Inflammation in Pediatric Health:
# Improving care through innovation and technology

June 22, 2015
Emory Conference Center Hotel
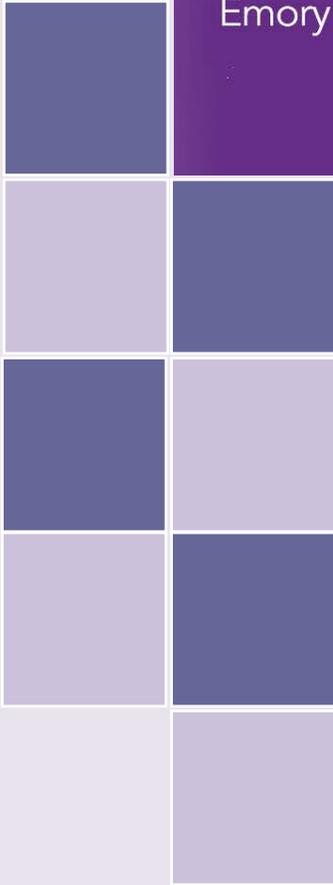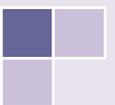
# Emory Conference Center Floor Plan
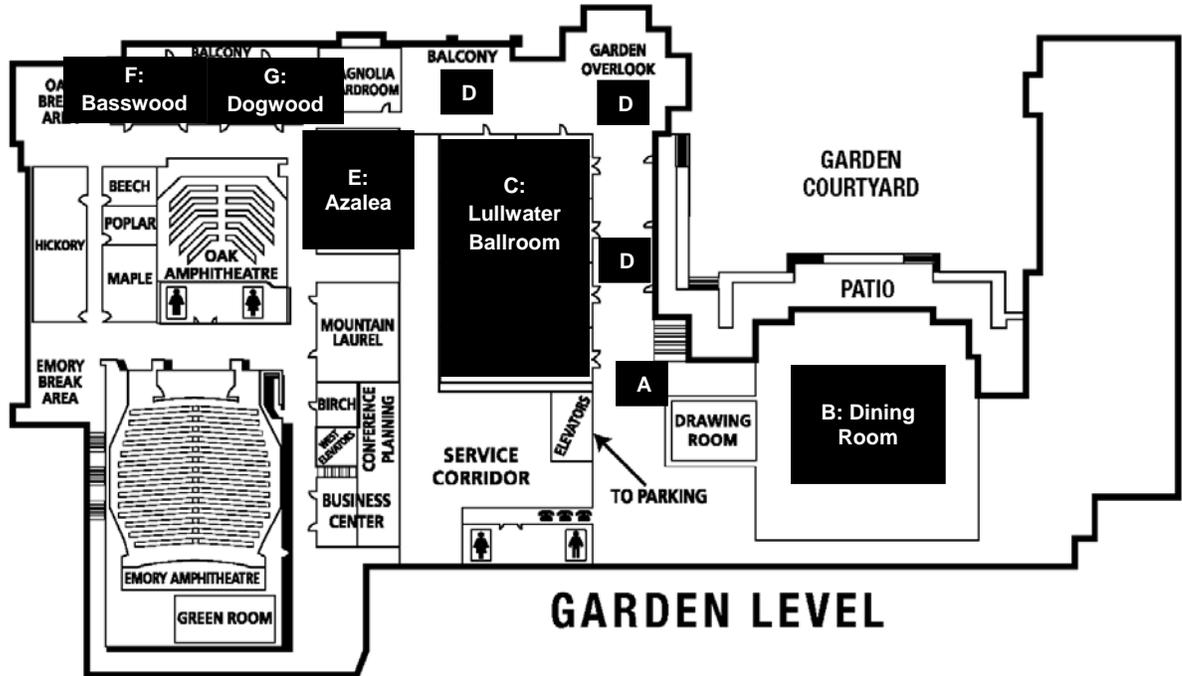
A   Registration and Information Desk

B   Lunch

C   Plenary Sessions

D   Center Posters, Core Posters and Children's Healthcare of Atlanta 100 Year Celebration Display

E   Scientific Posters

F & G   Technology Demonstrations and Displays

Parking: Please pick up a free parking voucher at the registration desk. You will need a voucher when exiting the North and South parking decks.

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Program Contents

Agenda

7:00 – 8:30	Registration and Continental Breakfast	
8:00 - 8:15	Welcome from Co-Chairs	
	Cynthia Wetmore, MD, PhD Director, Center for Clinical and Translational Research Department of Pediatrics, Emory University School of Medicine, and Director, Developmental Therapeutics Program Aflac Cancer and Blood Disorders Center Children's Healthcare of Atlanta	**Leanne West, MS** Chief Engineer of Pediatric Technologies, Georgia Institute of Technology Principal Research Scientist, Georgia Tech Research Institute
8:15 - 8:30	Opening Remarks	
	Donna Hyland President and Chief Executive Officer Children's Healthcare of Atlanta **Pat Frias, MD** Chief, Children's Physical Group Chief Operating Officer, Children's Healthcare of Atlanta	**David Stephens, MD** Vice President for Research, Woodruff Health Sciences Center Chair, Department of Medicine Chief of Medicine, Emory Healthcare **Christopher Jones, PhD** Associate Vice President for Research Georgia Institute of Technology
8:30 - 8:45	Presentation of Poster Awards	
8:45 - 9:25	"Toward Precision Medicine in Neuro Developmental Disease"	
	David Goldstein, PhD Director, Institute for Genomic Medicine John E. Borne Professor and Professor of Genetics and Development Columbia University Medical Center	

9:25 - 10:00	"3D Printed Devices for Pediatric Patients: The Triumphs and Trials"
	Scott J. Hollister, PhD Professor of Biomedical Engineering and Mechanical Engineering The University of Michigan
10:00 – 10:30	Break and Poster Preview
10:30 - 11:15	"A Genomic Approach to Understand Pediatric Rheumatic Diseases"
	Virginia Pascual, MD Investigator and Co-Director Baylor Institute for Immunology Research Baylor Health Care
11:15 – 11:50	Abstract Presentations
	Moderated by **Beatrice Gee, MD, FAAP** "Quantification and Origin of Differential Pulmonary Blood Flow in the Patients with a Fontan Circulation" *Senthil Ramamurthy, MS*; Sassan Hashemi, MD; James Parks, MD; Denver Sallee, MD; Gary McNeal, MS; and Timothy Slesnick, MD "Monitoring Cerebral Blood Flow, Oxygen Saturation, and Oxygen Metabolism Using Diffuse Optical Spectroscopies" *Erin M. Buckley, PhD* "Respiratory Decompensation Following Immunization in Premature Infants" *Edwin Clark Montague, DO* and Anthony Piazza, MD
11:50 – 12:00	Morning Session Closing Remarks
	Yasmin Tyler-Hill, MD Chair, Department of Pediatrics, Morehouse School of Medicine Medical Director, CHOA at Hughes Spalding

12:00 – 1:30 Lunch & Poster Sessions	12:00 – 12:45	Odd Numbered Posters
	12:45 – 1:30	Even Numbered Posters

1:30 – 1:40	Afternoon Welcome
	Paul Spearman, MD Nahmias-Schinazi Research Professor and Vice Chair for Research, Department of Pediatrics, Emory University School of Medicine Chief Research Officer, Children's Healthcare of Atlanta Co-Director, Center for Childhood Infections and Vaccines
1:40 – 2:10	"Vaccine Discovery for Common Pediatric Respiratory Viruses"
	Marty Moore, PhD Assistant Professor Division of Pediatric Infectious Diseases Emory University School of Medicine Co-Director, Center for Childhood Infections and Vaccines Children's Healthcare of Atlanta

2:10 - 2:40	Abstract Presentations
	Moderated by **Cynthia Wetmore, MD, PhD** "Siglec-1 and Tetherin Cooperatively Lead to the Formation of the Virus-containing Compartment (VCC) in HIV-1-infected Human Macrophages" *Jason E. Hammonds, PhD; Neal Beeman, PhD; Lingmei Ding; Jaang-Jiun Wang, PhD; and Paul Spearman, MD* "Increased Survival and Phenotypic Reprogramming of Neutrophils in Cystic Fibrosis Airway Disease" *Osric Forrest, BSc; Sarah Ingersoll, PhD; Marcela Preininger, BSc; Julie Laval, PhD; Milton Brown, PhD; and Rabindra Tirouvanziam, PhD* "Novel Electroneuromyography Technique in Early Diagnosis of Infant Botulism" *Manisha Malik, MD and Sumit Verma, MD*
2:40 – 3:10	Break and Poster Review
3:10 – 3:55	"New Therapies for Sickle Cell Disease"
	Punam Malik, MD Marjory J. Johnson Chair of Gene and Cell Therapy Professor of Pediatrics University of Cincinnati College of Medicine Program Leader, Molecular and Gene Therapy Program Division of Experimental Hematology and Cancer Biology Director, Comprehensive Sickle Cell Program Division of Hematology Cancer and Blood Diseases Institute Cincinnati Children's Hospital Medical Center
3:55 – 4:15	Closing Remarks from Co-Chairs
4:15 - 5:00	Reception and Technology Demonstrations

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 6.0 *AMA PRA Category 1 Credits*[TM]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Chair and Speaker Biographies

Cynthia Wetmore, MD, PhD earned her Bachelor of Arts degree from Harvard University, medical degree from the University of Minnesota Medical School and Doctorate in Neurobiology from the Karolinska Institute in Stockholm, Sweden. She completed her residency training in Pediatrics at University of Minnesota and Mayo Clinic, and completed fellowship training in Hematology/Oncology and Neuro-oncology at St. Jude Children's Research Hospital. Dr. Wetmore joined the faculty at Mayo Medical School as Assistant Professor in 2001 where she founded the first interdisciplinary clinic for pediatric brain tumor patients. She provided clinical care to children battling brain tumors and also directed a basic research laboratory investigating the role of Sonic hedgehog pathway in the growth of normal and neoplastic neural stem cells. She then was recruited back to St. Jude in 2010 where she directed the Developmental Therapeutics Program for Neuro-oncology and also served as Director of the Molecular Clinical Trials Core, a shared resource within the Comprehensive Cancer Center that supports the conduct of clinical trials at St. Jude. In April 2014, Dr. Wetmore was recruited as the inaugural director of the newly established Center for Clinical and Translational Research in the Department of Pediatrics at Emory University School of Medicine and Children's Healthcare of Atlanta. She also heads the Developmental Therapeutics Program within the Aflac Cancer and Blood Disorders Center. Dr. Wetmore is actively involved in bringing new, targeted agents to Phase I/II clinical trials for the treatment of children with cancer. While her focus continues to be in the clinical care of children with brain tumors, she brings two decades of basic science research experience to the design and conduct of molecularly-based therapeutic protocols for children.

Leanne West, MS is the Chief Engineer for Pediatric Technologies for Georgia Tech and a Principal Research Scientist for the Georgia Tech Research Institute (GTRI). As Chief Engineer, she coordinates all research activities related to pediatrics across campus. She helps manage the formal relationship with Children's Healthcare of Atlanta and is Director of the Quick Wins funding program. Her research background is in mobile and wireless health system and sensor development, user interfaces, system integration, and diagnostic devices. Ms. West serves on the executive management team of the Parker H. Petit Institute for Bioengineering & Bioscience and is a member of the Institute for People and Technology Health Council, with the goal of creating large-scale, interdisciplinary collaborations across campus in the area of healthcare. She is author of a book chapter in Technology for Aging, Disability and Independence: Computer and Engineering for Design and Applications (John Wiley & Sons) and has written a number of papers and given several presentations on wireless technology device development and remote sensing systems. Ms. West has seen her invention of a wireless personal captioning system installed at commercial venues through her start-up Intelligent Access, LLC. She was a GTRI Innovative Research Award team member in 2014 and has received the following awards: Georgia Tech's Outstanding Achievement in Research Enterprise Enhancement Award in 2014, the Woman of the Year by Women in Technology in 2014, and the Optical Society's 2012 Paul Forman Engineering Excellence Award as a Lidar Team member. Ms. West also was named one of Georgia's "40 Under 40" by Georgia Trend magazine in 2004. In addition, she participated in the 2008 class of Leadership Georgia. Ms. West is an active participant at her organization and was twice elected Chair of the Georgia Tech Executive Board, the faculty governance body of Georgia Tech.

David Goldstein, PhD was trained in theoretical population genetics and has studied many aspects of human genetic variation over the last 20 years with a particular focus on the genetics of disease and treatment response. His early work focused primarily on genetic anthropology, while his more recent work has focused primarily on medical genetics and pharmacogenetics. Dr. Goldstein was Professor of Genetics at University College London from 1999 - 2005. In 2005, he moved to Duke University as a Professor in the Departments of Molecular Genetics and Microbiology and Biology, and as Director of the Center for Human Genome Variation (CHGV.) In 2010, he was appointed the Richard and Pat Johnson Distinguished University Professor. Under Dr. Goldstein's leadership, the CHGV emerged as a leading human genetics research center with a number of seminal discoveries, including de novo mutations in ATP1A3, the gene responsible for Alternating Hemiplegia of Childhood, and the role of IL28B in treatment response to Hepatitis C infection. He was a leader in the field of demonstrating the potential of next generation sequencing in diagnosing rare genetic and neurological conditions. As of January 1, 2015, Dr. Goldstein moved to Columbia University Medical Center to become director of the newly established Institute for Genomic

Medicine (IGM) where he will continue his research efforts in neurological and undiagnosed diseases while expanding new programs in precision medicine. Dr. Goldstein also is a principal investigator of Epi4K, the NINDS Epilepsy Genetics Center without Walls, and he directs its genome sequencing and bioinformatics core. Epi4K is currently the largest epilepsy genetics project in the world and is in the process of generating whole exome and whole genome sequence data on no less than 4,000 patients with epilepsy.

Scott J. Hollister, PhD is a Professor of Biomedical Engineering and Mechanical Engineering at the University of Michigan, where he directs the Scaffold Tissue Engineering Group (STEG). Dr. Hollister and his collaborators have designed and developed a variety of medical devices utilizing 3D printing, an area in which he has worked for 17 years, publishing his first paper in 1997. He and his colleagues first developed an approach for laser sintering for polycaprolactone in 2004. His general research focuses on the design, fabrication and evaluation of biomaterial platform systems for tissue reconstruction. Dr. Hollister is a fellow of the American Institute of Biological Engineering. His work on a bioresorbable tracheal splint with Dr. Glenn Green was published in the New England Journal of Medicine in 2013 and subsequently was given a Popular Mechanics 2013 Breakthrough Innovation Award. This implantation of this 3D printed device to save the lives of three children also has been featured on the Today Show, the New Yorker, USA Today, NPR, Time magazine, Nature, Science, and Popular Mechanics, among other media.

Virginia Pascual, MD served as Director of the Division of Pediatric Rheumatology at UT Southwestern Medical Center and Texas Scottish Rite Hospital for Children from 1998 to 2004. In 1999, Dr. Pascual joined the Baylor Institute for Immunology Research (BIIR) as an investigator, and has been the Director of BIIR's Centers for Inflammation and Genomic Medicine since 2012. Currently, she serves as co-director of BIIR. Dr. Pascual is a pediatric rheumatologist with long standing experience in Translational Research and a focus on Human Autoimmunity. She serves as the Principal Investigator of both an NIH-funded Autoimmunity Center of Excellence focused on the study of human lupus and an NIH-funded Human Immunology Program Consortium Center focused on vaccine responses in healthy individuals and patients with autoimmune disease. Dr. Pascual's pioneering genomic studies identified the role of dendritic cells and interferon in Systemic Lupus Erythematosus (SLE). Her lab also identified the role of cytokines such as IL1 in children with Systemic Onset Juvenile Arthritis, which has led to successful therapeutic interventions, including FDA approval of IL1 blockers to treat this disease. Dr. Pascual's lab is committed to applying basic immunologic and genomic approaches to the identification of pathogenic mechanisms and biomarkers in human autoimmune diseases.
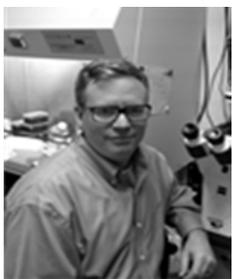
Marty Moore, PhD received his PhD in Genetics in 2003, studying adenovirus at the University of Georgia and University of Michigan. He was a postdoctoral fellow in the laboratory of Dr. Stokes Peebles at Vanderbilt from 2004 to 2008, working on mouse models of RSV pathogenesis. In 2008, Dr. Moore joined the faculty of Pediatric Infectious Diseases at Emory University. The main goals of the Moore laboratory are to elucidate molecular mechanisms of RSV pathogenesis and to advance vaccines for common pediatric respiratory viruses. Model systems utilized in pursuit of these goals include mouse models of RSV infection based on relatively pathogenic RSV strains and a novel RSV and rhinovirus reverse genetics systems for engineering recombinant viruses. Current NIH-funded research projects include studying the role of the viral fusion (F) protein in pathogenesis and defining mutations in circulating RSV isolates that impact virulence. The RSV vaccine approach in the laboratory is centered on using reverse genetics to engineer live attenuated vaccine candidates with improved immunogenicity. Another vaccine currently being developed is against rhinoviruses, causative agents of the common cold and acute asthma exacerbations.

Punam Malik, MD is a Professor of Pediatrics and a physician-scientist who has worked on hematological disorders, specifically those involving red blood cells, for the last 15 years. Dr. Malik treats children with hematological disorders and her research interests lie in studying the pathophysiology of hemoglobinopathies. She has been studying the pathophysiology of sickle cell disease, especially the mechanisms that lead to development of the protean manifestations in this disease. Another major area of research interest encompasses developing novel therapies, including gene therapy for inherited hematological disorders. Dr. Malik facilitates translation of research discoveries into clinical trials. She is the Program Leader of the Hematology and Gene Therapy Program at the Cancer and Blood Diseases Institute at Cincinnati Children's Hospital, Director of the Cincinnati Sickle Cell Center and Director of the Translational Core Laboratory, a state-of-the-art facility that supports translation of laboratory discoveries to early-phase clinical trials and specifically, complex gene therapy trials.

Technology Demonstrations and Displays

3-D Bioprint is developing a functional 3-D aorta valve for pediatric patients. Aline Yonezawa graduated from the University of Florida with a Bachelor's of Science in Biomedical Engineering, focused on biomaterials. She is a first year graduate student in Dr. Michael Davis' laboratory. This project is based on her NSF Graduate Research Fellowship proposal. Current heart valve replacements lack biocompatibility and integration into host tissue. As a result, there is a demand for a functional heart valve that can grow, repair, and remodel in patients. The team will develop a functional heart valve by combining valve-like cells derived from induced pluripotent stem cells and several biomaterials to 3-D bioprint an anatomical heart valve. A combination of biomaterials, polyethylene (glycol) diacrylate (PEGDA) and polycaprolactone (PCL) will be used to match the biomechanics of a native heart valve. Because of the flexibility with mechanics, biochemistry, and bulk shape, the proposed PEGDA based hydrogels and PCL offer significant improvements over current engineered valves for both pediatric and adult patients.

Anemocheck/Cellscope Stella Fagbemi was born in Staten Island, NY and raised in Lawrenceville, GA. She is currently a junior at Emory University, graduating in the fall, majoring in Neuroscience and Behavioral Biology with a minor in Global Health, Culture and Society. Stella began in the Lam Lab in September 2014 working on the chemistry of the point of care device, AnemoCheck. She will continue her work in the lab through the summer of 2016. She plans to apply to medical school with hopes of matriculating next year to earn an MD/MPH.

Bedside Monitoring Informatics in the Neonatal ICU In collaboration with Children's Healthcare of Atlanta, Dr. May Wang's lab has undertaken projects to explore the uses of big data analytics in neonatal critical care. Neonatal pain and distress is an area of specific interest, where the lab used informatics methods to understand how pain and distress are recorded in the NICU. The lab also has undertaken studies aimed at validating this data source to enable future research reuse.

