the Severe Behavior Clinic at Marcus. Three clinic staff enacted a variety of problem behaviors they typically observe (11 two-minute sessions; 1214 problem behavior events). 3-axis accelerometry data has also been collected from 15 individuals with autism in the course of their clinic assessments. To date, one child's data has been analyzed and is reported below (50 minutes; 325 problem behavior events). Results of the automated analysis were compared to human coding from video. Results: In the simulated data, our approach detected problem behaviors with an average precision of 42% and recall of 95%, and differentiated among the three classes of problem behavior with an average 80% accuracy. Analysis of data from the participant with autism resulted in precision and recall of 31% and 81% respectively, and an accuracy of 70%. Conclusions: We developed a body-worn sensing system and activity recognition techniques that effectively gather objective measures of the frequency of problem behaviors. While data analysis is ongoing, preliminary results demonstrate the feasibility of our approach for automated detection and classification of these behaviors. Our approach holds promise for gathering objective, quantitative data on problem behavior in naturalistic settings and over longer time scales.

184: Improving NICU Soundscapes to Improve Outcomes

Erica E. Ryherd, PhD; Jonathan Weber; Ashley Darcy Mahoney, RN, PhD; Ira Adams-Chapman, MD, MPH; Julie Swann, PhD

Healthy soundscapes are paramount to the missions of hospitals: patients need to sleep and heal with minimal environmental stress, and staff members need healthy working environments conducive to care processes and communication. Critical care wards such as Neonatal Intensive Care Units (NICUs) are of particular concern due to the extremely sensitive nature of the patient population. Concerns are rising over soundscape-related infant sleep disturbance, stress responses, hearing loss, retarded growth, cognitive and attention disorders, and speech and language problems. Although the NICU noise literature dates back 40+ years, even recent studies show that ambient NICU noise often exceeds recommended levels. This problem occurs in part because there are large and pressing gaps in the literature that must be filled before adequate evidence-based recommendations for reducing NICU noise can be implemented. This presentation will discuss what is known about the NICU soundscape, including opportunities for advancement. A pilot study will be introduced that aims to link detailed acoustic characteristics with occupant outcomes. The study is a unique collaboration between engineering, architecture, nursing, and medicine. Results will be used to identify and evaluate soundscape interventions and therefore advance understanding of how to design and implement healthy NICU soundscapes.

185: Platelets as Contractile Nanomachines for Targeted Drug Delivery in Hemostasis and Thrombosis

Yumiko Sakurai, MS; Caroline Hansen, BS; Andrew Lyon, PhD; Wilbur A. Lam, MD, PhD

Cardiovascular disease is the leading cause of death in the U.S. and an obvious public health problem. However, few efficacious therapies have been successfully developed to treat thromboembolisms that cause myocardial infarctions or strokes. A significant clinical need therefore exists for newer therapeutic strategies that can specifically target thrombotic lesions in real time and undergo "smart" release. Here we present a novel potential "smart" drug delivery system using the patient's own platelets as the sensors and actuators. Upon the activation, platelets bind to fibrin/fibrinogen and contract, performing physical work. As such, the platelet's contractile nanomachinery, which pulls with nanonewtons of force, can be leveraged for controlled rupture of the delivery vehicle and therefore, drug release. Activation of our system would occur only at sites of platelet agonist, such as

thrombin and ADP, are generated from developing thrombotic lesions, enabling specific targeted drug delivery. Fibrinogen coated emulsion droplets (5-50 µm in diameter) were prepared by homogenizing fibrinogen solution in PBS, containing 30% dodecane dyed with Sudan Black. We successfully created an in vitro model for thromboembolic lesions: heparin-treated human whole blood was perfused into a collagen-coated microfluidic device, which caused development of micro-scale thromboembolic lesions containing activated platelets and fibrin clots. When fluorescently tagged fibrinogen emulsion droplets were perfused into the device, they were trapped onto those "micro thrombi" via binding between fibrinogens on emulsion surface and platelet αIIbβ3 integrins. We also demonstrated and visualized the capture of single emulsion droplet on single activated platelet. Next, isolated and washed human platelets suspended in a buffer with calcium and magnesium were perfused into our microfluidic, which was filled with emulsion droplets trapped on micro-thrombi. Time lapse confocal microscopy images revealed that taken upon contact to the immobilized emulsion droplets, platelets instantly adhered and aggregated onto the emulsion surfaces coated with fibrinogen. These aggregated platelet masses then contracted 21.7% (SE ± 4.1) in size. Ongoing work focuses on optimizing the conditions, such as surface modification of our emulsion droplets and inclusion of different platelet agonists including thrombin, to induce cargo release. Our system will then be tested in animal thrombosis/bleeding models.

186: Establishment of Pre-Clinical Animal Model for Juvenile Osteochondritis Dissecans

Giuliana E. Salazar-Noratto, BSc; Nick J. Willett, PhD; Hazel Y. Stevens, BSc; Angela S. P. Lin, MSc; Dalia Arafat, MC; Greg Gibson, PhD; Robert E. Guldberg, PhD

Juvenile osteochondritis dissecans (JOCD) of the knee is a condition that predominantly affects adolescent and young adults, with a higher incidence in those who are athletically active and involved in organized sports. JOCD involves the formation of a lesion in the subchondral bone with secondary effects in the overlaying cartilage. During late stages of this musculoskeletal disorder, the lesion becomes unstable and separation of the osteochondral fragment ensues. JOCD can lead to pain, swelling, and may progress to early onset osteoarthritis. Its etiology and progression are not well understood, and this has led to limited therapeutic options. Furthermore, there are no disease models which recapitulate the development and progression of the disease. A mechanically-induced lapine model is currently available; however, this model only replicates a severe late stage in which the fragment is completely separated from the native bone. Therefore, a new pre-clinical model is needed such that the full disease progression mechanisms can be more fully understood, with a view of developing and testing new therapeutic interventions. The objective of this study is to develop and characterize a small animal model that will reproduce the progression of JOCD. An in vitro model of JOCD has been developed with the end goal of extrapolating the technique to an in vivo model. Pediatric rat femurs were harvested for explant culture. Lesion location was accessed through the lateral aspect of the medial femoral condyle, to an area just below the subchondral bone layer; and varying doses of monosodium iodoacetate (MIA) were injected to chemically induce the initial lesion. Forthcoming data will include contrast-enhanced µCT and histology evaluations of articular cartilage morphological changes in relation to the progression of the lesion as well as assessment of cartilage integrity by its proteoglycan content. Gene expression will also be analyzed. The in vitro MIA dose study will be presented in addition to the preliminary results from the in vivo pilot study. Establishing a small animal model of JOCD with the ability to emulate the progression of this disorder may serve as a platform to explore novel treatment procedures.

187: Towards Personalized Treatment for Osteochondritis Dissecans Based on Genomics and Micro-CT Imaging

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Juvenile osteochondritis dissecans (JOCD) of the knee is a musculoskeletal disorder that primarily affects the subchondral bone, with a secondary effect on the overlying articular cartilage. This condition can lead to pain, restricted motion of the knee, and formation of osteochondral fragments. Its etiology is unclear; JOCD is thought to be multifactorial with an underlying genetic influence, as suggested by the occurrence of this disorder in more than one family member and as polyarticular in some individuals. However, to this date, no study has investigated the covariance of the pathological characteristics and gene expression of JOCD. Previous research is predominantly composed of retrospective clinical studies. Insufficient information on JOCD hinders optimization of treatments and halts the design of new, innovative technique approaches. The purpose of this study is to characterize OCD in young individuals in order to gain new information about this disorder, with the long-term objective to develop a

bench-to-bedside program to better diagnose and treat this disorder. Our goal is to integrate morphometric and structural properties (EPIC-μCT and histology) with genetic data (RNA-sequencing) to evaluate the association between JOCD pathology and gene expression profiles. Human biopsy samples are currently being collected from 10 JOCD patients. Contrast-enhanced micro-CT will be used to evaluate articular cartilage morphology and bone structure in 3D. The integrity of the articular cartilage will also be assessed in terms of its proteoglycan content. RNA will be extracted and used to assess transcript abundance genome-wide. Preliminary results for a subset of patients will be reported. This study aims to classify JOCD patients by relating their gene expression profile to tissue degenerative changes, and thereby facilitate personalized treatment of the disorder.

188: The Effects of Race, Ethnicity, and Maternal Education on Diagnostic Profiles of Children with ASD

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Introduction: Research has shown that socio-cultural disparities are greater in children with ASD compared to other developmental disabilities (e.g., Magana et al., 2012). Black and Hispanic children with ASD are diagnosed later than White children (e.g., Valicenti-McDermott et al., 2012), and children with ASD tend to live in geographical areas comprised of adults with higher education and family incomes (Durkin et al., 2010). Methods: Participants included a clinically-referred sample of 157 toddlers (83 with ASD; 47 with DD; 27 with No Diagnosis; 28% female) between the ages of 10 and 30 months (Mean=22.11m; SD=4.31). Participants by Race: 100 White; 31 Black; 23 Mixed; 1 Asian; 2 Unknown). By Ethnicity: 134 non-Hispanic; 15 Hispanic. By Maternal Education: 28 High School or less; 49 Some College; 71 College or more. Measures included the Mullen Scales of Early Learning, Vineland Adaptive Behavior Scales, Second Edition, and the Autism Diagnostic Observation Schedule. Results: Analyses revealed no significant differences in age of diagnosis by race or ethnicity for the ASD, DD, or TYP samples. Children with ASD whose mothers had college or more degrees were diagnosed earlier (Mean age=21.54m) than children with mothers with only some college [Mean age=24.29m; $F(2.79)=4.82$; $p<.05$]. Within the ASD group, no significant differences were found in developmental, adaptive, or diagnostic features by race or ethnicity. Chi-Square analyses revealed no significant effects of race or ethnicity by diagnostic outcome or by maternal education, but did reveal a significant effect for maternal education by diagnosis, with 90% of mothers of children with ASD having at least some college or higher compared to only 60% of the DD sample and 86% of the TYP sample [$\chi 2(4)=22.61$; $p<.001$]. Conclusions: Results indicate that for toddlers with ASD, race and ethnicity have no effect on age of diagnosis and no bearing on developmental, adaptive, or diagnostic features suggesting that when ascertained early, racial and ethnicity factors do not appear to influence severity of ASD diagnostic or developmental features. Consistent with previous studies, the only factor contributing to lower age of ASD diagnosis is maternal education, which does not appear to be influenced by race or ethnicity. Given that most children are not diagnosed until after age 4, future studies need to investigate factors impeding access to clinical care.