Games That Work Dov Jacobson is the managing director of Games That Work. The Atlanta game studio is dedicated to improving players' real-world behavior, health and performance. Mr. Jacobson learned traditional animation in Los Angeles studios and learned to program using punch cards. He joined the videogame industry in the Golden Age of coin op and came to Atlanta to found a game company for Turner in the mid 90's. That studio survives as Big Fun Development (BFD). In 2003, BFD began a practical games endeavor called Games That Work. Games are precisely-designed and built and tested with clinical professionals.

Global Center for Medical Innovation The Global Center for Medical Innovation (GCMI) is a non-profit organization that represents the Southeast's first medical device innovation center. It is led by Executive Director Tiffany Wilson Karp, who has spent over a decade bringing innovative medical technology from benchtop to bedside. At GCMI, Tiffany works with universities, clinicians, industry, investors, and startups focused on innovation, patient care, and economic growth. Tiffany joined GCMI from Scientific Intake, where she was VP of Business Development & Strategy. In 2002, she launched ACell as VP of Corporate Strategy & Finance, leading a broad range of initiatives, including regulatory, reimbursement, and the scientific advisory board. A former consultant and investment banker, she brings considerable experience in strategic planning, business development, operations, and financial analysis. Tiffany serves as President of the Southeastern Medical Device Association (SEMDA), a Member of the National Advisory Council on Innovation and Entrepreneurship (NACIE), and Chair of the T3 Labs Advisory Board. She earned a BBA in International Business from Loyola University and an MBA from Georgetown University.

iEAT This project continues a line of research to develop and test exportable and cost effective treatments for feeding problems in young children. This is the first mobile platform decision support tool created for behavioral feeding intervention. Created by Will Sharp, PhD, the app was delivered to the Marcus Autism Center in February 2014 and is currently in use with 100% effectiveness. Over 300 children are on the waitlist for treatment.

KIDS Georgia is an advisory group of children, adolescents and families focused on understanding, communicating and improving the process of medical innovation for children. KIDS, Kids Impacting Disease through Science, is sponsored by the American Academy of Pediatrics (AAP) Section on Advances in Therapeutics and Technology (SATT) in collaboration with the Connecticut Chapter of AAP and children's hospitals. Jake Haygood, a member of Kids Georgia, is an upcoming ninth grader at Mount Paran Christian School in Kennesaw, GA. He is part of the AnemoCheck team in the role of app development. Jake serves as a co-technology officer on the Kids Georgia junior board. Since the age of nine when he received a book on Python, programming has been a passion of his. He is a self-taught programmer fluent in a variety programming languages including C, C++, Arduino, Python, Vb.net, C#, html, R, Swift, Java, JavaScript, VBScript, and VB.net. Also, he has an understanding of how computers work at a hardware level and has experience with micro controllers. Currently, Jake is learning how to program PIC microcontrollers in C and PIC assembly. He is knowledgeable in computer architecture and how electrical components interface to form logic modules and complex electrical systems. He recently earned his amateur radio license and is interested in exploring radio transmissions and the research in wireless communication outside this spectrum, as well as artificial intelligence design and implementation. In his free time, he enjoys hunting, programming, playing the clarinet, designing circuits, and hanging out with his friends.

MotionTalk is a tool to help the rehabilitation of traumatic brain injury, stroke and other patients suffering from physical injury to monitor improvement rehabilitation using 3-D body motions. MotionTalk develops measures to monitor progress of the patient at home during the rehabilitation process. It is based on the open source motion sensing device Kinect, cloud database, data analytics, and mobile app technologies. It is a low-cost and easy-to-use system.

Team Coalesce was challenged to improve upon spinal cages for spinal fusion surgeries in pediatric cancer patients. Current instrumentation used in spinal fusion surgeries interferes with monitoring of both bony fusion and progression of tumors, provides insufficient fixation of the spine, and causes spinal deformity in pediatric oncology patients. Team Coalesce has developed a new cage, the Sapling cage, which they believe will address all of these issues.

Emory+Children's Pediatric Research Center (ECPRC)

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

Center Descriptions

Aflac Cancer and Blood Disorders Center
Director: William Woods, MD
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 Childhood Infections and Vaccines
Directors: Paul Spearman, MD and Marty Moore, PhD
Infectious diseases are the leading cause of death in children worldwide. Researchers in the Center for Childhood Infections and Vaccines 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, HIV and more.

Center for Clinical and Translational Research
Director: Cynthia Wetmore, MD, PhD
This center provides organization and leadership for clinical trials science, and acts as a central point for training and recruiting clinical trialists in a variety of disciplines. The center also will serve as the scientific home for leaders in nursing research

Center for Clinical Outcomes Research and Public Health
Acting Directors: Paul Spearman, MD
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
Director: Nael McCarty, PhD
Cystic fibrosis 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. Asthma is the number one reason for admission at Children's Healthcare of Atlanta and has public health implications. Researchers at this center are working to develop new therapies, drugs, and tools to improve and extend the quality of lives of children with these conditions.

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

Center for Neurosciences
Director: Ton de Grauw, MD, PhD
The vision of Children's Center for Neurosciences Research is to conduct research that will 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
Directors: Bob Guldberg, PhD and Kevin Maher, MD
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 (CPI) focuses on utilizing cutting edge technologies to advance regenerative medicine based therapies for children; developing new diagnostic and therapeutic strategies for detecting and treating pediatric diseases; and designing 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 **Atlantic Pediatric Device Consortium** (APDC), funded by the U.S. Food and Drug Administration. 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 CPI and the APDC will help inventors with reviewing, testing and developing their devices. APDC provides assistance with engineering design, prototype development, pre-clinical and clinical studies and commercialization for novel pediatric medical devices.

Center for Pediatric Nanomedicine
Director: M.G. Finn, PhD
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 Transforming Pediatric Healthcare Delivery
Director: Beth Mynatt, PhD
The Center for Transforming Pediatric Healthcare Delivery (CTPHD) brings the talents and knowledge of diverse disciplines at Georgia Tech, Emory and Children's Healthcare of Atlanta to transform pediatric healthcare delivery to make pediatric care more effective, accessible and ubiquitous for all children in Georgia. In particular, CTPHD works towards transformation through six focus areas: modeling and simulation; actionable knowledge through big data; devices and sensors; mobile and distributed strategies; patient engagement and education; and policy and healthcare enterprise transformation.

Center for Transplantation and Immune-mediated Disorders
Director: Subra Kugathasan, MD
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.

Heart Research and Outcomes Center
Director: Mike Davis, PhD
The fields of pediatric cardiology and surgery have greatly improved the survival rate of children with congenital heart defects and heart disease. As this population now survives initial diagnoses, new efforts are focused on long-term developmental and neurological outcomes, as well as novel ways to study and treat continuing disorders. Exciting projects by Heart Research and Outcomes Center researchers include development of a biological pacemaker, stem cell therapy for heart failure, studies of developmental biology, understanding the links between heart disease and cognitive function, and tracking outcomes to enhance diagnosis and treatment of pediatric heart disease.

Marcus Autism Center
Director: Ami Klin, PhD
Director of Research: Warren Jones, PhD
Marcus Autism Center is a not-for-profit organization and subsidiary of Children's Healthcare of Atlanta that impacts over 9,000 children a year. As one of the largest autism centers in the U.S. and one of only three National Institutes of Health (NIH) Autism Centers of Excellence, Marcus Autism Center offers families access to the latest research, comprehensive evaluations and intensive behavior treatments. With the help of research grants, community support and government funding, Marcus Autism Center aims to maximize the potential of children with autism today and transform the nature of autism for future generations. Our research includes studies on social engagement, parent training and education, severe behaviors, feeding disorders, language acquisition, and vocal communication.

Egleston Pediatric Research Center

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. The PRC studies 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 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.

Oral Presentations

Quantification and Origin of Differential Pulmonary Blood Flow in Patients with a Fontan Circulation

Senthil Ramamurthy, MS; Sassan Hashemi, MD; James Parks, MD; Denver Sallee, MD; Gary McNeal, MS; and Timothy Slesnick, MD

Background: "Hepatic factor" is found in inferior systemic venous return, and is required by pulmonary tissue to prevent formation of pulmonary arteriovenous malformations (PAVMs). Therefore, quantification and origin of differential systemic venous return to branch pulmonary arteries (PAs) in the Fontan population is critical to assess the risk for PAVMs. Methods: Over the last few years, time-resolved, three-dimensional phase contrast (4Dflow) MRI technology has expanded due to increased speeds from parallel imaging and advances in MRI hardware. At CHOA, select patients undergoing a clinical cardiac MRI scan have been prospectively consented to undergo 4Dflow imaging since August, 2013. An expert reader defined the contours of the analysis planes for right and left pulmonary arteries (RPA and LPA), superior and inferior venae cavae (SVC and IVC) within the Fontan circuit using 4Dflow software (Siemens Healthcare, Erlangen, Germany). Particles (imaginary massless fluid elements) are emitted from either the SVC or IVC plane. The 3D streamlines (path taken by the particles) calculated by 4Dflow were then exported for further analysis. Custom software was written in MATLAB (Mathworks, Natick, MA) for flow quantification. The analysis planes for the RPA and LPA were refined using a best plane fit, and blood flow direction was specified interactively. A user-defined cylinder with its axis along the direction of branch PA flow was constructed to encompass the distal PA branches. Flow was simulated for 3 cardiac cycles, with separate experiments seeding the SVC and IVC, and the terminal spatial position of each particle from the streamline was determined. The number of particles that crossed into the RPA and LPA were counted. The differential pulmonary blood flow was calculated for each simulation as the ratio of the number of particles entering the LPA or RPA to the total number of particles entering the branch PAs. Results: The custom MATLAB software successfully analyzed differential pulmonary flow from both the SVC and IVC individually, as well as in combination. The quantitative values agreed with the visual inspection of the particle streamlines. Conclusion: We have developed a novel technique to assess the origin and quantify the differential pulmonary blood flow from 4Dflow MRI. Further analysis comparing the 4Dflow values to those derived from in vivo 2D phase contrast data, computational simulations, and flow phantom experiments are ongoing.

Monitoring Cerebral Blood Flow, Oxygen Saturation, and Oxygen Metabolism Using Diffuse Optical Spectroscopies

Erin M. Buckley, PhD

Cerebral blood flow (CBF) and oxygen metabolism (CMRO2) are critical biomarkers of brain health and function. Functioning neurons require an adequate supply of adenosine triphosphate (ATP), and ATP is produced almost entirely through oxidative metabolism. If the oxygen supply is insufficient, then energy-dependent neuronal processes cease, and irreversible cellular damage ensues. Adequate CBF ensures the delivery of oxygen and needed substrates to tissue, and it also ensures removal of metabolic waste products. Quantification of both CBF and CMRO2 is useful for diagnosis and management of any brain injury or disease associated with ischemia or inadequate vascular autoregulation. Further, the quantification of CBF and CMRO2 in healthy subjects, for example with respect to age or during functional activation, can elucidate connections between vascular physiology and neurophysiology, and these normative parameters, in turn, improve our ability to recognize and understand a diseased brain. In this poster/oral presentation, I will introduce two relatively new optical modalities (namely,

frequency-domain near-infrared spectroscopy and diffuse correlation spectroscopy) that are used to non-invasively quantify cerebral blood flow, oxygenation, and oxygen metabolism. In brief, frequency-domain near-infrared spectroscopy (FD-NIRS) enables quantification of absolute regional (microvascular) cerebral oxy- and deoxy-hemoglobin concentrations (in mmol/L) using photon diffusion theory. From this information, total hemoglobin concentration (THC, µM), cerebral oxygen saturation (SO2, %), and cerebral blood volume (CBV, ml/100g) are readily derived. Diffuse correlation spectroscopy (DCS) utilizes the intensity fluctuations of near-infrared (NIR) light to non-invasively quantify microvascular CBF without the use of exogenous tracers. When FD-NIRS measures of SO2 are combined with DCS measures of CBF, we can quantify CMRO2, a parameter that many believe is a direct measure of neuronal health; this information provides the clinician with a more complete assessment of cerebral health and physiology than either SO2 or CBF alone. I will present a brief background about FDNIRS/DCS theory, instrumentation and data acquisition, and I will summarize its most prominent cerebral monitoring applications to date. I will also discuss the advantages and limitations of current technology and indicate directions for improvement.

Respiratory Decompensation Following Immunization in Premature Infants

Edwin Clark Montague, DO and Anthony Piazza, MD

Objectives: Concern among neonatologists for respiratory decompensation following immunization in premature infants, particularly those with bronchopulmonary dysplasia, leads to delayed and altered immunization schedules. However, no previous studies have evaluated if respiratory decompensation is associated with immunization. Methods: A retrospective cohort of premature infants less than 32 weeks GA cared for in a tertiary level IV neonatal intensive care unit (NICU) and immunized while admitted were evaluated for respiratory decompensation within 72 hours of immunization including need for increased in respiratory support, increase in mean FiO2, and increase in number of apnea/bradycardia/desaturation (A/B/D) events. Primary outcome was respiratory decompensation (defined as a composite of increased respiratory support or increase in FiO2 greater than 10 percent) within 72 hours of immunization. Results: Of 403 infants admitted to the NICU and immunized, 240 were ≤ 32 weeks GA and met criteria for study entry. Of the 240, 170 (71%) had the diagnosis of bronchopulmonary dysplasia (BPD) and 70 (29%) did not. There was no difference in the composite outcome of respiratory decompensation following immunization between groups (OR 1.83 95% CI 0.618-5.94 P=0.354). There was also no difference in individual outcomes of increased respiratory support (OR 1.58 95% CI 0.53-4.72 P=0.474) or greater than 10 percent increase in FiO2 (OR unable to calculate P=0.578) following immunization. There was no significant increase in A/B/D events following immunization (OR 1.36 95% CI 0.81-2.30 P=0.254). There was no difference in respiratory decompensation in infants who received a single vs. multiple vaccines in a day (OR 0.77 95% CI 0.33-1.81 P=0.646). In subgroup analysis, there was no significant difference in respiratory decompensation following the administration of 2 month immunizations. There was, however, a significant increase in A/B/D events in the BPD group (OR 1.95 95% CI 1.07-3.57 P=0.031) Conclusion: Immunization of preterm infants with BPD is not associated with respiratory decompensation. Immunization of this vulnerable population should not be delayed.

Siglec-1 and Tetherin Cooperatively Lead to the Formation of the Virus-Containing Compartment (VCC) in HIV-1-infected Human Macrophages

Jason E. Hammonds, PhD; Neal Beeman, PhD; Lingmei Ding; Jaang-Jiun Wang, PhD; and Paul Spearman, MD

HIV-infected macrophages accumulate viral particles within an intracellular compartment that exhibits features common to the multivesicular body and of the plasma membrane. It remains to be determined whether particles assemble in macrophages by budding through the limiting membrane of the virus-containing compartment (VCC) or if assembly on the plasma membrane followed by internalization to the VCC is predominant. We identified Siglec-1 as a key determinant of the formation of the VCC. Siglec and tetherin were highly concentrated in the VCC along with HIV-1 particles, and depletion of either molecule greatly diminished the volume of the VCC. Notably, HIV virus-like particles applied exogenously were taken directly into the VCC of infected macrophages in a GM3- and Siglec-1-dependent manner. These results support a model in which infected macrophages capture endogenous budding particles at the plasma membrane through a combination of tetherin and Siglec-1, followed by internalization to create the VCC. Furthermore, these results suggest that virions in the VCC may originate from either the infected macrophage itself or from particles released from adjacent infected cells.

Increased Survival and Phenotypic Reprogramming of Neutrophils in Cystic Fibrosis Airway Disease

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

Background: Cystic Fibrosis (CF) lung disease is characterized by the massive recruitment of neutrophils (PMNs) into the bronchiolar lumen. Recruited PMNs produce reactive oxygen species (ROS) and release granule enzymes like human neutrophil elastase (HNE) and other proteases that contribute to inflammation and tissue destruction. HNE that is released from PMN primary granules, is a strong predictor of lung function and survival in CF patients. However, the process by which CF airway PMNs exocytose HNE is not well understood and not reproduced in animal models of CF airway disease. Similarly, it is still not clear why and how long PMNs are able to survive in the CF airway. Methods: Blood and sputum were collected from CF and HC patients stained and then analyzed by flow cytometry for viability, degranulation, and inflammasome activation. In order to study the dynamics and mechanism that control PMN functional reprogramming, we designed a novel transmigration model in which we used a surface collagen-coated 3D porous polystyrene scaffold (Alvetex) to mimic the airway lamina propria and grew human bronchiolar H441 cells at air-liquid interface on top. In the transepithelial migration assay, blood PMNs were placed on the basal side and allowed to migrate towards to CF airway fluid placed apically, after which PMNs were analyzed by flow cytometry for rate of migration, survival, and degranulation. Results: Our results both ex vivo and using our in vitro model we show that (i) PMNs persist in the CF airway lumen and in vitro the airway fluid from patients is able to induces rapid transepithelial migration and increased survival of neutrophils when compared with other known chemoattractants and healthy control airway fluid. (ii) Live PMNs actively release their primary granules ex vivo and in vitro upon exposure to CF airway fluid, and (iii) in vitro migration towards CF airway fluid induces PMN reprogramming allowing for the activation of the inflammasome and pinocytosis. (iv) In our model system we can utilize inhibitors of neutrophil migration (LTA4H inhibitor) and inflammasome activation (CRID3) to significantly reduce the chronic influx and activation of PMNs. Conclusions: These results suggest a primary role for the CF microenvironment in inducing increased survival and phenotypic reprogramming of PMNs and establish our model as a robust platform for deconstructing CF airway PMN dysfunction and developing new therapies for CF inflammation.

Novel Electroneuromyography Technique in Early Diagnosis of Infant Botulism

Manisha Malik, MD and Sumit Verma, MD

Introduction: Infant botulism is recognized as the most frequent form of human botulism in USA. Traditional techniques of electroneuromyography such as repetitive motor nerve stimulation are usually not sensitive for detecting early disease. Stool studies may take several days. Stimulated jitter analysis (stim-JA) is a sensitive and rapid neurophysiological test that can be reliably performed in infants. This study demonstrates how application of this novel technique yielded early diagnosis and expedited treatment of infant botulism. Methods: Two infants with poor suck, weak cry, drooling and constipation were studied. They were exclusively breastfed and had no known exposure to honey. Examination showed bilateral ptosis, sluggish pupillary response to light, facial weakness, weak gag, head lag, lack of spontaneous antigravity movement in all extremities and normal reflexes. Stool sample was obtained following an enema and sent to the botulinum reference laboratory at the Center for Disease Control (CDC), Atlanta. Stim-JA was performed on the right orbicularis oculi muscle. Using the stimSFEMG program (Synergy, Natus Medical Incorporated, San Carlos, CA) with the filter settings of 10 KHz to 20 KHz stimulations were given at 10 Hz and action potentials were recorded. Results: Stim-JA showed increased jitter and blocking, indicative a disorder of neuromuscular junction. Clinical-electrophysiological diagnosis of infant botulism was made. Human botulinum immunoglobulin (BabyBIG 50 mg/kg; single intravenous infusion) was given within 72 hours of admission. Both infants made rapid recovery of their strength and were feeding by mouth in less than two weeks. Stool toxin analysis came back positive on day 5-10 of admission. Discussion: Early diagnosis of infant botulism is crucial to facilitate early. BabyBIG administered within 3 days of admission has shown to reduce the average length of hospital stay to 2.0 weeks vs 2.9 weeks in patients who received BabyBIG at 4-7 days. In infants, young children, or patients having difficulty in making a controlled activation, stim-JA is a sensitive measure for localizing abnormal NMJ although it is not specific to pre- or post-synaptic disorders.

Poster Index by Author

Poster Abstracts

101. Pediatric Cardiac Progenitor Cell Therapy in Right Ventricular Failure

Udit Agarwal MD, PhD; Amanda W. Smith, PhD; Kristin M. French, BS; Archana V. Boopathy, PhD; Ming Shen, BS; Rong Jiang, MD, PhD; Janet D. Fernandez, BSN; Brian E. Kogon, MD; Kirk R. Kanter, MD; Mary B. Wagner, PhD; Manu O. Platt, PhD; and Michael E. Davis, PhD

Congenital heart defects are the leading birth defect in newborns and can lead to right ventricular (RV) heart failure in the pediatric population. Surgery is palliative and children go on to increased morbidity and mortality, warranting better treatment strategies. Recent animal studies with myocardial infarction models have demonstrated that cardiac progenitor cells (CPCs) derived from either younger or female hearts have improved cardiac benefits compared with adult CPCs. The goal of this study was to investigate the role of age on human pediatric (h)CPC therapy in a model of juvenile RV heart failure. Human CPC's isolated from children undergoing reconstructive surgeries were divided into three groups based on the donor's age – neonate (1- 30 days), infant (30 days to 1

year) and child (1 - 5 years). Cells showed >90% expression of c-kit, GATA-4 and NKX 2.5 in the pooled population from 3 different patients in each group. Adolescent nude rats (Crl:NIH-Foxn1rnu) were subjected to sham or pulmonary banding surgery to generate a model of RV heart failure. Two weeks following surgery, animals were randomized and 1 million DiR coated hCPCs were injected in RV musculature of randomized animals. Cardiac function analysis was performed via echocardiography at 2, 4 and 6 weeks after banding procedure. Results demonstrate >20% of cell retention at day 21 post injection in all the groups with no effect of age on retention. Cardiac function analysis demonstrate significantly increased TAPSE (2.58 ± 0.11 mm vs 1.98 ± 0.25 mm, $p < 0.05$), right ventricular EF (63 ± 2 % vs 48 ± 2 %, $p < 0.05$) and significantly decreased wall thickness (1.43 ± 0.08mm vs 1.73 ± 0.05mm, $p < 0.05$) in animals transplanted with neonatal hCPCs (n=9) compared to saline only (n=5) animals 4 weeks post transplantation. No significant difference was present among the other groups. Immunostaining showed significantly decreased fibrosis in animals transplanted with neonate hCPC's compared with saline only animals. Statistical modeling and systems biology was performed on patient arrays and gave insights in to potential mechanisms at the microRNA and gene level. Conclusion: This is the first study to assess the role of human pediatric CPCs in RV heart failure. We conclude that neonatal CPC's have the most beneficial effect in RV heart failure. While systems biology has given important information, the exact mechanisms related to this observation still need to be investigated.

102. More Rapid Delivery of Parenteral Analgesia by Adding Intranasal Fentanyl (INF) to the Management of Sickle Cell Disease (SCD) Vaso-Occlusive Pain Episodes (VOE) at a Pediatric Emergency Department (ED)

Bolanle Akinsola, MD; Robert Hagbom, MS; April Zmitrovich, MSW, MPH; Patricia Kavanagh MD; Ashley Ashkouti, RN, BSN, CPN; Amy Fletcher, RN, BSN, CPN; Natalie Vinson, RN, BSN; Harold K. Simon, MD, MBA; Alesia Fleming, MD; Shabnam Jain, MD, MPH; Olufolake Adisa, MD; Carlton Dampier, MD, CPI; and Claudia R. Morris, MD

Background: VOE are the leading cause of hospitalizations & ED visits in SCD. INF provides rapid & powerful parenteral analgesia, with an onset of action of 5-10 min; peak 30 min. INF is a safe & effective method of pain management for children in the ED & other settings, yet underutilized in SCD. Objective: To study the impact of the addition of INF to standard ED management for SCD VOE on time to parenteral opioid, pain scores, ED length of stay (LOS) & admission rate. Methods: In a pediatric ED from Nov 2013-May 2014, patients with SCD ages ≥2 years with VOE & pain scores >6/10 were offered INF within 15 min of triage (1.5mcg/kg/dose; max 100mcg/dose X2, 5 min apart). Patients also received standard protocol VOE treatment. Outcomes included: Time from arrival to 1st parenteral opioid, pain scores, ED LOS, admission rates & patient satisfaction. We compared patients in this study to those who did not receive INF during the study period (n=48) & historical controls from Jan-Dec 2012 (n=231) for the first 3outcomes.Results: 248 visits met inclusion criteria, 228 received parenteral opioids (92%) & 180/228 (79 %) received INF. Mean age was 12±5 years, 56% were female, 65% had HbSS. 48 patients did not receive INF; 36 were not offered INF &12 refused. Pain scores were similar in all groups. 100 families of patients receiving INF completed the satisfaction questionnaire: 61% were satisfied & would like to receive INF again. Conclusions: The addition of INF significantly improved time to receipt of 1st parenteral analgesia & was well tolerated. Admission rates were significantly higher in INF-group during our study period. The associated delay in time to receipt of 1st parenteral analgesia may have contributed to increased admission rate, although causality cannot be determined without further study. INF did not impact ED LOS compared to historical controls, however rapid admission turn-around time likely decreased LOS in the INF- group. INF is a safe & effective strategy to provide rapid pain relief in children with SCD & VOE.

103. Automated Analysis of Histopathological Whole Slide Images to Diagnose Pediatric Heart Transplant Rejection

Ajay K. Bhatia MD, PhD; John Phan PhD; Sonal Kothari, PhD; William Mahle, MD; Bahig Shehata, MD; and May Wang, PhD

Background: Rejection of a transplanted heart by the recipient is the most common cause of death within 5 years in the pediatric heart transplant population. Current methods to diagnose transplant rejection rely on hematoxylin and eosin (H&E) staining and immunohistochemistry-based methods to analyze endomyocardial biopsy (EMB) samples. Unfortunately, the interpretation of these data is subjective and non-quantitative. The goal of this pilot study was to determine whether extraction of salient image features via automated whole slide imaging can

accurately diagnose rejection. Methods: H&E–stained slides that had previously been prepared from formalin fixed, paraffin embedded (FFPE) EMB samples were obtained from a single pediatric tertiary care center. High-quality digital histopathological whole-slide images (WSIs) were derived from these slides. Images were tiled into 512x512-pixel images to enable efficient image feature extraction. Image tiles with greater than 90% tissue content and no image or slide artifacts were retained for feature extraction. Over 400 image features were extracted from each tile, with features representing a wide variety of properties such as stain color, texture, nuclear shape, and nuclear topology. Raw tile image features were then combined for each WSI to produce a single feature vector. Vectors were then compared across the entire labeled dataset to identify image features that may potentially predict heart transplant rejection. Results: Using an initial set of 17 WSIs in a pilot study, we identified potential image features for prediction of acute cellular rejection (ACR) and antibody mediated rejection (AMR). Results suggest that nuclear and cellular shape properties are differential between ACR and non-ACR EMB samples. Similarly, cell size may be informative of AMR. These features produced distinct clusters of rejection and non-rejection. Conclusions: Automated extraction of image features from EMB WSIs may provide a more objective means of pathologic analysis to predict pediatric heart transplant rejection. Moreover, the comprehensive extraction of over 400 image features may reveal interesting histopathological properties of heart transplant rejection.

104. Anticoagulation and Coagulopathy in Ventricular Assist Device Patients: What Correlates and What Does Not?

Ajay K. Bhatia, MD, PhD; Mallory Carroll, FNP; Silvia Bunting, MD; Kevin O. Maher, MD; Kirk Kanter, MD; and Shri Deshpande, MD

Background: Failure to achieve appropriate anticoagulation in patients supported with ventricular assist devices (VADs) increases the risk of serious complications such as post-operative bleeding, gastrointestinal bleeding and neurologically devastating stroke. This study attempts to provide additional data to guide management of anticoagulation by assessing the utility of various measures of anti-coagulation, including thromboelastography (TEG) Methods: Anticoagulation parameters from four patients supported with a Berlin Excor VAD at a single center during 2013 were studied (Table 1). PT, aPTT , INR, anti Xa assay, complete blood count as well as TEG results were reported for the duration of VAD support. In addition, clinical data including heparin dose, outcomes, adverse events, morbidities and mortality were described for each patient. Results: In a comparison sample of more than 100 individual data points, we demonstrated definitive associations between aPTT and R-TEG values (rs = 0.65, p<0.001) and between anti Xa assay and R-TEG values (, rs = 0.54, p<0.001). The strongest correlation was seen between aPTT and anti Xa assays (rs = 0.71 , p<0.001). Elimination of the heparin effect using heparinase revealed a statistically significant correlation between platelet counts and the maximum amplitude of TEG (MA-TEG) (rs = 0.71 , p<0.001). Importantly, there was no association between aPTT and heparin dose (rs = -0.031, p = 0.45) and a negative correlation between the heparin dose and both R value and anti Xa levels. Conclusions: This study suggests that while there is strong correlation between aPTT, anti Xa assay and R-TEG values for patients requiring VAD support, there is a lack of relevant correlation between heparin dose and degree of effect, as measured by these parameters. This raises concern as various guidelines continue to recommend using these parameters to titrate heparin therapy.

105. Identification of Candidate MicroRNAs as Pathological Markers of Pediatric Heart Transplant Rejection

Ajay K. Bhatia, MD, PhD; John Phan, PhD; Bahig Shehata, MD; William Mahle, MD; and Hanjoong Jo, PhD

Purpose: Rejection of a transplanted heart by the recipient is the most common cause of death within 5 years in the pediatric orthotopic heart transplant (OHT) population. The gold standard for diagnosing rejection is direct pathologic analysis of endomyocardial biopsy samples (EMB). Current methods of hematoxylin and eosin staining and immunohistochemistry-based diagnosis are non-quantitative, subjective, have limited early prognostic value, and, in up to 20% of cases, do not correlate with clinical status. The aim of this study was to develop microRNAs (miRNA) as specific and quantitative pathological markers of pediatric OHT rejection. Methods: Samples representing various grades of rejection were identified from a large biobank of formalin-fixed, paraffin-embedded (FFPE) EMB tissue derived from pediatric OHT recipients at a single center. Histopathological grading of rejection was made by three independent pathologists. Deep sequencing methods were employed to profile miRNA expression from a panel of 12 FFPE EMB representing Grade 2 acute cellular rejection (ACR) and 11 samples with no evidence (Grade 0 ACR) of rejection. The sequencing data was processed through multiple high-quality analysis

pipelines to identify candidate miRNAs that may be dysregulated in pediatric OHT rejection. Validation of specific miRNA expression was achieved via quantitative real-time PCR studies. Results: RNA sequencing revealed 12 miRNAs that demonstrated significant fold differences in expression levels (P value < 0.01) between samples with and without evidence of severe rejection. Specifically, miRs-141, 142, 146a, 155 and 188 were upregulated in FFPE EMB samples with evidence of severe rejection. Interestingly, miR 142 and miR155 are known to be significant regulators of inflammation, specifically via modulation of B and T-cell function. MiR 146a has also been implicated in regulation of innate immunity. Conclusions: Here we demonstrate that the upregulation of miRs-141, 142, 146a, 155 and 188 can serve as a signature of high-grade ACR in pathological samples. Importantly, these results suggest that miRNAs are well preserved in FFPE EMB and have the potential to be developed as specific and quantitative markers of heart transplant rejection.

106. Heterogeneity in the Host Response to West Nile Virus Infection of Human Dendritic Cells

James R. Bowen, BS; Steven E. Bosinger, PhD; Gregory K. Tharp; Mehul S. Suthar, PhD

West Nile virus (WNV) is a neurotropic Flavivirus and a leading cause of mosquito-borne encephalitis in the United States. With the lack of specific therapeutics or vaccines approved for use in humans, there is a pressing need to define the virus-host interactions that govern immunity to infection. While previous studies in mice have established that dendritic cells (DCs) are pivotal for viral control and programming of antiviral immune responses, we still have a rudimentary understanding of WNV infection in human DCs. We generated monocyte-derived DCs (moDCs) from healthy donors and infected them with WNV-TX, a pathogenic strain. We observed productive infection at 12 hours post infection (hpi) as determined by intracellular viral protein staining, ranging from 1-6% infected at 12hpi and increasing to 5-14% by 24hpi. There was noticeable variability in viral replication between the donors, ranging from 6 to 65-fold increase in infectious virus over a 12hr period as determined by plaque assay, suggesting that host genetics has a strong impact on viral control. We did not observe productive infection of moDCs by WNV-MAD, a nonpathogenic strain, suggesting that viral factors also contribute to infection of human DCs. To better understand the global host response to WNV infection, we performed next generation mRNA-sequencing on uninfected and WNV-infected moDCs. Consistent with variability in virus replication, we observed significant heterogeneity in the induction of antiviral effector genes and inflammatory cytokines between the different donors. In contrast to infection with WNV, treatment of moDCs from these same donors with highly specific RIG-I and MDA5 agonists elicited similar expression patterns for these genes, suggesting the observed variability is specific to virus infection and not explained by a differential ability of these donors to activate RLR signaling. Overall, these studies reveal the important role that host and viral genetics play in the host response to WNV infection.

107. Monitoring Cerebral Blood Flow, Oxygen Saturation, and Oxygen Metabolism Using Diffuse Optical Spectroscopies - ORAL PRESENTATION

Erin M. Buckley, PhD

108. Prevalence and Predictors of Inflammation in a Cohort of Bolivian Infants

Rachel M. Burke, MPH; Juan S. Leon, PhD, MPH; Parmi S. Suchdev, MD, MPH

BACKGROUND: Despite growing interest on inflammation and its relationship to different health outcomes, particularly its bidirectional relationship with nutrition, there is little longitudinal data available on the development and predictors of inflammation in pediatric populations. More data is needed especially in developing countries, where inflammation and malnutrition occur with high prevalence. The goals of the present study were to identify prevalence of inflammation and predictors of elevated levels of two acute phase proteins [C-Reactive Protein (CRP) and alpha(1)-acid-glycoprotein (AGP)] in a cohort of Bolivian infants 2 to 6 – 8 months of age. METHODS: Healthy infants were recruited from 2 hospitals in El Alto, Bolivia, and followed from 1 to 6 – 8 months of age. Anthropometric measurements and sociodemographic and recent illness data were collected at each visit. Blood taken at 2 and 6 – 8 months was analyzed for CRP and AGP. Inflammation was defined as CRP ≥ 5 μg/L or AGP ≥ 1 mg/L. Binary logistic regression with backwards elimination was used. Initial predictors considered included age, sex, preterm birth, birth type (Caesarean section vs. vaginal), 2-week recall of diarrhea, 2-week recall of cough, 2-week recall of fever, 48hr recall of fever, elevated CRP or AGP at 2 months of age, maternal inflammation at the 6 – 8-month visit, previous or concurrent stunting (length-for-age Z score < -2), previous or concurrent wasting

(weight-for-length Z score < -2), exclusive breastfeeding until 6 months, maternal employment, maternal education, and water source. RESULTS: The prevalence of inflammation in the sample was 3.8% (4/160 infants) at 2 months and 20.2% (33/163 infants) at 6 – 8 months. In the final model, 2-week history of cough (adjusted OR: 2.97 [1.14, 8.44]), 2-week history of diarrhea (adj. OR: 3.63 [1.25, 10.41]), and history of stunting (adj. OR: 3.67 [1.44, 9.67]) were significantly (p < 0.05) associated with inflammation at 6 – 8 months. CONCLUSIONS: This analysis demonstrated a 5-fold increase in the prevalence of inflammation between 2 and 6 months of age. Our results suggest that a history of infection may be useful as a proxy for detecting subclinical inflammation. Further, the association of stunting with inflammation may suggest that infants who suffer from chronic malnutrition may be more vulnerable to infection and chronic inflammation. Next steps include additional analysis with full sample size of 350 infants.

109. A Pilot Feasibility Study of Parent Training for Young Children with Autism Spectrum Disorder in Rural Georgia Via Telehealth

Anusha Challa, BA; Lauren Pascarella, MA; Karen Bearss, PhD; and Lawrence Scahill, MSN, PhD

Background Autism spectrum disorder (ASD) is a chronic neurodevelopmental condition characterized by social communication deficits, restricted interests and repetitive behaviors (APA, 2013). It affects 6 per 1,000 children worldwide (Elsabbagh et al., 2012). Up to 50% of children with ASD also exhibit disruptive behaviors, including tantrums and aggression (Mazurek, Kanne & Wodka, 2013). A 24-week parent training (PT) program for children with ASD and disruptive behaviors, developed by the Research Units in Behavioral Interventions (RUBI) consortium, has been tested and shown to reduce disruptive behaviors when delivered in-person to families (Bearss et al., 2013). Therapists also are able to reliably deliver the intervention in-person. It is not clear if this program will work when delivered via telehealth.   Methods This open-label pilot study examines the feasibility of delivering the PT program via telehealth by therapists from the Marcus Autism Center to parents of children with ASD plus disruptive behavior in rural areas of Georgia. Parents are being recruited from four collaborating sites from the Georgia Partnership for Telehealth (GPT) network. Fourteen children and their parents are participating in the 24-week program (11 core, 2 optional sessions; 3 booster phone calls), which is based on principles of applied behavior analysis and provides parents with specific techniques to manage the child's behavioral problems.   To assess feasibility of delivering the program via telehealth, data on therapist fidelity to the manual and parent attrition, session attendance, homework compliance and overall satisfaction are being collected. Efficacy is being evaluated through the parent-rated Aberrant Behavior Checklist and Home Situations Questionnaire. Results Fourteen families enrolled in the study; 7 finished the 24-week trial; 3 more will finish by June 2015. Of the 7 completers, 1 dropped out after consent. Six families attended all core PT sessions. Preliminary feasibility data show 97% therapist fidelity to the manual, 90% parent adherence to treatment, 80% compliance with homework, and high parental engagement in the therapy sessions. Parents report greater confidence in managing problems and would recommend the program to other parents. Preliminary efficacy results will be reported on the poster. Conclusion Initial findings indicate that telehealth is a feasible means to deliver the PT program.

110. Age-related Differences During BMP-2-mediated Bone Repair

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

Background: Large bone defects are one of the most challenging problems faced by orthopaedic surgeons today. Current treatments involve bone grafts and/or delivery of osteoinductive proteins such as BMP-2. But BMP-2 is currently contraindicated by the FDA for use in pediatric patients due to the potential for inflammatory reactions and lack of appropriate dose information. Despite this warning, BMPs are still commonly used to treat traumatic injuries, bone defects from tumor resection, and spinal deformities in pediatric patients because there are currently no better alternatives. The objective of this study was to apply our established critically-sized segmental bone defect model to young rats to evaluate differences in the BMP-2-mediated healing response, particularly at the early healing stage when inflammation is likely to be a key player in the pathophysiology of bone healing. We hypothesized that compared to older animals, young animals would be able heal at a lower BMP-2 dose but also exhibit an increased inflammatory response at higher BMP-2 doses. Methods: Young 7-week-old and older 8-month-old male SD rats received bilateral surgeries to create 8 mm femoral bone defects. A cylindrical collagen sponge, 5mm in diameter, was loaded with 150 µl of BMP-2 solution and then placed in the bone defect. Each rat received two BMP-2 doses: a low 1 µg and a high 10 µg dose. After 1 week, all animals were euthanized and tissues from the bone defect and

surrounding musculature were collected for gene expression analysis. Results: A panel of 48 genes relating to osteogenesis, angiogenesis, myogenesis, chondrogenesis, inflammation, and matrix remodeling were analyzed. The young rats showed increased expression of genes linked to osteogenesis (OSX, COL1A1, OPG), chondrogenesis (COL2A1, ACAN, FRZB), and matrix remodeling (MMP2, MMP13). In contrast, the older rats demonstrated higher expression of inflammatory genes (IL-1B, IL-6, MCP1, CCL3) and curiously, the angiogenic gene VEGFA. Conclusions: Not surprisingly, the younger animals demonstrated upregulation of genes related to bone healing/remodeling in support of our hypothesis. However, contrary to our hypothesis, it was the older animals that showed increased inflammatory expression after 1 week. Forthcoming data will determine if there are any long term effects of these early differences in gene expression by measuring new bone formed and characterizing the biomechanical properties of the healed femurs.