189: SmashCap: Reduced Touch Contamination Connector

Joseph Schultz, MD

In recent years Hospital Acquired Infections (HAIs) have been identified as a major focus for quality and patient safety improvements. These HAIs include BSIs (Blood Stream Infections), e.g. higher profile CLABSIs (Central Line Associated Blood Stream Infections). Infection control and prevention efforts have generally been focused on surveillance and implementation of techniques and "bundles." These assure the aseptic insertion of central lines, improve the cleanliness of the female receiving hub and reduce access events. There have been some technologic efforts to improve the hub and skin preparation. There have also been efforts to determine which needleless valve designs are less prone to infection. Unfortunately most of these valved connector designs have features that make the mechanical connection with male luer connectors more difficult. Meanwhile, the potential role of the male luer connector in causing infection has largely been ignored. The ISO-594-2 international standard for male luer locks dictates that the male luer tip extends 2.1mm beyond the luer locking collar. This small bore exposed tip design makes it difficult to assemble and prone to contamination. Our hypothesis is that the design of standard male luer connectors is a significant cause of all BSIs. By changing the distal end connector to a recessed tip, the tip will become less prone to infection during connection. It is expected that this will also translate into fewer BSIs. To practically implement a change to the billions of luer connectors used each year, design constraints have been studied. Proposed solutions are being evaluated to provide a universally compatible retrofit system; a highly compatible proprietary system and/or a design that will allow simple modification of existing manufacturing tooling. Early stages of research have involved design, prototyping and production of new medical connectors. Next

benchtop testing has been done to document in vitro effectiveness of contamination reduction. Concurrently determination of the regulatory pathway and manufacturing of the devices has been begun with the goal of small production runs for clinical testing. Future goals are to obtain grant or industry funding to permit larger scale production and introduction of the reduced touch contamination connectors; and then test in larger populations whether these new connectors will lead to improved patient safety and reduced healthcare costs.

190: RheumMate: An mHealth Application to Improve Patient Engagement, Research and Disease Management of Children with Rheumatological Disease

Prabhu Shankar, MD, MS; Jiten Chhabra, MD, MS; Rob Solomon, MS; Sampath Prahalad, MD, MSc

Patients with chronic arthritis are required to report subjective levels and locations of joint pain, swelling and joint mobility, and give global assessment of their disease to their care providers. This is vital for accurate assessment of affected joints, diagnosis, as well as decision making and management. The providers use this data to evaluate effectiveness and change or escalate therapy based on the American College of Rheumatology guidelines. Further, joint pain, swelling and range of movement are central to many disease activity scoring systems, underscoring the importance to accurately record them. Based on the severity of the arthritis, disease activity monitoring requires frequent visits to healthcare providers. As it affects joints, travel can be cumbersome to both patients and families. Alternate ways to capture patient-generated data accurately and to assess patients remotely for evidence based practice are needed. Further, there is increased impetus nationally to use patient-generated data as a critical tool for population health management and to improve efficiency of care delivery. The ubiquitous mobile devices can play a major role and stakeholders can be empowered with better mobile applications that change the way care is delivered. The use of mobile devices can increase access to specialists, reduce resource utilization and impact healthcare affordability. We are following a user-centered design process to develop and evaluate such an application for IOS7, to manage chronic arthritis. Our stakeholder interviews and human-computer interaction literature about persuasive health applications has uncovered the need to integrate Game Design into our prototype joint diary application. Our goal is to test the hypothesis that the features, interaction flows and game mechanics that we have integrated into our application will result in sustained engagement from our end users and provide accurate clinical information to the care team. The results from our work could be extended to other interactive mobile interventions which are becoming increasingly popular due to their low cost of development and massive scaling potential. The reliable, consistent and discrete data captured by our novel artifact, will further support research and aid, comparative effectiveness and outcomes studies. To the best of our knowledge, this is the first effort to develop and test a mobile application to capture and communicate joint pain and other joint parameters.

191: Emergence of Social Engagement in Infants at High and Low Risk for ASD as Indexed by Cry

Yael Stern, BS; Shweta Ghai, PhD; Ami Klin, PhD; Gordon Ramsay, PhD

Background: Within the first months of life, infant cry evolves from a reflex into a volitional prelinguistic vocalization used to negotiate social interactions. Previous work has demonstrated that acoustic and durational features of cries determine parental perception of and response to cry, in typical development and in developmental disorders other than autism. As studies have shown that cry of infants at high genetic risk for ASD and toddlers with ASD have atypical characteristics, it is important to understand whether these atypicalities affect the quality of emergent social engagement between infants at risk for ASD and their caregivers. Objectives: The goal of this study was to determine whether the social function of cry is disordered in infants at high genetic risk (HR) for ASD, relative to those at low genetic risk (LR) for ASD, before deficits in social communication apparent in speech may emerge. We explore the hypothesis that high-risk infant cries evoke maternal responses that less effectively capitalize on the social value of cry, compared to cries of low-risk infants. Methods: As part of a larger NIH Autism Center of Excellence tracking vocal development in 230 HR infants and 100 LR infants, digital audio recording devices were sent to families' homes monthly, beginning at 1-2 months, for making day-long, naturalistic recordings of infants' vocalizations. In this study, we focused on an exhaustive analysis of 2 high-risk infants and 2 low-risk infants, at three time points between 1 and 6 months. We segmented cries and the corresponding maternal responses to these cries using a customized coding scheme. We then evaluated the nature of infant cry and maternal response to cry. Results: The quality of response to cry differed perceptually between the high-risk and low-risk infants. Maternal response to high-risk infant cry was less sustained and less varied than response to low-risk infant cry. Further, while cry was a definite means of communication for several of the low-risk infants by 6 months, one of the high-risk infants hardly cried at all throughout the 2-month recording. Conclusion: Systematic atypicalities in cry are likely to provoke sustained changes in interactional style between parent and child. The adaptive social function of

cry may be weakened in interactions between mothers and their high-risk infants. Sponsors: National Institute of Mental Health (P50 MH100029), Simons Foundation, Marcus Foundation, Whitehead Foundation.