111. The Maintenance and Induction of B Cell Mediated Immunity Against Influenza Vaccination after B Cell Ablative Therapy

Alice Cho, BS; Bridget Bradley, RN, FNP, CCRC; Lalita Priyamvada, BS; Yevgeniy Kovalenkov, BA; Ron Feldman, MD, PhD; and Jens Wrammert, PhD

Pemphigus is an autoantibody-mediated disorder targeting epithelial adhesion molecules, causing blistering sores on skin and mucous membranes. Historically treated with immunosuppressants, recent therapies include Rituximab, a depleting anti-CD20 monoclonal antibody. While Rituximab depletes naïve and memory B cells, it does not deplete long-lived plasma cells Thus, it has little effect on preexisting serological immunity, suggesting that pemphigus is an ongoing process rather than mediated by plasma cells. Little is known about the effects this treatment has on pre-existing memory B cells, how, or indeed if, they recover homeostatically, and what the quality of peripheral B cells are once their numbers recover. In this study, pemphigus patients were vaccinated against influenza at various time points after B cell ablative therapy to analyze the generated B cell response. Reconstitution of the peripheral B cell compartment begins around 6-9 months post-depletion, with a transient increase in transitional B cells during the initial recovery. Memory B cells are persistently decreased compared to healthy controls, even in patients who were 20 months post-treatment. Interestingly, in spite of this, patients mounted potent influenza vaccine-specific plasmablast responses at a magnitude comparable to healthy controls, dominated by isotype-switched IgG, suggesting that this is a memory recall response. Hemagglutination inhibition assay revealed comparable seroprotective titers generated by the vaccine in both patients and healthy controls, suggesting that vaccine responses are not impaired in treated patients. Memory B cell and microneutralization assays will further probe into the quality of these responses. Immunoglobulin repertoire sequencing of plasmablasts from these patients will allow us to address the origin of these cells by analyzing the clonality and somatic hypermutation of the repertoire. Using these methods, we also hope to generate a panel of pemphigus-specific antibodies to glean more information about this understudied disease. Excitingly, we were able to sort plasmablasts from a flaring patient who had a plasmablast population that comprised 40% of B cells. This is twenty-fold higher than that seen in non-flaring patients, suggesting that this is a pathogenic response. This study will enable us to address fundamental B cell biology, the clinical issue of when to vaccinate these vulnerable patients, and the disease pathogenesis of pemphigus.

112. A Truncated FIP1C/RCP Fragment Inhibits Incorporation of the HIV Envelope Glycoprotein into Budding Virions by Sequestering Envelope in the Endosomal Recycling Compartment

Junghwa Choi, MS; Mingli Qi, PhD; Lingmei Ding; Jason Hammonds, PhD; Lynne A. Lapierre, PhD; James R. Goldenring, MD; and Paul Spearman, MD

HIV-1 viral particle assembly takes place on the plasma membrane of T cells and model epithelial cell lines. The process of envelope glycoprotein (Env) incorporation into the developing viral particle is a crucial step in virion assembly that remains incompletely understood. We recently described an important role for Rab11-FIP1C (FIP1C) and Rab14 in mediating the incorporation of Env in a manner that depends upon the presence of an intact Env cytoplasmic tail (CT). Here we investigated the effect of expression of a C-terminal FIP1C/RCP fragment on Env trafficking. We expressed the C-terminal 89 residues of FIP1C/RCP as a GFP fusion protein (GFP-FIP1C560-649) together with NL4-3 proviral DNA. GFP-FIP1C560-649 had no effect on overall production of viral particles as measured by p24 release. However, GFP-FIP1C560-649 demonstrated a profound dominant-negative effect on HIV envelope incorporation. Released particles were depleted of Env in a dose-dependent manner, and particle infectivity was reduced in proportion to the depletion of Env. We next compared the subcellular distribution of

wildtype GFP-FIP1C and Env with distribution following expression of GFP-FIP1C560-649. Strikingly, GFP-FIP1C560-649 was predominantly localized in enlarged perinuclear endosomal structures where it strongly colocalized with HIV Env. Expression of a provirus lacking most of the Env CT, NL4-3 CT del-144, demonstrated a very different pattern, with no trapping of Env in this compartment. We next mapped the element involved in ERC trapping of Env to a tyrosine-tryptophan motif in the cytoplasmic tail, YW795. A YW795/SL mutant demonstrated a prominent loss of Env incorporation into particles. When co-expressed with GFP-FIP1C560-649, no ERC trapping of YW795/SL occurred. A second site revertant virus was then derived from YW that restored Env incorporation through a distal CT substitution (L850/S). The reversion restored Env incorporation on particles, and also restored the phenotype of ERC trapping by GFP-FIP1C560-649. We conclude from these data that HIV-1 Env is trapped within the enlarged ERC formed by the expression of a dominant-negative truncated form of FIP1C/RCP, while specific mutations of the CT lead to escape from ERC trapping. These results support a model in which Env normally traffics through the ERC for outward sorting to the plasma membrane assembly site in a FIP1C/RCP-dependent manner.

113. Exploring the Creation of a New Pediatric Clinical Translational Research Unit to Increase Productivity in Pediatric Research Aimed at Reducing Health Disparities in Georgia

Victoria Churchill, MPH; Elham Laghaie, MS; and Lilly Immergluck, MD, MS

BACKGROUND: There currently is a gap in the diversity and linkage of pediatric clinical researchers to address specific disease conditions which disproportionately affect minority populations. Although units to align pediatric clinicians in research exist in other areas of the United States, there is not a system to fully support these collaborations in Atlanta, despite a strong pediatric research presence. OBJECTIVE: To investigate the feasibility of developing a pediatric clinical research unit to facilitate community based participatory research aimed at impacting pediatric health disparities to improve outcomes of preventable diseases. Aim 1: To explore expanding the Community Physicians Network to include more pediatric practices from the state of Georgia with emphasis on practices which serve children and adolescents of color in both rural and urban communities. Aim 2: To research the development of a portal which streamlines the coordination of services and resources needed by pediatric clinical investigators to initiate/run clinical translational and community engagement studies which impact the health and well-being of children, particularly children of color living in medically underserved or rural areas. Aim 3: To meet with community pediatric leadership to explore and learn topics of concern which would improve the quality of health and healthcare delivery for specific disease conditions for which there are known health disparities. METHODS: Based on examples of successful Pediatric Clinical Translational Units in other regions, we propose to explore ways to strengthen existing relationships among Morehouse School of Medicine's Clinical Research Center and other pediatric clinical research organizations in the state of Georgia to form a collaborative effort in identifying areas of need within the pediatric clinical research setting. We plan to then focus on our potential to create and promote resources to facilitate the implementation of research within the community. Finally, we hope to develop a strategy to evaluate and sustain our efforts to continue our role in pediatric research. CONCLUSIONS: Our exploration in the unification of pediatric research through the creation of the Pediatric Clinical Translational Research Unit will supply us with the resources and support the implementation of collaborative efforts to address health disparities among children in Georgia.

114. Barriers to Access to Specialty Care for Youth with Autism Spectrum Disorders: Parent's Perspective

Kristen Criado, PhD; Ashley Martinez, BA; Caitlin Herring, BA; Nathan Call, PhD; and William Sharp, PhD

Background: Children with ASD often present with increased medical needs, including comorbid ear infections (Konstantareas & Homatidis, 1987), increased use of antibiotics (Niehus & Lord, 2006), and high prevalence of gastroenterological symptoms (McElhanon, McCracken, Karpen, & Sharp, 2014). Furthermore, children with ASD are twice as likely to utilize healthcare (i.e., outpatient visits and hospitalizations) and, when accessed, the cost of those services is three times greater compared to children without ASD (Croen, Najjar, Ray, Lotspeich, and Bernal, 2006). Evidence suggests this may be related to physician skill with managing heightened resistance to medical procedures exhibited by children with ASD (Davignon et al., 2014). For example, in a survey of 144 parents, caregivers rated their pediatrician's ability to address a majority of their child's ASD-specific needs as "poor" (Carbone et al., 2013). To date, the literature has been focused on primary care in the medical home. The current study seeks to assess parents' perspectives about their experiences with specialty healthcare. Methods: Parents of children diagnosed with ASD were recruited from a list of families who previously participated in research at the

Marcus Autism Center. Parents participated in focus group discussions which were audio-recorded and transcribed for data analysis. Results: Seventeen parents (16 mothers, 1 father) participated in 7 focus groups. Coding of the transcripts revealed barriers in 4 categories with 15 subcategories: Access to care (e.g., geography, provider availability and waitlists), practice (e.g., environment), provider (e.g., knowledge of ASD), and child factors (e.g., problem behavior). Conclusions: This study revealed that families experience barriers to care, many of which could be addressed. Clinical implications include the need for 1) ASD training for specialty healthcare providers, 2) reduction in waitlists, and 3) changes to the environment to make appointments more conducive to children with ASD. Psychologists have a unique opportunity to apply their expertise to improve the system, in addition to providing care for individual patients. Future directions include focus groups with healthcare providers from Emory and Children's Healthcare of Atlanta and the administration of a needs assessment survey to determine the necessity of intervention.

115. The Application of Simulation and Modelling to Optimize Outpatient Clinical Processes

Megan E. Denham, MAEd; Dennis Kim, MD, PhD; Cyrus Samai, MD; and Craig M. Zimring, PhD

Background: Sibley Heart Center Cardiology, the highest volume pediatric cardiology practice in the country, seeks actionable solutions to improve the quality and experience of care. Drawing on engineering and architectural expertise, SimTigrate developed a novel application of tools and data syntheses methodologies, combining clinical processes with complex virtual models in order to evaluate the impact of various schedule templates and resource utilization on patient experience (PE) and clinical team experience (CTE) measures. Objectives: To utilize simulation and modeling tools to optimize target PE outcome metrics (visit durations and wait durations) and CTE outcome metrics (indicator for staff quality of life at work). To develop a modifiable framework that can be expanded and further developed for applications in a broad range of disciplines. Methods: Time-motion studies were conducted in 3 outpatient cardiology clinics, over 14 days. One-year of historical appointment data was analyzed to validate observation findings. AnyLogic software was used to develop a discrete event model to simulate patient flow. Sensitivity analyses (SA) were completed to evaluate scheduling and resource allocation scenarios on PE and CTE metrics. Results: The SA showed a 20 minute reduction in mean visit and wait times when increasing the number of exam rooms from 1 to 3, but >3 rooms yielded no additional benefits. A 20 minute reduction in mean visit wait durations by adding a second echo room was the result of a process (keeping patients in the echo room for review) versus the procedure (scanning). Specific areas of time delay were identified as a consistent modifiable factor at all of the clinics. Virtual schedule modelling allowed for targeted modification of the clinic template. At one-month follow-up, clinics piloting recommended schedule changes report improved CTE measures, supporting the findings from SA schedule template simulations. Conclusions: Virtual simulation and modeling permits rapid virtual testing of "what if" scenarios. The value in this approach is that it integrates patient care needs (typically defined by patient demographics/diagnosis) with process (influenced by the provider's practice style) and breaks those processes down into a sequence of events or activities. Understanding this interaction between scheduling models, processes, resource utilization and target outcomes can result in improved practice efficiencies and satisfaction measures.

116. Designing Cancer Care for Kids, By Kids: Engaging Patients and Their Families in Creating More Efficient Patient-Centered Care

Megan E. Denham, MAEd; Amy Sherrod, MSN, CNP; Yousef Bushehri, MArch; Craig Zimring, PhD; and Karen Wasilewski-Masker, MD, MSCR

Background: Children receiving chemotherapy at the Aflac Cancer & Blood Disorders Center (Aflac Cancer Center) at Children's Healthcare of Atlanta (CHOA) go through a highly complex process which involves multiple steps, providers, and rooms across the outpatient and inpatient setting. The complexity of the system creates inefficiencies and unnecessary waits, lengthening the time children spend in the clinic and in the hospital, and consuming precious time that kids and families are not at home, school, and other places doing the things they truly want to be doing. Objectives: In this project we refocus on the child by challenging the existing definition of and approach to patient-centered care, and assert that kids can be our partners in care - not just the recipients. We propose a new level of engagement with children and parents by asking them to take an active role in describing, evaluating and improving the care they receive. Methods: The research team, patients, families and clinicians co-developed a "passport" data collection tool. Through an iterative process, the team developed a process model of the infusion care steps, using medBPM process modeling software. As partners in care, patients used the passport

tool to collect data about their visit, including time stamps at the beginning and end of each activity, and qualitative descriptions of feelings at each step in the process.   Results: This ongoing research project has revealed many complexities within the care process. These result in process deviations and missed opportunities for care coordination, negatively impacting the efficiency of care. The passport tool will continue to be used to collect data, revealing key processes most important to the children during their care as well as opportunities for simplifying and optimizing their journey through clinic for chemotherapy infusions in a way that is mutually beneficial for the children, families, and staff.   Conclusions: This research demonstrates a methodology to actively engage and empower kids to improve the care they receive.

117. Utility and Cost Effectiveness of Cranial Ultrasound Screening in Patients with Congenital Heart Disease

Carrie Ciccotello and Shriprasad Deshpande, MD, MS

Background: Cranial ultrasound (CUS) is commonly used as a screening tool for intracranial anomalies in infants undergoing cardiac surgery. Previous studies have suggested a correlation between CHD and abnormal CUS with as many as 22 % to 45% of infants with CHD demonstrating extra-cardiac abnormalities. When compared to healthy infants, infants with CHD are more frequently diagnosed with cerebral atrophy, linear echodensities, and intraventricular hemorrhage. However, all of the prevalence data is based on very small studies with about 30 to 70 patients. There is limited data regarding the specificity of CUS in this regard. Goal of our study is to determine the utility of CUS as a screening tool, determine the prevalence of intracranial anomalies in the CHD population and assess the cost associated with the screening. Methods: Newborns admitted to the CICU at Children's Healthcare of Atlanta for cardiac surgeries routinely have a screening CUS performed. We identified infants undergoing cardiac surgery from our institutional surgical database (2006-2014). Demographic, diagnostic, procedural and outcomes data were collected. CUS was performed using standardized protocol. Any follow-up studies triggered by an abnormal ultrasound were reviewed to assess specificity. Results : 1042 infants were included in the study that provided complete data. Of these patients, only 87 patients were found to have minor anomalies on the CUS (of no clinical significance) while only 11 (~1%) were found to have major abnormalities on the screening CUS. This prevalence rate for major findings is significantly lower than previous reports using very small sample sizes. Of the 11 with major findings on the screening CUS, 5 had a follow-up CT scan done. All 5 scans showed significant abnormalities confirming the findings from CUS. Similarly follow-up MRI was performed in 8 patients which were all abnormal and confirmed findings from the CUS. Although these are small numbers, we conclude that screening CUS has a 100% specificity. Lastly, cost analysis using published Medicare fee schedule showed that the cost to one detection of one major anomaly using screen CUS is about $11,700. Conclusion: In a large study of infants undergoing cardiac surgery, the prevalence of major intracranial abnormality is very low, as assessed by a cranial ultrasound. However, when major anomaly is detected by the ultrasound, the specificity is 100% in our experience. Lastly, there is a major cost associated with the screening test and may not justify its routine use for screening.

118. Sonic Hedgehog Induces YB-1 in a YAP-dependent Manner to Regulate Igf2 Expression and Proliferation in Cerebellar Granule Neuron Progenitors and Medulloblastoma Cells

Abhinav Dey, Mélanie Robitaille, Marc Remke, Caroline Maier, Anshu Malhotra, Alex Gregorieff, Jeffrey L. Wrana, Michael D. Taylor, Stéphane Angers, and Anna Marie Kenney

nteractions between the developmentally essential Sonic hedgehog (Shh) and Insulin-like Growth Factor (IGF) pathways play prominent roles in medulloblastoma (MB), the most common malignant pediatric brain tumor. MB patients undergo surgery, chemotherapy, and radiation, a regimen that carries devastating side effects, emphasizing the need for targeted therapies to improve survival and quality of life. Post-natal proliferation of cerebellar granule neuron precursors (CGNPs), proposed cells-of-origin for the SHH-associated subgroup of MB, is driven by Shh and IGF in the developing cerebellum. Shh induces the oncogene Yes-associated protein (YAP), which drives IGF2 expression in CGNPs and mouse Shh-associated medulloblastomas. To determine how IGF2 expression is regulated downstream of YAP, we carried out an unbiased screen for transcriptional regulators bound to IGF2 promoters. We report that Y-box binding protein-1 (YB-1), an onco-protein regulating transcription and translation, binds to IGF2 promoter P3 and is required for IGF2 expression in CGNPs. We show that YB-1 is induced by Shh in CGNPs in a YAP-dependent manner and is found in the germinal layer of the developing cerebellum. We observed that YB-1 is up-regulated across human medulloblastoma subclasses and is elevated in a mouse model for the Shh medulloblastoma subclass. Finally, shRNA-mediated knockdown experiments reveal

that YB-1 activity is required for CGNP and medulloblastoma cell (MBC) proliferation in primary cultures and organotypic slice cultures. Collectively, our findings describe a novel role for YB-1 in driving proliferation in the developing cerebellum and medulloblastoma cells and they identify the SHH:YAP:YB1:IGF2 axis as a powerful target for therapeutic intervention in medulloblastomas.

119. Increased Survival and Phenotypic Reprogramming of Neutrophils in Cystic Fibrosis Airway Disease - ORAL PRESENTATION

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

120. The Role of Stress Echocardiography in a Large Pediatric Cardiology Program: A Programmatic Perspective

Heather Friedman, MPH; William L Border, MBChB, MPH; Ritu Sachdeva, MD; and M. Eric Ferguson, MD

Background: Stress echocardiography is one of the cornerstones of non-invasive assessment of ischemia in adults. However, its role in the pediatric population is less well defined and the indications more varied. It takes a considerable commitment to resource such a program in terms of space, staffing, training, technology and equipment. We sought to describe our six year experience utilizing exercise stress echo (ESE) in a large single center to help inform others interested in initiating such a program.Methods: Records of all patients who underwent an ESE at our center from 2009 to 2014 were reviewed for patient demographics and the indications for ESE. Indications were categorized into: hypertrophic cardiomyopathy (HCM), left ventricular hypertrophy (LVH), coronary anomalies (congenital and acquired), congenital heart defects (CHD), which was subcategorized into tetralogy of Fallot (TOF), transposition of the great arteries (TGA), single ventricle and other, chest pain or syncope with exercise, research, and other. Yearly volume of ESE was obtained and compared to overall echocardiography volume and outpatient cardiology clinic volume. Results: During the study period, 582 ESE's were performed (mean age 13.8 ± 3.4 years, 383 (65.8%) males). The indications for the ESE included: CHD in 120 (21%), with TOF in 16, TGA in 26, single ventricle in 13, and other CHD in 67, HCM in 112 (19%), chest pain or syncope with exercise in 81 (14%), coronary anomalies in 51 (9%), with 38 congenital and 13 acquired, LVH in 20 (3%) research in 122 (21%), and other indications in 76 (13%). Approximately 100 ESE's were performed per year (2/week). This is in the context of a large volume pediatric cardiology program seeing nearly 30,000 outpatients and performing nearly 15,000 echocardiograms per year. Conclusion: ESE is performed routinely at our center for a wide variety of indications. It still comprises a relatively small percentage of overall echocardiography volumes. Since it does require a fair amount of resource allocation, programs need to balance cost and utility when implementing it. Future studies should examine its impact on clinical decision making and ultimately patient outcome.