192: Structural Characterization of Tethered HIV-1 VLPs by Light Microscopy and Cryo-Electron Tomography

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Tetherin (BST-2/CD317/HM1.24/PDCA-1) is a cellular restriction factor that prevents the release of enveloped viruses by physically linking virions to host cell plasma membranes. Determining the structure of the linkage between tethered HIV-1 and the host cell will enhance our understanding of cellular immunity and viral pathogenesis. Tetherin is a type II integral membrane protein composed of a short N-terminal cytoplasmic tail, a single transmembrane domain, a long extracellular ectodomain, and a C-terminal glycosyl-phosphatidylinositol (GPI) anchor. Ectodomain-dependent dimerization, membrane insertion of the single transmembrane domain and GPI anchor are required for viral retention. The spatial orientation and geometric arrangement of tetherin molecules engaged in viral retention remains unknown. The long-term goal of this investigation is to elucidate the biophysical mechanism underlying tetherin-mediated restriction of HIV-1 in the near-to-native state and in four dimensions (4D). To achieve this goal we use novel correlative imaging methods to directly visualize tethered virions and virus like particles (VLPs) attached to human cells. For this project HT1080 cells were grown directly on transmission electron microscopy (TEM) grids and transfected with eGFP-Tetherin and HIV-1 mCherry-Gag to produce HIV-1 VLPs tethered to cell membranes. Fluorescent light microscopy was used to characterize cell morphology and identify transfected cells that possessed regions enriched in tetherin and HIV-1 VLPs. Suitable samples were plunge-frozen and were then subsequently imaged by cryo-electron tomography (cryo-ET). In the three-dimensional reconstructions (tomograms), rod-shaped densities were seen linking together tethered HIV-1 VLPs. Detailed structural analysis of the tomograms is currently underway and will provide insight into the organization of the tethered HIV-1 VLPs and the spatial organization of tetherin molecules.

193: Asthma Baseline for Children in the Georgia Medicaid Program

Julie Swann, PhD; Nicoleta Serban, PhD; James Bost, PhD; Kevin Johnson, BS

Pediatric asthma is a significant problem affecting more than 10% of children age 0-10 and 15% of middle and high school students. To evaluate the impact of interventions, or to design interventions to have the greatest impact with limited resources, it is useful to understand the status quo within a system. This study uses retrospective Medicaid claims data to develop and quantify a set of measures around pediatric asthma in Georgia geographically and over time. The baseline measures were calculated using Medicaid MAX claims data for Georgia from 2005-2009. The baseline is built on several sets of measurements for costs, utilizations, and outcomes as outlined in the literature for asthma surveillance and management. We quantify visits to the emergency department and hospitalizations, by age group, by location and the costs of those services. We also develop measures to identify patients with persistent or severe asthma, and identify patients with uncontrolled asthma using medication information. We generate measures for patients and providers, within areas such as counties and at the state-wide level. We perform statistical analysis to determine significant variations in cost and outcomes across the network and associated factors. The findings include a set of baseline measures for pediatric asthma in Georgia 1) overall, 2) by geographical area, and 3) over time. The findings include basic measures (e.g. number of asthma visits by provider, age, location, etc.) along with more complex measures. These complex measures include use of appropriate medication, medication adherence, and controller medication ratio. Significant variations exist geographically within the state of Georgia, and some measures show changes over time. The cost measures tend to be higher in urban areas and vary by income of the associated geographies. Differences also exist by provider. Baseline measures for pediatric asthma are useful for both providers and payers in designing and evaluating interventions. The data can inform where interventions are needed the most in the system. The results from the study were used to inform ongoing asthma intervention projects within Georgia. Developing a baseline for asthma and an approach for targeting interventions for the most impact could also serve as a model for other types of diseases or conditions.

194: Determinants of Anemia Among School-Aged Children in Two Countries with Moderate and Low Anemia Prevalence

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BACKGROUND: Anemia affects approximately half of the global population of pre-school children and a quarter of the world's school-aged children (SAC). Anemia in children is most often ascribed to iron deficiency; however, other nutritional, infectious, and socio-economic determinants are often not measured. There is a lack of data on reliable international estimates of anemia and its determinants in SAC. Such statistics are important to guide anemia prevention and treatment programs. We aim to measure, in two countries with moderate and low anemia burden (Colombia and the USA, respectively), the prevalence of anemia in SAC and the association of anemia with anthropometric indices of growth (stunting, wasting, underweight, overweight, obesity), micronutrient deficiencies (iron, vitamin A), inflammation (using elevated acute phase proteins), demographic factors (age, gender, ethnicity, house-hold size) and socio-economic dynamics (income, education). METHODS: We used data from two cross-sectional surveys. Colombian data was from the 2010 Colombia National Survey of the Nutrition Situation (ENSIN). In the USA, data was from the 2003-2006 National Health and Nutrition Examination Survey (NHANES). Inclusion age was 5-15y. Sample size was 11274 in Colombia; 3605 in the USA. RESULTS: Preliminary data from the ENSIN data: mean age of the study participants was 10.5 y (SD 3.0), 51% were males. Hemoglobin had a mean of 14.0 (SD 1.6) mg/dL. Preliminary data from the NHANES data: mean age of the study participants was 10.4 y (SD 3.0), 49% were males. Hemoglobin had a mean of 13.5 (SD 1.0) mg/dL. Anemia prevalence will be calculated in each country and 95% confidence intervals computed. We plan to study the associations of our selected variables with anemia using bivariate logistic regression models. Subsequent analyses using a similar approach are also planned on pooled data from both countries. This is to compare associations of the leading factors found to be associated with anemia in this group of school-aged children across three countries. CONCLUSION: The completion of this study and its proposed outcomes will add to our knowledge of important determinants of anemia in school-aged children and to our understanding of cross-country differences. The potential impact of this analysis is far-reaching as results from this analysis will help inform policy and development of strategies to reduce anemia in diverse settings.

195: Continuous Nanoparticle Size Separation Using Microfluidic Technology

Bushra Tasadduq; Gonghao Wang; Wilbur Lam, MD,PhD; Alexander Alexeev, PhD; Todd Sulchek, PhD

High throughput size based separation of nanoparticles is important to improve the purity of pharmaceutical nanotherapeutics and to better understand and improve diagnosis of diseases that involve nanoparticles. Platelet microparticles are nano-sized platelet fragments that play an important role in hemostasis and thrombosis. The levels of platelet microparticles are elevated in patients with conditions as diverse as cardiovascular disease, diabetes, and leukemia, a common cancer in children. Due to lack of nanoparticle separation technologies, one cannot quickly separate platelet microparticles into homogeneous subpopulations for study and diagnosis. We propose a novel microfluidic device capable of continuous size-dependent separation of particles. The separation device will consist of a microchannel with periodically arranged diagonal ridges. The key to the separation is that the these diagonal ridges create helical flow fields. Simultaneously, inertial particle migration alters the particle height in a size-dependent manner, which then exposes the particle to different secondary flows. The height-dependent secondary flows then cause particles with different sizes to migrate transversely with unique trajectories. Our experimental data reveals that microparticles with different sizes separate laterally as they flow in the ridged microchannel. We are working on separating nanoparticles using the same device and studying the effect of flow rates, density and channel height on separation. The future work includes separation of blood-derived platelet microparticles into size fractions.

196: Measuring and Reducing Acoustic Noise in MRI Studies of Infants: A Review of Existing Guidelines and Development of New Methods

Michael Valente, BS; Sarah Shultz, PhD; Ami Klin, PhD; Warren Jones, PhD

Background: MRI is an important tool for charting brain development. However, one disadvantage is the intensity of acoustic noise scanners generate while in operation. With noise levels reaching up to 120db, hearing protection is critical to ensure the safety of infant participants. Effectively reducing noise exposure in infant populations poses unique challenges that are not readily met by commercially-available hearing protection devices (HPDs). Common HPDs do not have a mechanism to gauge if attenuation has been reduced during a session due to movement of

the HPD. These HPDs rely on proper initial placement to facilitate noise reduction. In addition, few guidelines exist for what constitutes an acceptable level of noise in an MRI study of infants or how to reliably measure infants' acoustic environment. In the current study, we aim to attenuate the intensity of noise levels during infant MRIs. Objectives: The aims of this project are to: (1) review existing guidelines for sound measurement and attenuation in MRI studies of infants; (2) record accurate measurements of acoustic emissions from a Siemens 3T Tim Trio to determine the amount of sound attenuation necessary for a safe infant scan; and (3) create a HPD that provides sufficient sound attenuation and allows researchers to monitor the level of sound attenuation in real time, thereby ensuring effectiveness. Methods: Studies on acoustic emissions from MRIs, ANSI standards for measuring HPD effectiveness, and sound conduction pathways in the human body were reviewed. Acoustic emissions generated by the MRI and the effectiveness of a HPD designed for infants will be measured and tested in 1-to 9-month-olds (n=20). Results: The attenuation properties of our HPD will be tested outside the scanner by playing recordings of scanner sounds (at reduced amplitudes (~60db). Attenuation will be measured with built-in MR-safe microphones outside each ear. The noise reduction (NR) scale will be used in recording these measurements with the transfer function of open ear correction to account for natural amplification by the pinna and ear canal. Conclusion: This research demonstrates a first step towards the development of an HPD, custom-made for infants, that reduces scanner noise to a safe level and allows real-time monitoring of the effectiveness of the HPD. Using the principles learned from the existing literature, our immediate next steps include completing the design and testing of this customized HPD.