121. The Role of Practice Variation in Length of Stay for Children with Perforated Appendicitis

Teresa Gross, BS; Courtney McCracken, PhD; Kurt F. Heiss, MD; Mark L. Wulkan, MD; and Mehul V. Raval, MD, MS

BACKGROUND. Length of stay (LOS) is an easily tracked outcome that may reflect health care efficiency and surgical resource utilization. While current focus has been to decrease LOS by minimizing complications, the purpose of this study was to determine the influence of practice variation on LOS for children with perforated appendicitis. METHODS. Children ages 2-18 years who underwent appendectomy for complicated appendicitis were selected from the 2012-2013 ACS National Surgical Quality Improvement Program-Pediatric. Extended LOS (eLOS) was defined as >/=7 days (75th percentile). The contribution of specific comorbidities, operative traits, and postoperative complications to eLOS were evaluated using regression models and matched subgroup analyses. RESULTS. Of the 2,585 children identified, 835 had eLOS. Increasing numbers of comorbidities and complications were associated with increasing LOS. In the fully adjusted regression model, eLOS was associated with wound dehiscence (Odds Ratio (OR) 13.53 95% Confidence Interval (95%CI) 1.62-113.19), wound infection (OR 6.66 95%CI 2.39-18.62), organ space infection (OR 95.24 95%CI 35.08-258.63), and pneumonia (OR 4.96 95%CI 1.18-20.82). Over three-fourths of the variation in LOS could not be explained by the variables in our fully adjusted model, and 73% of eLOS patients could be matched to patients with normal LOS based on preoperative and postoperative characteristics. Of the 382 patients with no complications or comorbidities, 28% had an eLOS.

CONCLUSION. There is significant variation in LOS for children undergoing appendectomy for perforated appendicitis that is not accounted for by comorbidities, operative traits, or complications indicating an opportunity to improve outcomes through modifying practice patterns.

122. Ultra Wideband Monitoring in the Pediatric Patient

Claire Hailey; Nikhil Chanani, MD; Jiten Chhabra, MD, MS; and Leslie Smitley, RN, MSN, CCRC

Background: Children commonly experience cardiac and pulmonary issues that require continuous monitoring in the inpatient setting and at home. Current monitoring systems require wires and electrodes that irritate skin, predisposing them to pain and infections, along with restricting movement. This study's goal is to form an initial assessment of the Virtual Medical Assistant™ (VMA) in a pediatric setting. The VMA has been developed by Sensiotec® and is currently FDA-approved for use in adults only. The VMA uses ultra wideband radio waves to monitor heart rate, respiratory rate, and patient movement wirelessly, thus eliminating the need for attachments. We hypothesize that the VMA will be able to accurately detect the heart rate and respiratory rate of pediatric patients. Additionally, we hypothesize that the VMA will not cause any level of discomfort and that the majority of participants will prefer wireless monitoring to the current technology. Methods: The Virtual Medical Assistant™ was placed under the mattress of six patients admitted to the Pediatric Cardiac Intensive Care Unit at Children's Healthcare of Atlanta to monitor the patients' heart rates and respiratory rates. The patient's heart rate and respiratory rate were collected from telemetry as a standard for comparison. Based on current industry standards, analysis with root mean square error was used to assess the device's accuracy. Additionally, the study participants were given a survey about comfort and preferences for vital sign monitoring. Results: The VMA detected the heart rate and respiratory rate with root mean square errors of 7.89 and 4.72, respectively. All but one of the survey participants did not feel the device under the mattress. One participant felt the device under the mattress but it did not affect the patient's comfort level. All of the participants in the study preferred to have vitals monitored wirelessly rather than with the conventional wired system. Conclusion: The Virtual Medical Assistant™ can be safely used to wirelessly monitor the heart rate and respiratory rate in pediatric patients. The accuracy of the device is near industry standards but requires further optimization for pediatric patients. Patient comfort level was unchanged by having the device placed under the mattress, and patients preferred wireless monitoring to the conventional wired system. Further studies should test the device for accuracy in larger pediatric populations as well as in neonates.

123. Siglec-1 and Tetherin Cooperatively Lead to the Formation of the Virus-containing Compartment (VCC) in HIV-1-infected Human Macrophages. - ORAL PRESENTATION

Jason E. Hammonds, PhD; Neal Beeman, PhD; Lingmei Ding; Jaang-Jiun Wang, PhD; and Paul Spearman, MD

124. Detection of Human Pluripotent Stem Cells Using Surface-enhanced Raman Scattering Nanoparticles

Jingjia Han, PhD; Ximei Qian, PhD; Kevin O. Maher, MD; Shuming Nie, PhD; and Chunhui Xu, PhD

Human pluripotent stem cells (hPSCs) hold great potential as valuable cell sources for cell therapy and regenerative medicine. However, a major concern in clinical translation is their risk of teratoma formation, giving rise by residual undifferentiated stem cells in the preparation of specific cell types derived from hPSCs. Current cell-based assays including flow cytometry lack sufficient sensitivity (>0.1%) so as to meet the stringent safety standard for stem cell products, thus requiring the development of a cell-based assay with high sensitivity and specificity. We hypothesize that surface enhanced Raman scattering nanoparticles (SERS) can be developed to detect residual undifferentiated cells in a highly sensitive and specific manner. To develop such an assay, we conjugated SERS nanoparticles with an antibody against a well-recognized pluripotency surface marker (TRA1-60), and modified the PEG-SH shielding layer and the ligand concentration to improve the detection of pluripotent stem cells. The SERS assay protocol was then established by comparing different blocking buffers as well as titrating TRA1-60-conjugated SERS nanoparticles. Subsequently, the specificity of the established TRA1-60-SERS assay was confirmed by examining SERS signals from undifferentiated stem cells (IMR-90, H7) and negative cells (cardiomyocytes, fibroblasts). The high sensitivity of the SERS assay was validated using cell mixtures containing varied numbers of undifferentiated hPSCs at final concentrations of 0.01, 0.1, 1, 10, and 100%. We found that the SERS assay was able to detect stem cells at as low as 0.01% whereas flow cytometry analysis carried out in parallel only showed a detection sensitivity of 0.1-1%. We conclude that our SERS assay is highly sensitive and

specific, and thus can be applied as a stringent tool for the quality control of stem cell-based products as well as the detection of undifferentiated cells in stem cell-related biomedical research.

125. The Effect of Aligned Electrospun Fibers on the Maturation of Human Pluripotent Stem Cell-derived Cardiomyocytes

Jingjia Han, PhD; Qingling Wu, MS; Younan Xia, PhD; Mary B. Wagner, PhD; and Chunhui Xu, PhD

Human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) provide a promising source for drug screening and disease modeling. Although several high-yield protocols exist for generating hPSC-CMs, methods capable of significantly advancing hPSC-CM maturation are still lacking. We hypothesize that the anisotropic alignment of hPSC-CMs imposed by the underlying aligned electrospun fibers can improve the maturation of hPSC-CMs. To examine whether cardiomyocyte maturation can be modulated by the anisotropic feature of a fibrous substrate, aligned and random polycaprolactone (PCL) fibers were prepared by electrospinning and all substrates, including the use of tissue culture polystyrenes (TCPs) as a control, were coated with matrigel. Directed differentiation of hPSC-CMs was carried out using growth factors activin A and BMP4 or small molecules that target the Wnt signaling pathway. The cells were further enriched via Percoll gradient centrifugation, if necessary. At differentiation day 16-20, the hPSC-CMs (>70% purity) were replated on all substrates. After two weeks of culturing on various substrates, the structural and functional properties of the ensuing hPSC-CMs were evaluated. The aligned and random electrospun fibers had well-defined anisotropic and isotropic features with an averaged fiber diameter of approximately 700 nm, according to scanning electron microscopy. As expected, hPSC-CMs grown on the aligned fibers exhibited anisotropic alignment and elongation whereas cells on the random fibers remained isotropic and round. In comparison, cells cultured on TCPs formed large cellular bundles with random orientations. Like the case of TCPs, hPSC-CMs cultured both on the aligned and random fibers exhibited CM-specific protein expression, were pharmacologically responsive in a dose-dependent manner to various drugs, including α- or β- adrenergic receptor agonist, muscarinic agonist, and gap junction uncoupler, and displayed CM-specific calcium handling properties. In particular, the hPSC-CMs grown on aligned fibers displayed the highest expression levels of genes encoding sarcomere proteins and ion channels, such as troponin T, titin, calsequestrin 2, and Kir2.1. Our results suggest that aligned electrospun fibers can improve the maturation of hPSC-CMs which may be useful in future studies of drug screening and disease modeling.

126. Changing the Landscape: Application and Optimization of Novel MRI Pulse Sequences in Pediatrics

Sassan Hashemi, MD; W. James Parks, MD; Denver Sallee, MD; Animesh Tandon, MD; Xiaodong Zhong, PhD; Gary McNeal, MS; and Timothy Slesnick, MD

Background: The field of magnetic resonance imaging (MRI) has evolved drastically in terms of hardware and pulse sequence design to allow imaging of tissues in a more complete and complex manner. Work in Process (WIP) pulse sequences are novel imaging techniques that require parameter optimization and clinical testing to achieve optimal performance before widespread application. CHOA and Siemens Healthcare have initiated a research collaboration to test cardiac WIP pulse sequences for validation and optimization for pediatric population. Method: Patients referred for cardiac MRI studies are prospectively consented for appropriate WIP pulse sequence(s). WIPs currently require 10 seconds to 8 minutes to complete, and are performed at the end of the clinical MRI scan. Images are post-processed locally, and select examples are anonymized and shared with the developer for feedback and refinement. Results: Since August, 2013, we have performed 156 WIP acquisitions (75 four-dimensional phase-contrast (4D PC), 41 self -coronary imaging, 21 T1 mapping, 11 compressed sensing and 8 in-line phase-contrast) on 145 patients. 4D PC has been used primarily to delineate abnormal flow patterns in dilated aortas or streaming of systemic venous return in Fontan patients. The initial sequence shared with CHOA required 15+ minutes, but we have refined it to 5-8 minute acquisitions. Self-navigated coronary imaging (5-8 minute acquisition) parameters were extensively modified and now yield 3D coronary images with equal quality and more reliable acquisition time compared to conventional methods. T1 mapping (10-60 second acquisitions) is an emerging subfield in cardiac MRI, and we found reproducible results for left ventricular myocardium, while analysis on the thinner right ventricular myocardium or aortic vessel wall have been less robust. Compressed sensing (15 second acquisition) allows increased spatial and temporal resolution via selectively under-sampling K-space and iterative reconstructions. Finally, in-line phase-contrast (60 second acquisition) allows semi-automated flow analysis with improved background phase correction. All WIP sequences have been successfully performed, with marked improvements in several compared to the initial versions developed by industry. Conclusion: Our ongoing

collaboration has resulted in pulse sequence optimization, while allowing novel, patient specific physiologic insights for children undergoing cardiac MRI at CHOA.

127. Development of a 3D, Contrast Enhanced, Self-Navigated Inversion Recovery Gradient Echo Coronary Imaging Pulse Sequence in Pediatric Patients

Sassan Hashemi, MD; Davide Paccini, PhD; Denver Sallee, MD; W. James Parks, MD; Animesh Tandon, MD; Michael Zenge, PhD; Gary Mcneal, MS; and Timothy Slesnick, MD

Background: Coronary arterial imaging in pediatric patients is challenging due to higher heart rates and smaller vessel sizes. 3D respiratory navigator inversion recovery gradient echo (NAV IR GRE) imaging after administration of a blood pool contrast agent has shown advantages compared to 3D T2 prepared bSSFP imaging. Both techniques, however, provide unreliable acquisition timing since respiratory navigation efficiency varies between patients. Self-navigated (SN) whole heart imaging with a bSSFP readout has been previously introduced. This technique, however, has not been applied using an IR preparation and GRE readout (SN IR GRE). We therefore sought to apply the SN IR GRE methodology in pediatric patients. Methods: A previously described 3D radial phyllotaxis SN pulse sequence was converted to perform an IR preparation pulse and GRE based readout. A series of iterative experiments was performed to optimize flip angle, bandwidth and inversion time after administration of gadofosveset trisodium. Once optimal parameters were determined, 15 patients underwent both NAV IR GRE and SN IR GRE 3D imaging on a 1.5T scanner. Images were assessed for coronary artery clarity, including quantitative assessment of SNR and CNR, vessel sharpness, and visualized length Results: SN IR GRE image quality was optimized with flip angle = 15°, bandwidth = 1000 Hz/Px, and inversion time = 290 ms. The median age of the patients was 13.6 years (range 7.1 – 17.6), with an average heart rate of 77±13 bpm, and a variety of congenital heart diseases. Acquisition duration for the SN IR GRE was extremely predictable, with an inverse linear relationship with the heart rate of the subjects. Image quality was excellent and diagnostic for all patients with both methodologies. On side-by-side comparison, the SN IR GRE was qualitatively superior in 7, inferior in 6, and equivalent in 2 patients. SNR and CNR were higher using the NAV IR GRE (p<0.01), but vessel sharpness and visualized length were not statistically different for the LCA and RCA.   Conclusion: Self-navigated IR GRE can be consistently and robustly performed in pediatric patients. It has highly predictable acquisition times without the efficiency variation inherent to respiratory navigation, and thus facilitates planning of coronary scans. The diagnostic quality of the images is excellent, and though SNR and CNR are higher with NAV IR GRE, there were not differences in vessel sharpness, length, or qualitative visual grading.

128. Talk With Me Baby: Georgia's Language Nutrition Strategy

Lauren M. Head, BSN, RN; Ashley E. Darcy Mahoney, PhD, NNP; Jennifer Stapel-Wax, PsyD; Bryan Williams, PhD; Brenda Fitzgerald, MD; Kenney Moore, PhD; Arianne Weldon, MPH; and Comer Yates, JD

Background: An early environment that includes language-rich, adult-child interactions, or language nutrition, is critical for a child's brain development and subsequent educational achievement. Research demonstrates that the strongest predictor of a child's academic success is the quality and quantity of words spoken to a child in the first three years of life, which is directly related to third grade literacy. Third grade marks a time when children shift from "learning to read" to "reading to learn", and those who cannot make this shift are four times more likely not to reach high school graduation. Children from low-income families hear thirty million words less than peers from more affluent families and currently, only 21% of fourth-grade children from low-income families in Georgia can read at grade level.   Methods: Talk With Me Baby (TWMB) is a cross-sector coalition focused on bridging the word gap in Georgia by building the capacity of parents to provide early language nutrition to their babies. TWMB seeks to create statewide systemic change by establishing a wide-reaching public health, clinical, and early childhood education workforce that can coach parents to talk with their babies by demonstrating dynamic language exchanges and encouraging language-rich home and educational environments.   Results: TWMB has developed a curriculum to train nurses to educate parents how to be conversational partners with their infants. Currently, all Women, Infants, and Children (WIC) nutritionists across the state of Georgia have been trained to deliver messages about language nutrition to families, which is reaching approximately 60% of all infants in the state of Georgia. TWMB has also created a website and developed a smart phone app to provide parents of young children with resources about language nutrition. Conclusions: TWMB has the potential to help close the nation's educational achievement gap, leverage dramatic results for children's literary success, and holds promise for children of future generations.

129. Temperature Programmed Sample Collection from EBC for Multi-dimensional GC Analysis

S. Surappa; P. J. Hesketh, PhD; L. A. S. Brown, MD, PhD; J. M. D. Dimandja, PhD

We have been investigating methods to improve the quality of the sample, and ease the burden for the patient, when an exhaled breath sample is collected. In medical diagnostics and for monitoring of therapeutic progress, exhaled breath condensate (EBC) has attracted renewed interest because it is less invasive method of sample collection than is currently in use during treatment. We have developed a system for the capture of the volatile organic compounds (VOCs) as well as the liquid breath condensate present in exhaled human breath. The collected fractions are then analyzed using gas chromatography-mass spectrometry (GC-MS) and 2-dimensional GC/MS, which provide analysis of both volatile organic compounds present in human breath and liquid analysis of higher molecular weight components, after suitable derivatization. The system is also capable of separating the dead-space breath from the alveolar breath, allowing us to analyze each fraction independently. We have been able to analyze over 100 compounds in the EBC sample. GC-based methods have seen increased use in medical applications, ranging from analyses of exhaled breath for allergic asthma and the detection of markers indicating oxidative stress, to studies on cystic fibrosis, monitoring plasma glucose, detection of lung cancer, and several areas in veterinary medicine.

130. Sphingosine 1-Phosphate Receptor 3 (S1PR3) is Highly Upregulated on Human Neutrophils Upon Migration to the Airways

Sarah A. Ingersoll, PhD; Osric Forrest, BSc; Milton Brown, PhD; and Rabindra Tirouvanziam, PhD

Background and hypothesis: Migration of polymorphonuclear neutrophils (PMNs) from blood into the airway lumen is accompanied by changes in surface receptors and responsiveness to environmental cues, such as sphingolipids. In particular, signaling via extracellular ceramide / sphingosine 1 phosphate (S1P) was suggested to contribute to human airway disease, such as cystic fibrosis (CF). We hypothesized that airway PMNs would alter expression of the S1P receptor, S1PR3, which was recently implicated in lung inflammation and fibrosis. Methods: We collected blood and sputum from healthy control (HC) and CF subjects and analyzed S1PR3 expression in live PMNs gated by flow cytometry. In addition, we used a novel in vitro model to study the effect of transepithelial migration of blood PMNs on S1PR3 expression. Results: We observed a 10-fold upregulation of surface S1PR3 expression on HC and CF airway PMNs, in vivo, compared to their blood counterparts. This major increase was recapitulated in vitro, when naive blood PMNs were induced to transmigrate through an airway epithelial layer upon exposure to apical CF airway fluid. S1PR3 expression increased over time, by 10-fold after 10 hours, and up to 20-fold at 18 hours. Conclusions: Modulation of S1PR3 expression follows PMN migration to both HC and CF airways. Further studies will determine the importance of this receptor in mediating responses to ceramide/S1P signaling in these cells, including PMN migration, apoptosis and activation.

131. Simulated Microgravity Improves Efficient Generation and Survival of Cardiomyocytes from Human Pluripotent Stem Cells

Rajneesh Jha, PhD; Qingling Wu, MS; Monalisa Singh, MD, PhD; Marcela K. Preininger, BS; Hanjoong Jo, PhD; Kevin O. Maher, MD; Mary B. Wagner, PhD; Chunhui Xu, PhD

Background: Three-dimensional (3D) cardiac aggregates have the potential to improve efficient cardiac differentiation, cell growth, maturation and enrichment. Microgravity (MG) has profound effect on cell proliferation and cell survival. Therefore, we propose to study the effect of combining 3D tissue engineering and MG on proliferation, survival, differentiation and functional properties of cardiomyocytes (CMs) to overcome the disadvantage of commonly used 2D culture. Methods: 3D engineered progenitor cardiospheres were expanded under standard gravity (SG) or MG and were compared for their survival, purity and yield with parallel 2D cells differentiated under SG. Further, cardiac progenitors survival and proliferation were also determined by AnnexinV/PI staining and co-staining of NKX2-5 with Ki-67 or EdU respectively. Expression of genes related to cell survival, cell cycle and stress proteins was also compared among the groups. Finally, derived CMs were characterized for their pharmacological responses using multi-electrode array recordings, calcium-handling properties, and expression of CM-associated genes. Results: The viability and purity of cells differentiated in 3D conditions were significantly higher than in 2D cultures (p<0.01). CMs yield from each input of iPSC was significantly higher in 3D-MG (~5 fold) and 3D-SG (~3 fold) than 2D-SG cultures (p<0.01). 3D progenitor

cardiospheres under both SG and MG expressed genes related to cell proliferation (MKI67 and PCNA), cell cycle (ANLN, AURKA, AURKB, CCNB1 and PLK1), heat shock responses (HSP60, HSP70 and HSP90) and cell survival (BIRC5) at significantly higher levels than did the 2D cells (p<0.01). Immunocytochemical analysis showed more cells positive for CM markers (cTnT, cTnI and cadherins) from 3D-MG and 3D-SG as compared to 2D-SG. Further, qRT-PCR analysis revealed that 3D cardiosphere expressed ATP2A2, βMHC, cTnI, CASQ2, SLC8A1, TNNT2 and TTN at higher levels than 2D cells. Furthermore, CMs derived under MG had appropriate calcium handling, electrophysiological properties and pharmacological responses.

132. Plasma Metabolomics in Pediatric NAFLD Reveals Altered Lipid and Amino Acid Metabolism

Ran Jin, PhD; Sophia Banton, PhD; Shuzhao Li, PhD; Dean Jones, PhD; and Miriam Vos, MD, MPH

Background: Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in both children and adults and is predicted to become the most common indication for liver transplant within the next 10 years. Known metabolic disturbances in NAFLD include upregulated de novo lipogenesis and elevated free fatty acids; but metabolic pathways affected by NAFLD have not fully identified and therapeutic strategies are still lacking. Methods: Fasting plasma samples of 30 Hispanic-American adolescents with MRS-documented NAFLD (intrahepatic fat > 5%) and 9 age, race, and BMI matched non-NAFLD controls (intrahepatic fat < 5%) were analyzed using LC-MS high-resolution metabolomics. Metabolite features of m/z value between 50 and 2000 were scanned in triplicates on a Thermo Fisher Velos LTQ Orbitrap mass spectrometer, coupled with C18 reverse phase liquid chromatography. Data were processed using apLCMS and xmsAnalyzer, with quality control and correction of batch effects. Significant metabolite features were selected by student's t-test (p<0.05), followed by pathway analysis with Mummichog, a set of algorithms specifically designed for high-throughput metabolomics. Results: The metabolomics analysis yielded 9,583 metabolite features and 7,711 metabolite features remained for statistical testing and analysis with 80% presence across all samples. The student's t-test determined 478 metabolites that were differentially expressed between NAFLD and controls (p < 0.05). Pathway analysis by Mummichog identified 13 pathways significantly differed between adolescents with NAFLD and controls, including tyrosine metabolism (p=0.0009), fatty acid activation (p=0.0009), linoleic acid metabolism (p=0.0014), de novo lipogenesis (p=0.0032), fatty acid metabolism (p=0.0059), tryptophan metabolism (p=0.0064), and vitamin B9 metabolism (p=0.0093). Conclusions: Multiple pathways plausibly related to lipid and amino acid metabolism are altered in adolescents with NAFLD. This approach of detailed metabolic phenotyping may be useful to accelerate our understanding of NAFLD pathophysiology in children, and improve knowledge of therapeutic targets for future management of the disease.

133. Biomechanical Benchmarking and Development of an Early Warning System for Non-Union in Pediatric Bone Fusion

Brett S. Klosterhoff; Angela S. P. Lin; Robert E. Guldberg, PhD; and Nick J. Willett, PhD

Background For pediatric patients, it is difficult to monitor the success of a bone fusion procedure. Computed tomography is the current clinical standard to assess bone fusion. However, it is imperative that radiation exposure is curtailed in pediatric populations. Thus, radiographic imaging is usually minimized and complications in bone fusion are challenging to diagnose until evident failure has occurred. There is a clear clinical need for a minimally invasive metric that will enable clinicians to longitudinally monitor the progression of a bone fusion procedure. We have designed an innovative MEMS based sensor that wirelessly transmits real-time measurements of fusion success in vivo. Methods To monitor the success of bone fusion, we have designed sensors that measure local mechanical strain across the fusion interface. The sensors developed for this application utilize an active nickel-chromium piezoresistive sensing unit miniaturized to integrate onto bone fixation plates used in our rodent segmental defect model. Ex vivo mechanical testing of excised rodent femur was performed in axial compression under physiologically relevant loads to determine the range of strain magnitudes for the sensor design. Bones were prepared with a fixation plate and left intact or a defect was created; they were then tested in compression to determine the anticipated differences in mechanical strain between fused and non-fused bones. Results Mechanical testing results established that the desired strain range for the bone fusion sensor is between (-500) to (-15000) με. Piezoresistive sensor prototypes have been fabricated to meet strain range requirements, and microfabrication processes are being tuned to optimize repeatability and precision. Circuitry components have been defined to ensure safe operation of the sensor for 12 weeks with sufficient battery power to acquire 150 minutes of longitudinal strain data. Instrumented mechanical tests of sensor prototypes and in vivo trials are planned upon conclusion of fabrication and rigorous validation of the sensor's fusion evaluation capabilities. Conclusion We have

designed a miniaturized sensor which measures physiologically relevant mechanical strains across the fusion gap to monitor the success of bone fusion. This innovative monitoring system has the potential to mitigate the risks of radiation exposure from computed tomographic imaging, and improve the fidelity of pediatric bone fusion evaluation.

134. Lymphocyte Cell Adhesion Molecule L-Selectin Plays a Dynamic Role in Ischemia Reperfusion Injury of a Steatotic Liver

Vasantha Kolachala, PhD; Sirish K. Palle, MD; Ming Shen, BS; Alayna Feng; Carlos Abramowsky, MD; Dmitry Shayakhmetov, PhD; and Nitika Gupta, MD

Background: A steatotic liver is increasingly vulnerable to ischemia reperfusion injury (IRI), which is commonly encountered during hepatic resection, shock and liver transplantation. The underlying mechanisms of the resultant cell death and hepatocellular dysfunction of the steatotic liver undergoing IRI, are incompletely defined. Adhesion molecules and T cell trafficking are an area of intense research in IRI and pro-inflammatory states, but their significance in IRI of a steatotic liver is largely unknown. Aim: The aim of this study was to investigate the role of adhesion molecules, T cell trafficking and cytokines in IRI of a steatotic liver. Methodology: Male C57BL6 mice were fed a high fat diet (HFD) for 12 weeks. The mice were subjected to 40 minutes of hepatic ischemia, followed by 24 hours of reperfusion. Hepatocellular injury was assessed by presence of liver necrosis and level of serum ALT. Splenocytes were subjected to flow cytometry for T cell activation markers and for adhesion molecules by immunofluorescence and RT-PCR. Cytokines were assessed by a 20-Plex Luminex assay. L selectin was blocked and hepatocellular damage after IRI was assessed to mechanistically define the role of the adhesion molecule. Results: Mice fed a HFD diet showed significant increase in body weight (p<0.0001) and presence of hepatic steatosis by ORO stain. Splenocytes from HFD mice undergoing IRI demonstrated significant increase in CD8+ T cell activation markers, such as PD1 (p<0.0009), CD69 (p<0.01), and CD62L (p<0.001), in addition to higher levels of serum ALT and significant increase in hepatocellular necrosis. The T cell proliferation marker Ki67 (p<0.0089), was significantly higher in HFD IRI as compared to lean IRI. Expression levels of L-selectin (p<0.03) but not P or E-selectin were elevated in HFD IRI. Increased cytokines such as IFN, IL-1, IL-10, IL-6 and IL-17, suggested a pro-inflammatory milieu in HFD IRI. Blockade of L-selectin, lead to a significant attenuation of hepatocellular injury. Conclusion: A steatotic liver undergoing IRI is associated with elevation of adhesion molecule L-selectin along with activation and proliferation of CD8+ T cells, and a pro-inflammatory cytokine milieu. Blocking the adhesion molecule L-selectin leads to mitigation of hepatocellular injury, thus offering an important and clinically relevant therapeutic intervention in the increasingly prevalent clinical condition of IRI of fatty liver disease.

135. Functionalized Electrospun Membrane for Spatial Control of Bone Regeneration

Marian H. Hettiaratchi, BS; Catherine Chou; Nikhil Gupte; Nicholas Servies; Todd C. McDevitt, PhD; Johnna S. Temenoff, PhD; Robert E. Guldberg, PhD; and Laxminarayanan Krishnan, MBBS, PhD

Musculoskeletal deficiency is the leading cause of disability in the USA, often requiring surgery in cases of severe bone loss. The potent osteoinductive protein BMP-2 has emerged as an alternative to bone grafting, but is limited by poor dose control, necessitating use of supraphysiological doses of BMP-2 clinically, in turn leading to inflammation and heterotopic bone growth. Despite this, the off-label use of BMP-2 in the pediatric population has increased. Mitigating the risks of BMP-2 therapy by limiting BMP-2 diffusion outside the intended area will improve clinical care for both adults and children. To address this need, we localized heparin microparticles (HMP), known to bind and retain large amounts of bioactive BMP-2 onto a polycaprolactone (PCL) mesh (HMPmesh), to act as a barrier and trap released BMP-2 as it diffuses out from the delivery site. HMPs were deposited on PCL meshes by an airbrush during electrospinning such that 5mg of HMP was interspersed in two layers between 3 corresponding layers of PCL. Control meshes were manufactured without HMPs. 6mm discs from the membrane were incubated for 18hrs at 4C with 100ng of BMP-2 and BMP-2 binding was measured by ELISA. An isolated region of interest was also created using a dialysis chamber to enclose a collagen sponge containing 500ng BMP-2 with diffusion permitted only across the HMPmesh or control mesh. Diffusion of BMP-2 across this membrane was tracked over 7 days. HMPmeshes bound more BMP-2 after 18 hours and allowed lower amounts of BMP-2 through the mesh. This study demonstrated the ability of the HMPmesh to bind and spatially limit BMP-2 by reducing its diffusion across the functionalized membrane. Future in vivo studies in a bone defect model are necessary to demonstrate its functional efficacy.

136. Type 2 Diabetes in Atlanta Population

Yoonji Ahn; Karen Lindsley, RN,MSN; and Andrew Muir, MD

Type 2 diabetes (T2DM) is increasing world-wide in in children and adolescents. It has formerly been seen primarily in adults. Early T2DM onset has long-term health consequences as these children will have elevated glucose for a longer duration and the probability of debilitating complications occurs earlier. Medication classifications such as meglitindes, DPP-4 inhibitors, thiazolidinediones, and alpha-glycosidase inhibitors have been developed for treatment of adult T2DM. Similar pediatric trials have been initiated but are failing completion due to lack of enrollment nationwide. At the Children's Center, there are 5 IRB approved studies for T2DM pediatric subjects. The objective of this research was to identify barriers to enrollment in T2DM pediatric studies and to characterize our population. Study design was a retrospective, cross-sectional analysis of existing clinical data from paper medical records over a 12-month period. Data was collected on a consecutive series of 84 patients with visits occurring over a one-year period from the most recent year that the patient visited the clinic. Results showed the total percentage of patients who were taking metformin and insulin as treatment were higher than the national average of 50% at almost every appointment. This statistic is significant meaning we were unable to successfully wean the patients from insulin over the 1 year course of visits. Insulin is also a disqualifier for most T2DM studies. We detected the silent existence of pre hypertension and hypertension in greater than 50% of our patients. Furthermore, the age of diabetes onset appeared to be earlier than cited in the literature, and the age difference between males and females was significant, with girls diagnosed with diabetes at the clinic at 11.7 years and boys at 13.8 years old. The difference in BMI between races was significant, as well. African Americans' average BMI was 37.5 and Caucasians' BMI was 33.8. This initial review merits further analysis of our population for variances to the national norm. This also highlights the disparity between the real populations and the inclusions for ongoing trials. Nationally, we may need to re-align the mandated trial criterion with the actual presentation in the population.

137. Cell-intrinsic Role of RIG-I in Regulation of T Cell Responses

Daphne Y. Ma and Mehul S. Suthar

T cell responses are critical for protection against most viral infections, including West Nile virus (WNV). Engagement of pattern recognition receptors (PRRs) with their cognate non-self ligand on antigen presenting cells (APCs) leads to innate immune signals (antigen presentation, co-stimulatory molecule expression, and cytokine production) that are critical for controlling T cell responses. Recent findings from our laboratory now suggest that one class of PRRs, the cytosolic RIG-I like receptors (RLRs) function in a T cell-intrinsic manner to regulate proliferation, activation, and effector functions, but the mechanism of regulation is not well understood. We seek to fill this gap in our knowledge and propose to investigate the T cell-intrinsic role of RIG-I in regulating CD8+ T cell responses during virus infection, which would challenge the conventional dogma that PRRs solely function in APCs to prime T cell responses. There is mounting evidence that implicates a novel role for RIG-I beyond its function as a cytosolic sensor of viral RNA, implicating RIG-I as a regulator of T cell responses in diverse pathogenic environments. Our findings clarify a cell-intrinsic role for RIG-I in regulation of T cell responses: a) TCR signaling induces expression of RLRs; b) Cell-intrinsic RIG-I deficiency enhances CD8+ T cell proliferation, apoptosis and upregulation of early activation markers in vitro; c) Cell-intrinsic deficiency of MAVS, an essential signaling adaptor molecule downstream of RIG-I, in CD8+ T cells results in diminished antiviral effector cell differentiation in vivo; d) Cell-intrinsic expression of RIG-I affects T cell effector functions during WNV infection in vivo. These results suggest that RIG-I plays a crucial cell-intrinsic role in regulation of T cell responses, and could have significant implications to the control of T cell responses during inflammation and pathogen encounter. This work is supported by start-up funds provided by the Children's Healthcare of Atlanta, Emory Vaccine Center, the Georgia Research Alliance, the Emory University Research Council and NIH grants R03AI109194, U19AI083019, R56AI110516 and 5U19AI057266.

138. Yes-associated Protein: A Master Metabolic Regulator in Medulloblastoma

Anshu Malhotra, PhD; Abhinav Dey, PhD; and Anna Marie Kenney, PhD

Downstream of mitogenic Sonic hedgehog (Shh) signaling, Yes-Associated Protein (YAP) can drive proliferation in Cerebellar Granule Neural Progenitor (CGNP) cells. CGNPs are the proposed cells of origin of SHH medulloblastomas, whose developmental expansion requires signaling by Shh. Approximately 30% of human

medulloblastomas bear an activated Sonic hedgehog pathway gene expression signature. Ectopic expression of YAP promotes highly aggressive Shh-driven medulloblastoma growth and radio-resistance (Fernandez et al., 2009). Therefore, identification of novel modes of molecular targeted therapies is critical for the improved quality of life for survivors and reduced incidence of recurrence and metastasis. Recently, there has been renewed interest in how altered metabolic patterns in tumors could be exploited for therapeutic purposes. Previously, our lab made the novel observation that Shh mitogenic/oncogenic signaling is tightly coupled to the reprogramming of mitochondrial bioenergetics: Shh inhibits fatty acid oxidation (FAO, or β-oxidation) while driving increased fatty acid synthesis (FAS). We analyzed the effect of Shh treatment and ectopic YAP expression on CGNPs and observed a surprising decrease in mitochondrial membrane potential. Ultrastructural analysis of mitochondria of Shh-treated or ectopic YAP-expressing cells using Transmission Electron Microscopy revealed a swollen morphology, along with an expanded matrix space and deformed cristae structure, typical of morphologically aberrant mitochondria. These differences in mitochondrial structure were also visible in ultrastructures of SmoA1 tumor tissue as well as in vitro cultures of SmoA1 tumor cells (MBCs). Expression of fusion genes Mitofusin 1 and 2 was reduced while DRP1, a fission promoting gene was highly induced in all samples under study. Ectopic expression of Mitofusin 1 and 2, and knock down of DRP1 in CGNPs and MBCs not only restores the membrane potential to the non-proliferating state, but also indicates a reduction in proliferation. Our study thus implicates YAP-regulated metabolic pathways and enzymes as potential targets for novel medulloblastoma therapies. Our goal is to determine whether hampering YAP-mediated mitochondrial fragmentation can restore the metabolic profile of tumor cells to that of non-transformed, non-proliferating cells, thus suggesting a potential novel treatment paradigm that may reduce or eliminate the requirement for high dose radiation.

139. Novel Electroneuromyography Technique in Early Diagnosis of Infant Botulism - ORAL PRESENTATION

Manisha Malik, MD and Sumit Verma, MD

140. Pediatric HIV Cure: A Rhesus Macaque Model

M. Mavigner, PhD; J. G. Habib; B. Lawson; F. Amblard, PhD; R. F. Schinazi, PhD, Hon DSc; R. Geleziunas, PhD; J. Hesselgesser; B. Li; J. Hattersley; and A. Chahroudi, MD, PhD

Antiretroviral therapy (ART) greatly reduces mortality/morbidity of pediatric HIV infection, but ART interruption results in viral rebound due to HIV persistence in latent reservoirs. Recent work showed limited HIV reservoirs in infants started on ART in the first days of life. However, incomplete knowledge of the determinants of HIV persistence presents a barrier to HIV cure.   In this pilot study to establish the model, 4 infant rhesus macaques (RM) were orally infected with SIVmac251 at 19-20 wks of age and treated with a potent ART regimen initiated 35 d post-infection. SIV RNA and DNA levels were measured by real-time PCR and immunological parameters by flow cytometry. A comprehensive analysis of the sites of viral persistence is planned at elective necropsy.   The frequency of memory CD4+ T-cell subsets pre-infection was significantly different in infant compared to adult RM. As expected, the total estimated circulating number of CD4+ T memory stem cells, transitional memory T-cells and effector memory T-cells in the body was lower than in adults, thus suggesting a smaller potential reservoir of these cells in infants, especially if ART is started very early. Consistent with prior reports in HIV/SIV-infected infants, plasma SIV RNA levels peaked at 106-107 copies/ml and did not exhibit the typical post-peak decline seen in adults. After ART initiation, SIV RNA levels declined 2-3 logs in the first 2 wks, reaching undetectable levels at wk 4 (1 RM), wk14 (2 RM) and wk22 (1 RM) on ART. A net decline in SIV DNA was also seen in PBMC following ART. This study establishes a novel model of pediatric SIV infection under ART, providing an in vivo platform to study SIV reservoirs in infancy. As the developing immune system of infants differs from that of adults, strategies to cure HIV infection in the pediatric population will benefit from research conducted in ART-treated SIV-infected infant RM. This study is supported by Emory+Children's Pediatric Center Seed Grant Program and PHS Grant UL1TR000454 from the Clinical and Translational Science Award Program, National Institutes of Health, National Center for Advancing Translational Sciences.

141. Cholesterol Homeostasis in Medulloblastoma

Victor Maximov, PhD and Anna Marie Kenney, PhD
Background: Medulloblastomas (MBs) are the most common solid malignant pediatric brain tumors. The current standard of care combines surgical resection with chemo- and radiotherapies, resulting in an approximately 70% 5-year survival rate. However, survivors are frequently left with life-long side effects such as hormonal dysfunction, seizures, and intellectual impairment that greatly affect quality of life. MBs originate in the developing cerebellum as a result of aberrant activity of critical developmental pathways, such as WNT, Notch or Shh (Sonic hedgehog) and they can be divided into 4 subtypes according to unique gene expression patterns, genomic abnormalities, and histological traits. Methods: We investigate mouse MB that has been modeled in vitro by activation of Shh pathway with exogenous Shh ligand in cerebellar granule precursors (CGNPs) extracted from murine neonatal cerebella. We also use an in vivo mouse MB model that arises in mice due to expression of an activated allele of Smoothened under control of NeuroD2 promoter. These mice develop tumors genetically similar to human Shh MBs. Results: 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. However, contrary to anticipated elevated levels of cholesterol in MB tissue or Shh treated cells, we have found reduced cholesterol accumulation in cells or tissues with activated Shh pathway. Our preliminary data show expression alterations for cholesterol transport and synthesis genes and corresponding proteins in MB tissues compared to adjacent cerebellum (CB) and in proliferating Shh-treated CGNPs. Conclusions: Disturbed cholesterol homeostasis in MB cells could play a significant role in tumor cell survival and proliferation. Our preliminary data suggests that there are several potential targets in the cholesterol homeostasis regulation pathways that could be exploited for therapeutic application.