197: Towards an Interactive Education Assistant for Transition in Pediatric Sickle Cell Care

Saumya Venkatesan; Anya Griffin, PhD; Aiswaria Nair; Chihwen Cheng; Ify Osunkwo, MD; May. D. Wang, PhD

Sickle cell disease is one of the leading chronic diseases and reasons for hospitalization among adolescents. A sound transition from child care to adult care is very significant for adolescents with a history of sickle cell disease. The fads and fallacies teenagers have about their medical condition and its course of treatment are often not recognized or addressed in clinical consultations. Improving patient knowledge has been shown to positively ameliorate patient engagement, compliance and ultimately improve the patient's personal hold over his condition. Although patient education is important, it is time consuming and not all individuals respond to the same style of education, which makes it challenging for providers. Studies conducted by several health institutes highlight the importance and utility of technological intervention in healthcare education. Children are known to respond favorably to human-computer interfaces which can effectively address the challenge of patient education and engagement in health care system. It is important to design health information technologies which target the adolescent population and can be used to improve health care outcomes. Our application is an education assistant which aims at delivering healthcare education in an interactive yet effective way. We target adolescents and provide SCD specific educational content via a six-fold lesson technique through our application in the form of animated videos. The children complete a questionnaire towards the end of every video which assesses what they comprehended from the lesson. This platform rewards kids for their regulated activity, and helps them build the skills that can equip them to self-manage their chronic illness. The Interactive Education Assistant was designed with a user centric design perspective wherein it ushers in a platform that combines creativity, design and healthcare intervention in a simple yet effective manner. This idea has been developed by the Bio-MIB laboratory at Georgia Institute of Technology in conjunction with Children's Healthcare of Atlanta (CHOA). We are aiming to test the efficiency of this application by performing usability testing experiments by deploying it to a group of 20-25 adolescents. We shall record their performance throughout the session and include the results of the complementary medical tests to evaluate their performance against a backdrop of regular check-ups and assessments over a period of about six-seven weeks.

198: Time-Series Data Analysis to Predict Mortality and Cardiac Arrest in Pediatric Populations

Janani Venugopalan; Ryan Hoffman; Chih-wen Cheng; May D. Wang, PhD

More than 5 million patients are admitted annually to ICUs in the United States, with children and adolescents accounting for 18% of the hospital stay. Studies have also shown that prolonged duration of intensive care unit (ICU) stay has significant contributions to increased life-threatening outcomes such as cardiac arrest, mortality, ICU/hospital readmissions, and acute kidney injury. Analysis of patient data to predict adverse events have been largely performed on adults and have made use of techniques such as logistic regression (LR) or artificial neural networks (ANN). These models use only a snapshot of data available to make predictions. This is opposed to medical practice, where physicians rely on temporal data to make interventions. In addition, these models either fill in missing data or delete records with missing values. Filling in of missing values is done using population

averages or the means of the dataset. This introduces errors in the data and does not reflect the underlying disease. The deletion of records with missing values does not help in the ICU, since not all values are obtained because tests or measures are only recorded when the clinical team suspects a clinical condition. In this study, we address these issues by proposing a retrospective study of pediatric population to discover factors indicative of mortality and cardiac arrest, using Conditional Random Field (CRF) models capable of making prediction of time series data by utilizing the parameters learned from a large patient population. In ICU clinical decision support, CRF modeling is advantageous over LR because, CRF handles missing data and accounts for the inherent time series relationship. We test our models using de-identified data from Children's Healthcare of Atlanta containing 5000 patient records spanning an 11 month period. Each ICU stay record consists of the patient's demographic information, diagnosis, birth related events, microbiology and laboratory events. The dataset consists of approximately 15 million entries covering over 150 parameters. After outlier removal, we perform feature selection using Maximum Relevance (mRmR) technique and use the reduced parameter for subsequent modelling. In this study we compare CRF with traditional techniques of LR and feed-forward ANN for patient data derived from pediatric populations using 10 x 5 cross validation using accuracy and area under the curve as performance metrics.

199: Continuous Electroencephalography for Nonconvulsive Seizures in Pediatric Intensive Care Units: Who to Monitor and How long?

Mingyoung Jo, BS; Qing Li, BS; Jan Vlachy, MS; Larry Olson, MD; Atul Vats, MD; Pinar Keskinocak, PhD; Julie Swann, PhD; Turgay Ayer, PhD

Background: Nonconvulsive seizures can be detected using continuous electroencephalography (cEEG), but there are currently no reliable guidelines for pediatric ICU (PICU) about which children to monitor and how long to monitor them. The objectives of the study were 1) to review a single PICU's experience with cEEG, 2) to develop a predictive model for the seizure risk taking into account different diagnoses and the effect of multiple diagnoses, and 3) to test if the optimal monitoring time varies by diagnosis. Methods: This was a retrospective study on 517 children monitored by cEEG in the PICU of the Children's Healthcare of Atlanta. Logistic regression was used to assess seizure risk and likelihood of a long time (> 6 hours) to first seizure, using referring diagnoses, occurrence of previous seizures, and stratification on age. Several seizure risk models were compared for predictive accuracy according to misclassification rate and AUC. To further assess the effect of diagnosis on monitoring time, the mean time to first seizure by diagnosis was tested using the t-test. Results: For children under 12 months, hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage (ICH), previous seizures, and CNS infection were associated with significantly higher risk of seizures (alpha=0.05). Simultaneous ICH and HIE, or ICH and trauma further aggravated seizure risk. Seizures manifested in 46% of monitored children under 12 months. The logistic regression model for children under 12 months achieved AUC equal to 0.69. For children over 12 months, the analysis did not reveal any significant risk factors. Having multiple neurological diagnoses was associated with higher seizure risk for both age groups. Children (all age) with spells and CNS infection had significantly lower average time to first seizure. Children over 12 months with ICH and under 12 months with HIE were significantly more likely to have long time to first seizure. Conclusions: Incidence of seizures is higher in younger children, particularly those with HIE, ICH, previous seizures, or CNS infection. We recommend to monitor all PICU patients under 12 months with one of these conditions or with multiple neurological diagnoses; other patients must still be considered on a case-by-case basis. A larger prospective study is needed to further elucidate the effect of multiple-diagnoses interactions, risk under younger patients, and provide guidelines on required monitoring time for different diagnoses.