142. Bioactive Nanoparticles Improve Calcium Handling in Failing Cardiac Myocytes

Joshua T. Maxwell, PhD; Inthirai Somasuntharam; Warren D. Gray, PhD; Ming Shen; Michael E. Davis, PhD; and Mary B. Wagner, PhD

Nearly 1 in every 120 children born has congenital heart disease (CHD). Patients with CHD also manifest the patholophysiological criteria to be classified as chronic heart failure (HF). HF in the pediatric population is a progressive syndrome that results in characteristic signs and symptoms accompanied by molecular remodeling of the heart. The correction of dysregulated protein levels of key Ca^{2+} handling proteins in HF have provided a therapeutic target for many years. Recently, the cardiac Ca^{2+}-binding protein S100A1 has emerged as an attractive therapeutic target based on its interaction with Ca^{2+} handling proteins and has become the basis for ongoing preclinical trials for HF therapy. Although promising, these trials lack the efficacy necessary for a viable therapeutic strategy for HF. We previously described the development of a small molecule delivery system for enhanced cardiomyocyte (CM) uptake. By decorating degradable, biocompatible nanoparticles with N-acetylglucosamine (GlcNAc), rapid internalization by CMs and functional effects of the cargo were shown. In addition, the GlcNAc released by nanoparticle degradation can be used as a substrate for modification of Ca^{2+} handling proteins, making it a "bioactive" nanoparticle. We hypothesized that the GlcNAc nanoparticles would have a "two-hit" effect on Ca^{2+} handling in CMs whereby the cargo and also the GlcNAc moiety itself can modulate intracellular protein activity. To test this hypothesis, we utilized CMs isolated from rats with right ventricular HF induced by pulmonary artery banding and assessed various physiological Ca^{2+} handling parameters. After treatment with either Empty-GlcNAc or S100A1-GlcNAc nanoparticles, we observed a decrease in the amplitude and frequency of arrhythmogenic Ca^{2+} release in the form of Ca^{2+} sparks. Additionally, we recorded an increase in electrically-induced Ca^{2+} transient amplitude, an increase in cell shortening, and a decrease in the diastolic Ca^{2+} in the cytosol after treatment with either Empty-GlcNAc or S100A1-GlcNAc nanoparticles. These data indicate that GlcNAc nanoparticles are suitable vehicles for delivery of small molecules to CMs, and Empty-GlcNAc nanoparticles are themselves biologically active and able to regulate the Ca^{2+} handling proteins. We report the development of a bioactive nanoparticle that provides a "two-hit" treatment to CMs that can be utilized for further encapsulation of therapeutic molecules and proteins for efficient delivery to CMs.

143. Parent-Child Agreement on Health-Related Quality of Life Using the PedsQL End Stage RenalDisease Module

Maria Jay, MA; Bonney Reed-Knight, PhD; Kristin Loiselle, PhD; and Laura Mee, PhD

Objective: Little research has been conducted examining the level of agreement between children diagnosed with end stage renal disease and their parents in regards to health-related quality of life (HRQOL). This study investigated agreement between child and parent responses on the PedsQL EndStage Renal Disease Module (PedsQL ESRD). Methods: Participants included 32 children ages 9 to 17 (M = 13.71, SD = 2.34; 53% male) diagnosed withend stage renal disease and their caregivers. The sample was primarily African American (60%), followed by Caucasian (25%), Asian (6%), and other (9%). All participants were recruited between 2011 and 2013 and were receiving peritoneal dialysis or hemodialysis at the time of study participation. Participants completed the PedsQL ESRD questionnaire during dialysis clinic; parents completed parent proxy report of HRQOL. Parent-child agreement was evaluated using the intraclass correlation coefficient (ICC) and paired samples t-tests. Results: Overall, high levels of agreement were found between children and parents across the majority of subscales (ICC's from .53 to.78). The lowest level of agreement was found on the Family Peer Interaction subscale (ICC = .53). When examining the data using paired-samples t-tests, parents rated their children as experiencing significantly poorer HRQOL with regards to the General Fatigue subscale. Conclusions: The current study found higher levels of agreement across all subscales on the PedsQL ESRD module than previous research (Golstein et al., 2008). Relative ranking of agreement across subscales was similar to past research. Results suggest that even though parents and children may share similar HRQOL perspectives in many areas, it is important to obtain both viewpoints in order to gain a more comprehensive depiction of the child's level of functioning. Areas of relative agreement and disagreement may offer targets for therapeutic discussions with youth and their parents.

144. Examining Relationships Between Personality, Psychosocial Factors, and Medication Adherence in Children Awaiting Solid Organ Transplantation and Their Parents

Jennifer L. Lee, MS; Kristin A. Loiselle, PhD; Bonney Reed-Knight, PhD; Cyd K. Eaton, MS; Laura L. Mee, PhD; Rochelle Liverman, PharmD; and Ronald L. Blount, PhD

Objective: Past research documents that up to 50% children with chronic health conditions do not take their medication as prescribed, and that illness factors, as well as child and parent adjustment may influence this behavior. No literature currently exists examining medication adherence in children being evaluated for heart, liver, or kidney transplantation. This study examined medication regimen, illness, and parent personality factors as predictors of child health-related quality of life (HRQOL), parent medication knowledge, and medication adherence in families undergoing transplant evaluations.   Method: Sixty-five caregivers (M age=36.65, 89.2% female) of children (M age=7.94, Range: 0-20 years) undergoing evaluation for an organ transplant were recruited on the day of their pre-transplant assessment. Parents completed questionnaires about their psychological distress, personality, medication knowledge, medication adherence, and proxy-report of child HRQOL. Illness factors (e.g., time since diagnosis and medication information) were collected via medical record review.   Results: Number of medications prescribed (- association), parent conscientiousness (+ association), and psychological distress (-) predicted child HRQOL, while parent neuroticism did not ($R2 = .40$, $p < .01$). Time since the child's diagnosis (-) predicted parent medication knowledge, while number of medications and parent neuroticism did not ($R2 = .19$, $p < .01$). Parent medication knowledge (+) and conscientiousness (+) predicted medication adherence, also resulting in a significant moderation effect ($R2 = .38$, $p < .01$): parents with low knowledge and low conscientiousness exhibited the lowest levels of medication adherence.   Conclusions: Parent personality significantly influences child HRQOL, medication knowledge, and adherence prior to transplant. A thorough, family-focused evaluation during the pre-transplant period could help to determine which families are at risk for negative outcomes. Parent medication knowledge and psychological distress are modifiable factors that could be targeted for intervention during the pre-transplant period, as they may affect adherence and health outcomes for children post-transplantation as well.

145. Changes in Health-Related Quality of Life and Psychological Functioning from Pre- to 6-months Post-Solid Organ Transplantation

Jennifer L. Lee, MS; Cyd K. Eaton, MS; Bonney Reed-Knight, PhD; Kristin A. Loiselle, PhD; Laura L. Mee, PhD; Rochelle Liverman, PharmD; and Ronald L. Blount, PhD

Objective: While success rates of solid organ (i.e., heart, liver, or kidney) transplantation in treating pediatric illness have improved, no published research studies have followed families from pre- to post-transplant to examine changes in psychological functioning, health-related quality of life (HRQOL), and adherence during this significant transition period. This study prospectively assessed outcomes from the pre-transplant evaluation to 6-months post-transplant to inform current clinical care. Method: Twenty-four caregivers (M age=36.61, 79.2% female) of children (M age=11.23, Range: 2-20) undergoing organ transplant were recruited. Caregivers reported on their psychological distress (i.e., anxiety, depression, somatization, and post-traumatic stress [PTSS]), medication knowledge, medication adherence, and proxy-reported child HRQOL and psychological distress (i.e., anxiety and depression) at both time points. Paired-samples t-tests compared functioning across time; Cohen's d is reported for effect size. Results: Following transplantation, caregivers experienced decreases in overall psychological distress, including anxiety and depression (ds=. 59-.75, p< .05). Somatization was stable. PTSS decreased post-transplantation, including intrusion, hyperarousal, and avoidance symptoms (ds=.61-.96, p< .01). Medication adherence remained stable. Medications taken late decreased (d=.80, p< .05). Medication knowledge decreased (d=.80, p< .05). Children's overall HRQOL, including physical, emotional, and social functioning increased (ds=.43-.79, p< .05). Children's school-related HRQOL, anxious, and depressive symptoms were stable. Conclusions: Consistent with the overall goal of organ transplantation, significant improvements in HRQOL were observed post-transplant. Caregivers also experienced reductions in psychological distress, likely due to decreased disease burden and reduced risk of mortality for children. Child psychological distress remained in normative ranges across time points and did not significantly change. Encouragingly, medication adherence was stable or improved. Alarmingly, caregiver knowledge of the medication regimen decreased, suggesting focused, continued education is necessary post-transplant. Continued assessment of outcomes following transplantation is critical to assess changes as families return to normative activities and adjust to caring for a transplanted organ.

146. Respiratory Decompensation Following Immunization in Premature Infants - ORAL PRESENTATION

Edwin Clark Montague, DO and Anthony Piazza, MD

147. Preoperative Echocardiographic Measures in Interrupted Aortic Arch: Which Ones Best Predict Surgical Approach and Outcome?

Gemma Morrow, RDCS; Ritu Sachdeva, MD; William L. Border, MBChB, MPH; Brian Schlosser, RDCS; Bahaaldin Alsoufi, MD; Michael Kelleman, MS; and Ginnie Abarbanell, MD

Background: There are two approaches to the surgical management of interrupted aortic arch (IAA): a primary repair (aortic arch reconstruction with ventricular septal defect closure) or a single or two-staged Yasui repair (ventricular outflow bypass procedure). We sought to determine whether echocardiographic parameters could help differentiate which neonates will have improved outcomes with a primary versus a Yasui repair. Methods: Patient demographics, cardiac surgery type, complications, need for reoperation and/or interventional catheterization, and date of last follow-up were collected on neonates who underwent a biventricular repair for IAA from 2003 to 2014. Pre-operative echocardiograms were reviewed in regards to: IAA type, valve annulus size, ventricular size and aortic arch anatomy. Results: Of the 77 neonates with IAA, 60 had a primary and 17 a Yasui repair. Neonates that underwent a Yasui repair had significantly smaller mitral (p=0.005) and aortic valves (p<0.001), smaller right ventricle (p=0.03), and hypoplasia of the ascending aorta (p=0.006). Overall mortality was 13% with higher mortality in those infants that underwent a Yasui repair (8.3% vs 29.4%, p=0.04). Multivariate analysis showed that repair type and aortic root z-score were associated with higher likelihood of reoperation (p<0.01). There was a significant interaction between repair type and aortic root z-score identified. For aortic root z-scores less than -2.5 the probability of reoperation was significantly higher in the primary repair group compared to a Yasui repair (64.3% versus 37.5% respectively, p=0.02). Additionally, as the aortic root z-score decreases by 1 unit the odds of reoperation nearly double [OR 1.9, 95% CI (1.1-3.4)]. Conclusions: Neonate with IAA and an aortic root z-score less than -2.5 have a lower probability of reoperation with a Yasui repair compared to a primary repair. Additionally, neonates with smaller mitral and aortic valves with ascending aortic arch hypoplasia may also benefit from a Yasui

repair. Careful evaluation of these morphologic predictors on pre-operative echocardiograms can be helpful in surgical planning in neonates with IAA.

148. A Unique Case of a 6 Chambered Heart

David Cox, BA, RDCS; Gemma Morrow, RDCS; Brian Schlosser, BS, RDCS; Joseph Kreeger, RCCS; Timotheus Watson, MD; and Ginnie Abarbanell, MD

Clinical Presentation: Dicephalic parapagus (side by side, fused trunk) conjoined twins with dibrachius (2 arms) were diagnosed prenatally. Infants were delivered at 37 weeks gestation and required intubation soon after birth secondary to hypercarbia. Echocardiogram demonstrated the cardiac anatomy. At about 12 hours of life, the right sided twin developed atrial flutter and the infants clinically deteriorated leading to support being withdrawn at about 36 hours of life. Imaging Findings: Echocardiogram after birth demonstrated a complex single fused heart with 3 atria and 3 ventricles. The left sided heart demonstrated essentially normal cardiac anatomy with 2 atria, 2 ventricles, normal pulmonary venous return, a superior vena cava (SVC) to the right atrium, atrioventricular and ventriculoarterial concordance. The fused right sided heart was consistent with a univentricular heart (right ventricular morphology), single atrium (broad based appendage), single atrioventricular valve, transposed great vessels with pulmonary stenosis. 2 pulmonary veins, a SVC and inferior vena cava (IVC) emptied into the single atrium. The twins shared an IVC and descending aorta. The only intracardiac connection within the fused hearts was at the atrial septum. Role of Imaging in Patient Care: Echocardiography provided strong evidence that the cardiac structures should have been sufficient to provide perfusion for both twins. Adequately defining the cardiac anatomy was essential in determining that separation of the twins was not possible.

149. Development of Preferential Attention to Biological Motion and its Role in Autism Spectrum Disorders: A Prospective Longitudinal Study

Lindsay Olson, BA; Robin Sifre, BS; Warren Jones, PhD; Ami Klin, PhD; and Sarah Shultz, PhD

Background: Preferential attention to biological motion is present at birth in human infants and plays a key role in guiding social interaction (Simion et al., 2007). 24-month-olds with Autism Spectrum Disorders (ASD), however, do not show a preference for biological motion (Klin et al., 2009). The absence of preference for biological motion in toddlers with ASD suggests a disruption of normative social engagement. Little is known, however, about the longitudinal development of preferential attention to biological motion in typically developing (TD) or ASD populations. Knowledge thereof would be critical in understanding when deviations are first observed in ASD and what their developmental consequences may be. Methods: 95 infants at high-risk (HR) for ASD and 88 low-risk (LR) infants were shown point-light biological motion animations as in Klin et al. (2009). An upright point-light animation was presented on one half of the screen, with the inverted version playing on the other half in reverse order. Piloting revealed that trials lasting <30sec failed to elicit interstimulus shifting in young infants; as a result, we increased trial time to 60 seconds and analyzed data after the 30-second mark. Eye-tracking data, collected at months 2, 3, 4, 5, 9, 15, and 24, were used to calculate percentage of fixation time. Results: Analyses of percent fixation revealed an absence of preferential attention to biological motion at 2 months in LR infants (M(SD) = 47.1(17.5)%, t(11) = -.565, p = .584). LR infants have a preference for the upright figure beginning at 3 months (M(SD) = 57.9(19.4)%, t(31)= 2.32, p<0.05) an effect that remains robust at 4, 5, 9, 15, and 24 months (all p's <0.05). Conclusions: Our results map the development of preferential attention to biological motion in TD infants during the first two years of life. The absence of preferential attention to biological motion at 2 months, followed by preference at 3 months and thereafter, matches the existing literature regarding preferential attention to faces, which is present at birth but declines at 4-6 weeks of age before re-emerging at 2-3 months. The current findings provide evidence for a similar transition in orienting to biological motion, and highlight this developmental period as a critical focus for future research into the unfolding of social disability in ASD. Future analyses will examine early departures from normative trajectories in infants later diagnosed ASD.

150. Prevalence Of Initial Coagulopathy And Associated Outcomes In Neonates With Moderate-To-Severe Hypoxic-Ischemic Encephalopathy

Mitali A Pakvasa, MD; Anne M. Winkler, MD, MSc; Shannon E. Hamrick, MD; Cassandra D. Josephson, MD; and Ravi M. Patel, MD, MSc

Background: Although survival has improved for infants with hypoxic-ischemic encephalopathy (HIE) with use of therapeutic hypothermia, managing co-morbid complications remains challenging. The prevalence of initial coagulopathy among infants with HIE and the association with bleeding has not been well described. Objective: To evaluate the prevalence of initial coagulopathy upon admission in neonates with moderate-to-severe HIE and to determine associated transfusion burden and bleeding outcomes. Design/Methods: Retrospective observational cohort study at an academic neonatal intensive care unit in Atlanta, GA. We included infants with moderate-to-severe HIE using the NICHD definition who underwent coagulation testing and were born from 1/1/08 to 12/31/13. We used logistic regression to evaluate the association between initial prothrombin time (PT) and any abnormal bleeding events, after controlling for severity of HIE. Results: Of 63 infants with moderate-to-severe HIE, 50 underwent initial PT testing and met study criteria. Forty-nine of 50 infants received whole body hypothermia. Fourty-four (70%) had moderate HIE and 19 (30%) had severe HIE. The median initial PT was 24 sec (interquartile range 17-34). Thirty-six (72%) infants had a PT >18 sec and all of these infants received transfusion of fresh frozen plasma (range of 1-9 transfusions) and 16 (32%) infants also received cryoprecipitate. Any abnormal bleeding was noted in 18 of 50 (36%) infants and the level of initial PT was associated with a risk of abnormal bleeding. Conclusions: Among infants with moderate-to-severe HIE, coagulopathy is prevalent and associated with a high transfusion burden and increased risk of bleeding.

151. Necroptosis, A Critical Cell Death Pathway in Steatotic Mice Undergoing Ischemia Reperfusion Injury

Sirish K. Palle, MD; Vasantha Kolachala, PhD; Ming Shen, BS; Carlos Abramowsky, MD; Dmitry Shayakhmetov, PhD; and Nitika Gupta, MD

Background: Steatotic livers undergoing ischemia reperfusion injury (IRI) demonstrate significant hepatocellular dysfunction and cell death leading to increased morbidity and mortality in obese people who have a fatty liver. Necroptosis is a form of regulated necrosis, which is triggered by death receptors and toll like receptors. Though well studied in some organ systems, its role in steatotic liver IRI remains unknown. Aim: The aim of this study is to investigate the role of the Necroptosis pathway in steatotic mice undergoing IRI Methodology: Human hepatoma cells (HuH7) were made steatotic by addition of free fatty acids and exposed to hypoxia, ischemia and reperfusion (HIRI) in vitro. Additionally, C57BL/6 mice were fed a high fat diet (HFD) for 12 weeks and subjected to 40 minutes of hepatic ischemia, followed by 24 hours of reperfusion. To assess liver damage, serum ALT was measured. Total RNA was extracted from liver tissue and mRNA levels for genes involved in necroptosis pathway (RIPK1, RIPK3, MLKL, FADD, TRADD, TRAF 2, FAS, FASL) were assessed by RTPCR. Immunohistochemistry (IHC) was done for localization of RIPK 1 and RIPK 3 in the liver tissue of steatotic mice undergoing IRI. Western blot was also performed. Results: Steatotic mice undergoing IRI demonstrated significantly higher levels of mRNA for death receptors TRAF2 (p<0.03), FASL(p<0.03) compared to control HFD fed mice. There was a significant increase in mRNA levels of necroptosis inducing-complex proteins RIPK3 (p<0.002) and MLKL (p<0.008). These findings were confirmed in steatotic hepatocytes demonstrating increased RIPK1 and RIPK3 protein expression levels. There was increased RIPK3 in neutrophils and hepatocytes of steatotic liver undergoing IRI as compared to the normal liver. Conclusion: Our preliminary results indicate that Necroptosis, is an important cell death pathway in a steatotic liver undergoing IRI. Death receptors TRAF2 and FASL provide critical therapeutic targets for developing therapies aimed at mitigation of hepatocellular death after IRI. Further studies utilizing RIPK1 inhibitors and RIPK1 KO mice are ongoing.