200: Altered Beta-Adrenergic Signaling in Newborn Human Ventricular Myocytes

Guoliang Ding, MD, PhD; Hua Cheng, PhD; Xioaping Jin, PhD; Ming Shen, BS; Gitanjali Baroi, BS; Brain E. Kogon, MD; Kirk Kanter, MD; Mary B. Wagner, PhD

For children with congenital heart disease (CHD), therapies developed for adults may have different effects on immature myocardium. Thus, to develop therapies for young cardiac patients, it is critical to understand calcium handling in the developing human heart. Methods: Human ventricular cells were isolated from tissue removed as part of the surgical repair for CHDs. Newborns (<1 week of age) were compared to infants (2-12 months of age). Single cell patch clamp was performed to isolated calcium current (ICa). Dose response curves for isoproterenol (beta1 and beta2-adrenergic agonist) and for zinterol (beta2-adrenergic agonist) were measured. mRNA levels of beta-adrenergic receptors were measured by real time PCR. Results: Both newborn and infant cells had a robust increase in ICa in response to isoproterenol. Dose response curves in response to isoproterenol had similar Emax

for newborn compared to infants (159±12% vs. 154±19%, n=4-9). EC50 was shifted to the left slightly in newborn compared to infants (2.4±1.8 nM vs.5.9±2.9 nM) which was associated with higher levels of the inhibitory G protein isoform, Gialpha3, in newborns (0.90±0.08 vs. 0.52±0.07 a.u., $p<0.05$, n=6). In contrast, zinterol was significantly more effective in increasing ICa in newborn compared to infant (147±36% vs. 52±18%, n=8-12, $p<0.05$). To begin to understand this difference, we examined mRNA levels of beta1-adrenergic receptors (beta1-ARs), beta2-ARs and caveolin-3 (Cav-3) in newborn (n=6), young infant (3-5 mos., n=5) and older infants (6-12 mos., n=5) human ventricle. We found a dramatic (nearly 5 fold) increase in beta1-AR mRNA levels with no changes in beta2-AR mRNA levels between newborns and infants. Furthermore, the levels of beta1-AR increased very early in the postnatal period. These results suggest that the overall beta-AR density may increase with postnatal age in humans and that the ratio of beta1/ beta2 may also change. Cav-3 is a protein that associates with beta2-ARs and we show that mRNA levels decrease with increasing age. Conclusions: Newborn human ventricular cells have a similar response in calcium current to a dual beta1/beta2 agonist but have a greater response to beta2 agonist alone compared to infant cells. This is associated with higher levels of Gialpha3 and beta2 ARs in the newborn. Alterations in sympathetic stimulation with developmental age may suggest novel inotropic agents for the newborn pediatric cardiac patient.

201: Enrichment of Cardiac Subtypes from Human Pluripotent Stem Cells Using Molecular Beacons

Rajneesh Jha, PhD; Brian Wile, PhD; Gang Bao, PhD; Chunhui Xu, PhD

Cardiomyocytes derived from human pluripotent stem cells (hPSCs) represent an opportunity to regenerate cardiac tissues in over 1 million cardiac disease patients in the United States. The current hPSC-derived cardiomyocyte preparations include non-cardiac cells and cardiomyocytes of both nodal and working subtypes. The preparations of mixed cell populations pose risks including teratoma formation and arrhythmias; therefore, further purification of subtypes without losing their functional properties is required. We have tested relative expressions of several nodal and working markers during the course of cardiac differentiation and compared them with undifferentiated cells. Further we have identified and designed molecular beacons (MBs) to target nodal (T-box 3; TBX3 and Short stature homeobox 2; SHOX2) and working (Natriuretic pre-peptide A; NPPA and Myosin regulatory light chain 2; MYL2) cells and confirmed their specificity by microplate solution assays. We have also made over-expressing target genes in NIH-3T3 (ATCC) cell-lines to screen these MBs to be tested in cardiomyocytes. The selected MBs will be used to generate enriched nodal or working cells for functional characterization. The method developed in this study will facilitate clinical applications of hPSCs.

202: Preference-Sensitive Risk Cutoff Values for Prenatal Integrated Screening Test for Down Syndrome

Jia Yan, MS; Turgay Ayer, PhD; Pinar Keskinocak, PhD; Aaron B Caughey, MD, PhD

Objective: Down syndrome (DS) is the most common chromosomal abnormality. For a pregnant woman considering integrated prenatal screening, there are at least two major outcomes of interest: undetected DS live births (O1) and euploid procedure-related fetal losses (O2). One-size-fits-all type risk-cutoff-values (CUTOFFs, such as 1/270) are used in DS screening to identify women with a higher risk of having a DS baby to recommend invasive confirmatory testing. However, evidence suggests that women at different ages may have different preferences about the pregnancy outcomes. The objective of this study is to assess the impact of women's preferences for different pregnancy outcomes on the optimal CUTOFFs for integrated screening. Methods: We built a mathematical model to quantify the optimal CUTOFFs given the women's preferences for different age groups. Our model considered the procedure-related fetal loss rate, DS spontaneous miscarriage rate, maternal age distributions and age-specific prevalence. We used Monte Carlo simulation of 100,000 singleton second trimester pregnancies to assess the probabilities of O1 and O2 for various CUTOFFs. Optimal CUTOFFs were chosen to minimize a preference-weighted sum of O1 and O2. We compared the probabilities of O1 and O2 for one-size-fits-all and age-specific CUTOFFs when women had the same or age-specific preferences. Results: When the weights for O1 and O2 were equal for all women, the optimal age-specific CUTOFFs were 1/430, 1/451 and 1/446 for 20, 30 and 40 year-old women respectively, while the optimal one-size-fits-all CUTOFF was 1/454. The probabilities of O1 and O2 were 0.0123% and 0.0081% respectively for the age-specific CUTOFFs, while they were 0.0121% and 0.0083% respectively for the cutoff value 1/454. Furthermore, we found that age-specific CUTOFFs would lead to better results than one-size-fits-all CUTOFF when women's age-specific preferences were considered. In particular, if the weights for O1 and O2 were 1:2, 1:1 and 1:0.5 for women below 25 years, 25-34 years and above 34 years respectively, then the weighted sum of O1 and O2 of the age-specific CUTOFFs was 3% lower than that of 1/435, the optimal one-size-fits-all CUTOFF. Conclusions: Preference-sensitive risk cutoff values for DS screening have the potential to improve the pregnancy outcomes and patient satisfaction.

203: Determining Quantitative Best Practices for Point Of Care Testing in Pediatric Intensive Care Units

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Background: Children's Healthcare of Atlanta (Children's) conducted over 450,000 point of care tests (POCTs) combined at the Egleston (EG) and Scottish-Rite (SR) campuses in 2012. Each campus has approximately 10,000 patient admissions per year, with 255 and 249 beds respectively, and equally sized pediatric intensive care units (PICUs). Children's does not have guidelines for when to administrate POCTs instead of traditional laboratory testing. Similar institutions around the country also lack quantitative best practices. Purpose: This project qualitatively and quantitatively assesses the current POCT practice at Children's to determine best practices. Methods: We interview PICU physicians and nurses, and conduct patient data analysis at EG and SR. The interviews consist of 20 questions to identify operational and clinical inefficiencies. In quantitative data analysis, we collect patient data from EPIC system from September 2012 to August 2013 for both campuses. We have identified respiratory diseases as the most prevalent primary diagnosis category. In addition, we have conducted an analysis in a subgroup of patients with Acute Respiratory Failure (ARF). In particular, we cluster patients by demographic (payment method, age, campus, etc.), frequency of POCT administered during length of stay, and prevalent PICU diagnoses. Furthermore, we determine physician-specific POCT patterns. Results: During the one year period from Sep 12 to Aug 13, there are 67,213 and 18,474 POCTs were administrated at EG and SR respectively. We find that EG has 55.5 POCTs per patient compared to 23.6 POCTs per patient at SR. In EG, critical care physicians performed about 70% of POCTs. A large part (36%) of glucose POCTs administrated for ARF patients in EG lead to normal numerical results. EG patients covered by government health insurance have 56.11 POCTs per patient compared to 44.19 POCTs per patients with private insurance. Conclusions: We find EG conducted more POCTs both in the grand sum and volume per patient. A large proportion of glucose POCTs with an out-of-range result might be a factor leading to more follow-up tests. The study requires further analysis of patient acuity to explain the significant difference in number of POCTs conducted at EG and SR, significant difference in number of POCTs per patient using government insurance versus private insurance, and to identify POCT frequency patterns for patient with similar primary, secondary, and tertiary diagnoses.

204: In Situ Kinetic Analysis of HIV Envelope Glycoprotein Interaction with Host Cells

Ke Bai, PhD; Mariana Marin; Gregory Melikian, PhD; Cheng Zhu, PhD

HIV is one of the most serious and deadly diseases in human history. T cells are the main targets of HIV in the blood, especially the helper T cells that express CD4. The first step of HIV infecting T cell is through the binding of the viral envelope glycoprotein (Env) gp120 subunit to its primary receptor CD4. This leads to the conformational change of gp120 to expose the binding site for its co-receptor CCR5 or CXCR4 on the T cell membrane, which eventually mediates fusion between the viral and cell membrane. Although the specific interaction between CD4 and co-receptors with gp120 has been broadly studied, the direct physical binding kinetics between them remain unclear. To fill this gap we measured the two-dimensional (2D), or in situ kinetics of the gp120–CD4 bimolecular and gp120–CD4–CXCR4 trimolecular interactions between HIV virus liked particles (VLPs) and CD4-expressing 3T3 cell line with or without co-expression of CXCR4. We used the micropipette adhesion frequency assay, which evaluate the kinetic on- and off-rates from the dependence of adhesion probability on contact duration, and the biomembrane force probe (BFP) force-clamp assay, which measure the force-dependent single bond lifetimes of these interactions. The trimolecular interaction has higher 2D affinity than the bimolecular interaction (24.8 vs. 15.1 10-4μm4). Both gp120–CD4 and gp120–CD4–CXCR4 exhibit catch bonds whose lifetime increases despite increasing force, with the gp120–CD4–CXCR4 trimolecular bond lasting longer at optimal force than gp120–CD4 bimolecular bond (1.5±0.23s at 6pN vs. 0.93±0.42s at 4.25pN). These data provide the first in situ kinetic measurements of HIV Env protein to its receptor and co-receptor on living cells.

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