152. Blockade of RIP Kinase Pathway Exacerbates Ischemia Reperfusion Injury in a Steatotic Liver

Sirish Palle, MD; Vasantha Kolachala; Ming Shen; Carlos Abramowsky, MD; Dmitry M. Shayakhmetov, PhD; and Nitika Arora Gupta, MD

Background: Steatotic livers undergoing ischemia reperfusion injury (IRI) demonstrate significant hepatocellular dysfunction and cell death leading to increased morbidity and mortality in obese individuals with fatty liver. Necroptosis is a form of regulated cell death, which is triggered by death domain receptors and mediated through

receptor interacting protein kinase (RIP). Though well studied in renal IRI, its role in steatotic liver IRI is largely unknown. Aim: The aim of this study was to investigate the role of the necroptosis pathway in steatotic mice undergoing IRI. Methodology: C57BL/6 mice were fed a high fat diet (HFD) for 12 weeks and subjected to 40 minutes of hepatic ischemia, followed by 24 hours of reperfusion. They were pretreated with necrostatin, a RIPK1 inhibitor and hepatocellular injury was assessed by serum ALT, necrosis by H&E and propidium iodide (PI) staining. Western blot (WB), and RTPCR were done. RIP3$^{-/-}$ / Caspase8$^{-/+}$; TNF α $^{-/+}$ / TRAF2 $^{-/-}$, and RIP KD (kinase dead) mice were fed a HFD and subjected to IRI. Hepatocellular injury was assessed as above along with evaluation of the NF-$\Box \beta$ survival pathway. Results: After IRI, HFD fed mice treated with necrostatin showed substantially increased necrosis (76.6 ± 6.6 vs 30 ± 1.2 %; $p<0.0005$) and serum ALT (2040 ± 0.5 vs 706.7 ± 49.2 IU/l; $p<0.0003$) as compared to saline treated HFD fed mice. This was confirmed by presence of increased PI staining ($p<0.05$), signifying increased cell membrane permeability and necrotic death. Similarly, after IRI, RIP3 $^{-/-}$ / Caspase8 $^{-/+}$; TNF α $^{-/+}$ / TRAF 2 $^{-/-}$, and RIP KD mice fed a HFD, showed increased necrosis and serum ALT as compared to WT HFD fed mice. Confocal microscopy showed absence of necrosome formation and there was reduced expression of RIP 3 in HFD fed mice as demonstrated by mRNA ($p<0.001$) and WB ($p<0.002$). Interestingly, there was a concomitant decrease in level of NF-$\Box \beta (p<0.04)$ in HFD fed mice compared to lean mice. Conclusion: Our results indicate that RIP kinase pathway, which is an established cell death pathway in IRI of other organs is not the principle mechanism of hepatocellular injury in IRI of a steatotic liver. In fact, blockade of this pathway leads to increased hepatocellular injury, which is likely a combination of unmasking of other death domain pathways such as FAS and TLR4; and mitigation of the survival NF-$\Box \beta$ pathway. This provides critical therapeutic targets for developing therapies specifically aimed at mitigation of hepatocellular death after IRI of a steatotic liver, which is a burgeoning clinical problem.

153. Comparison Between Direct Assessment and Parent Report in those with Autism Spectrum Disorder, Developmental Delays, and Typically Developing Toddlers

Lauren Pascarella, MA; Anusha Challa, BA; Cheryl Klaiman, PhD; and Sara Hoffenberg, PsyD

Background: Assessment of Autism Spectrum Disorder (ASD) is often variable. Some children receive comprehensive assessment whereas others are diagnosed solely on parent report. Some previous studies have shown agreement among direct assessment and parent report measures (Luyster et al., 2008) while others describe inconsistencies (Weismer et al., 2010). Given these inconsistencies further research is needed to understand the relationship between the two and the potential implications for diagnosis and treatment planning. The current study examined the relationship between parent report and directly assessed communication and motor skills in those with ASD as well as comparison groups of children with a Developmental Delay (DD) and those who are Typical Development (TD). Methods: Participants included 215 clinically-referred toddlers between 16 to 40 months with ASD (n=125), DD (n=45), and TD (n=45). The Vineland Adaptive Behavior Scale, Second Edition, Survey Form (Sparrow et al., 2005) and Mullen Scales of Early Learning (Mullen, 1995) were administered. Comparisons were made between age-equivalence scores of the language and motor domains. Results: TD children scored higher in all domains on both the Mullen and the Vineland. With regard to correlations, TD children had the lowest correlations between parent report and direct assessment (receptive language (r=.328, p>.01), expressive language (r=.631, p<.01), fine motor (r=.181, p>.01), gross motor (r=.400, p<.01)). Strong correlations were found for both the ASD and DD groups. In ASD, correlations were moderate to strong (receptive language (r=.614, p < .01), expressive language (r=.789, p<.01), fine motor (r=.435, p<.01), gross motor (r=.518, p<.01)). In DD, correlations were stronger (receptive language (r=.767, p<.01), expressive language (r=.727, p<.01), fine motor (r=.733, p<.01), gross motor (r = .803, p<.01)).Conclusions: This study shows consistencies between parent report and direct assessment. Correlations are stronger for children with DD and ASD compared to TD children. This may be a result of closer parental monitoring of each developmental accomplishment or struggle in the DD group. Future research should focus on the subgroups of children that demonstrate inconsistencies. This may enable parents to better understand their child's strengths and weaknesses and more accurately report their child's abilities.

154. Induced Pluripotent Stem Cell-Derived Cardiomyocytes Recapitulate Clinically Observed Refractoriness to Therapeutic β-Blockade in a Patient-Specific Model of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Marcela K. Preininger; Rajneesh Jha; Qingling Wu; Monalisa Singh; Bo Wang; Joshua T. Maxwell; Aarti Dalal; Peter S. Fischbach; Mary B. Wagner; and Chunhui Xu

Background: The autosomal dominant form of CPVT is linked to mutations in the gene encoding cardiac ryanodine receptor 2 (RyR2), an ion channel that regulates the coordinated release of Ca2+ from the sarcoplasmic reticulum (SR) to the cytosol during systole. RyR2 defects disturb channel gating, leading to aberrant Ca2+ release from the SR during diastole. This SR Ca2+ leak is exacerbated under adrenergic stimulation, providing a substrate for potentially lethal arrhythmias. Although over one hundred CPVT-associated RyR2 mutations have been identified, very few have been characterized. Methods: Dermal fibroblasts from a CPVT-affected child harboring a novel RyR2 mutation (Leu3741Pro) and a control child were reprogrammed into induced pluripotent stem cells (iPSCs) which were then differentiated into cardiomyocytes (CMs). CPVT and control CMs were loaded with the cytosolic Ca2+ indicator Fluo-4, and imaged by live-cell confocal to evaluate Ca2+ handling properties. For both groups, cells were recorded at baseline, during stimulation with isoproterenol (β-agonist, 100 nM), and following treatment with Nadolol (β-blocker, 10 μM) or Flecainide (Na+ channel and partial RyR2 blocker, 10 μM). Results: At baseline, 92% of control cells (n=12) and 78% of CPVT cells (n=46) demonstrated normal cyclic calcium handling. Following adrenergic stimulation with Isoproterenol, only 34% of CPVT cells (n=53) maintained normal cycling, compared to 82% in controls (n=12). Under this condition, 32% of CPVT cells exhibited intense, diastolic propagating Ca2+ waves; in contrast, any abnormalities observed in control cells were only small, local Ca2+ releases. Following treatment with Flecainide, both groups returned to baseline, with 92% normal in controls (n=12) and 79% normal in CPVT cells (n=14). Nadolol fully restored baseline cycling in controls (92% normal, n=12), but was not effective in restoring contractility in CPVT cells (29% normal, n=17), although it did reduce the percentage of arrhythmogenic waves from 32% to 12%. Conclusions: Cardiomyocytes differentiated from CPVT patient-specific iPSCs recapitulate the calcium abnormalities of RyR2-mediated disease pathophysiology in vitro and respond to pharmacological drugs in a manner that is consistent to the in vivo efficiencies of these agents administrated to the patient.

155. Human Plasmablast Responses to Secondary Dengue Virus Infection

Lalita Priyamvada; Alice Cho; Nattawat Onlamoon, PhD; Kulkanya Chokephaibulkit, MD; Kovit Pattanapanyasat, PhD; Rafi Ahmed, PhD; Patrick C. Wilson, PhD; and Jens Wrammert, PhD

Despite the massive disease burden and pressing need for antivirals and vaccines against dengue, the immunology of dengue virus (DENV) infections remains poorly understood. In this study, we describe B cell responses generated during the acute phase of DENV infection. Our lab has previously shown that a large population of DENV-specific plasmablasts appears in the blood of dengue patients around the time of fever subsidence. To understand the functional properties of these acute-phase cells and what role the antibodies they make play in an immune response, we isolated plasmablasts from 4 Thai patients experiencing secondary DENV infection and generated 53 monoclonal antibodies (mAbs) by single-cell RT-PCR and cloning of the plasmablast VDJ genes. We determined that a large majority of the DENV envelope-specific mAbs in our panel was either fully (4 serotypes) or partially (2-3 serotypes) cross-reactive, with a large majority also exhibiting cross-neutralizing activity in vitro. Serotype-specific neutralizing mAbs represented <20% of the entire mAb panel. Interestingly, more than half of the mAbs generated from two patients displayed stronger neutralization of DENV1 than DENV2 even though they were diagnosed with DENV2 at the time of sample collection. This is reminiscent of original antigenic sin, given all patients had prior DENV exposures. Further, a majority of serotype-specific neutralizing mAbs either moderately or potently enhanced DENV infection of U937 cells indicating that the potential for ADE is not limited to cross-reactive mAbs. These initial characterizations of plasmablast-derived mAbs give insight into the specificity and function of early antibody responses in dengue infection at a single-cell level.

156. Mechanisms of LGP2-dependent Regulation of RIG-I Signaling and Dendritic Cell Activation

Kendra Quicke; Kristin Kim, MS; James Bowen; Daphne Ma, PhD; and Mehul Suthar, PhD

Pattern recognition receptor signaling is essential for regulating innate and adaptive immune responses to infection. In particular, the retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) signaling pathway plays a major role in regulating protective immunity during virus infection. The RLRs are a family of cytosolic RNA helicases that, upon binding non-self RNAs, trigger robust antiviral immune responses characterized by expression of type I interferon (IFN), pro-inflammatory cytokines, and antiviral effector genes. LGP2 is a host RNA helicase that is structurally related to the RLRs RIG-I and melanoma differentiation-associated gene 5 (MDA5) and is a known regulator of the RLR signaling pathway. However, the underlying mechanism by which LGP2 regulates RLR signaling and antiviral defense is poorly understood. To this end, we utilized a highly specific RIG-I agonist to evaluate the impact of LGP2 on RIG-I signaling independent of virus-mediated effects. First, we performed transcriptional profiling studies in dendritic cells and found that genetic ablation of LGP2 leads to an enhanced and broader type I IFN transcriptional program, characterized by increased type I IFN, proinflammatory cytokine and antiviral gene expression. Concomitantly, we found that LGP2 is essential for controlling DC maturation processes and T cell priming. To define the mechanism by which LGP2 negative regulates RLR signaling, we performed biochemical and molecular analyses and found that: 1) RNA binding and ATP hydrolysis functions of LGP2 are dispensable for inhibition of RIG-I signaling; 2) a region within amino acids 1-176 of LGP2 mediates RIG-I signaling inhibition; and 3) LGP2 inhibits RIG-I ubiquitination by forming a complex with TRIM25, an E3 ubiquitin ligase that post-translationally modifies RIG-I into a signaling 'active' form. Based on these findings, we believe LGP2 negatively regulates RIG-I-specific signaling by inhibiting RIG-I activation. Combined, these findings demonstrate an important, yet underappreciated, role for LGP2 in regulating inflammation during virus infection, particularly in light of recent studies investigating RLR agonists as candidates for broad-spectrum antiviral therapeutics and adjuvants to enhance immunogenicity during vaccination. Thus, it is highly important to define regulators of the RLR signaling pathway in order to successfully augment immunogenicity and prevent cytokine-mediated tissue damage during virus infection.

157. Automated Evaluation of Tricuspid Annular Plane Systolic Excursion from 2D Echocardiographic Images

Senthil Ramamurthy, MS; Falon McGaughy, RDCS; Michael S. Kelleman, MS; and Ritu Sachdeva, MD

Background: Tricuspid Annular Plane Systolic Excursion (TAPSE) has emerged as a reliable marker of right ventricular (RV) systolic function. Recently, TAPSE derived using 2D images (2D-TAPSE) was shown to correlate with M-mode TAPSE (MM-TAPSE). We have developed a technique using active contour models for automatic evaluation of TAPSE (Auto-TAPSE). The purpose of this study was to determine the accuracy of this novel technique and validate it on normal and diseased hearts. Methods: Fifty-six patients (44 with normal heart and 12 with pulmonary hypertension) who previously had MM-TAPSE were identified. The novel algorithm requires the user to initialize contours for tracking the RV wall and tricuspid valve. The algorithm then automatically identifies the end-systolic and end-diastolic frames, tricuspid valve hinge point (TVHP) and apical points from the apical 4-chamber view. Auto-TAPSE was calculated as the difference in distance between the TVHP and apical points in end-systole and end-diastole. The same parameters were manually identified on 2D in apical 4-chamber view using a custom-developed software to derive 2D-TAPSE. Positional accuracy of TVHP and apical points identified by auto-TAPSE was compared to that obtained by 2D-TAPSE. Results: The system was able to accurately identify systolic and diastolic frames in 51 (91%) patients within 3 cardiac frames. The system generated a list of 6 (11%) patients, where it failed to identify the TVHP for manual review. There was strong agreement between manually and automatically identified TVHP (r=0.99) and apical points (r=0.99). The automatically identified TVHP and apical points were within 1.34 mm and 1.54 mm respectively from the manually identified points. Bland-Altman analysis showed a strong agreement between Auto-TAPSE and 2D-TAPSE (ICC = 0.97, 95% CI = 0.96 – 0.98). There was significant correlation between Auto-TAPSE and MM-TAPSE (r=0.85). Conclusion: Using our novel custom-made software, TAPSE could be measured automatically in majority of our patients and was accurate when applied to normal and diseased hearts. Future work is being done to make this system fully automated without the need for manual initialization. This will allow automatic retrospective analysis of TAPSE in a short period of time.

158. Quantification and Origin of Differential Pulmonary Blood Flow in the Patients with a Fontan Circulation - ORAL PRESENTATION

Senthil Ramamurthy, MS; Sassan Hashemi, MD; James Parks, MD; Denver Sallee, MD; Gary McNeal, MS; and Timothy Slesnick, MD

159. Lessons Learned: Telemedicine to Improve Access to Cancer Survivorship Care

Elizabeth Record, DNP, CPNP; Ann Mertens, PhD; Kristin Vangile, MPH; Lillian Meacham, MD; and Karen Wasilewski-Masker, MD, MSCR

Background: Cure of childhood cancer has significantly increased in the last decades; however, treatment can result in life threatening and debilitating conditions. Annual surveillance using national guidelines is recommended and usually begins at two years after completion of therapy. However, studies indicate that less than 50% of survivors seek survivorship care. The aims of this study were to evaluate the feasibility of using telemedicine as an alternative to an in-person clinic visit to improve access to survivorship care and to identify patient perceived barriers to annual clinic visits Methods: Methods: Eligibility included treatment at the CHOA Aflac Cancer and Blood Disorders Center between 2000 and 2011 , 2-21 years of age, and distance greater than 90 miles from the CHOA clinic. Medical complexity based on treatment and medical history was graded by review of the medical record. High complexity patients were excluded. Surveys were given pre and post visit to those patients who were seen through Telemedicine and those patients choosing in person visits (n=16).   Results: Of 150 eligible patients, 64 were excluded due to complexity (43%), 39 patients were closer to CHOA than a telemedicine site (26%), 23 had transitioned from CHOA during the time span of the study (15%); 4 were being followed by another provider (3%), and 4 were unable to be contacted (3%). Those 16 patients were asked to complete surveys: 5 completed the surveys, 3 are pending, and 8 refused. Surveys completed indicated that missing school/work, distance to survivor clinic and transportation concerns were barriers to in person clinic visit. Additionally, surveys indicated that having a complete medical checkup, having more information about how to best care for the survivor, and learning about possible health problems that may occur later in life were the most important reasons for patients to seek survivor care.   Conclusions: Many survivors are medically complex and need annual in-person clinic visits. Despite perceived barriers including missing work or school, distance to survivor clinic and transportation concerns, survivors often prefer an in-person visit.

160. Disease Activity Doesn't Explain it All: How Internalizing Symptoms and Parent Depressive Symptoms Relate to Health-Related Quality of Life Among Youth with Inflammatory Bowel Disease

Bonney Reed-Knight, PhD; Jennifer Lee, MS; Jeffery D. Lewis, MD; and Ronald L. Blount, PhD

OBJECTIVE: Health-related quality of life (HRQOL) is a multidimensional construct, influenced by disease, individual, and environmental factors. Greater disease activity has understandably been demonstrated to predict poorer HRQOL, though disease status alone does not fully account for HRQOL.   METHODS: Participants include 83 adolescents ages 11-18 (M = 14.77, SD = 2.29) diagnosed with IBD (76% Crohn's disease) and their caregiver. Adolescents completed the IMPACT-III (Otley et al., 2002), a disease-specific measure of HRQOL for youth with IBD. Parents rated their own depressive symptoms using the Symptom Checklist-90-Revised (SCL-90-R; Derogatis, 1994) and adolescents' internalizing symptoms using the Behavior Assessment System for Children, Second Edition (BASC-2; Reynolds & Kamphaus, 2004). Physicians rated disease activity using the Pediatric Crohn's Disease Activity Index (PCDAI; Hyams et al., 1991) and the Pediatric Ulcerative Colitis Activity Index (PUCAI; Turner et al., 2007). RESULTS: Greater disease activity was negatively associated with HRQOL (B = -.53, SE = .14, $p < .001$) but positively associated with adolescents' internalizing symptoms (B = .21, SE = .07, $p < .01$). Adolescents' internalizing symptoms were positively associated with parents' depressive symptoms (B = .42, SE = 11, $p < .001$) and negatively associated with HRQOL (B = -.44, SE = .22, $p < .05$). Parents' depressive symptoms were also negatively associated with HRQOL (B = -.65, SE = .20, $p < .001$). Mediation analyses found support for significant indirect effects in the relationship between disease activity and HRQOL through adolescents internalizing symptoms (point estimate = -.09, SE = .06, 95% CI = -.26 to -.01) and through both adolescents' internalizing symptoms and parents' depressive symptoms sequentially (point estimate = -.06, SE = .04, 95% CI = -.19 to -.01). CONCLUSIONS: Greater disease activity independently relates to poorer HRQOL. In addition, disease activity relates to greater internalizing problems, which in turn relate to higher levels of parent depressive symptoms and

poorer HRQOL. Providers may consider a family-based approach to screening for internalizing problems, especially as disease activity increases, since mood symptoms may partially explain worsening HRQOL.

161. Case Study of Juvenile Osteochondritis Dissecans (JOCD) Towards Personalized Medicine

Giuliana E. Salazar-Noratto, BSc; Monica L. Rojas-Peña, MSc; Dalia Arafat, DO; Hazel Y. Stevens, BSc; Nick J. Willett, PhD; S. Clifton Willimon, MD; Robert E. Guldberg, PhD; and Greg Gibson, Ph.D.

Juvenile osteochondritis dissecans (JOCD) of the knee is a musculoskeletal disorder that affects the subchondral bone, which then disrupts the overlying articular cartilage. This musculoskeletal condition can lead to significant morbidity and early onset of osteoarthritis. During late stages, the articular cartilage becomes unstable and the formation of an osteochondral fragment (progeny) ensues. Although the etiology of JOCD is unknown, it is thought to be multifactorial with an underlying genetic influence, as evidenced by its occurrence in multiple joint sites in some individuals and familial cases of OCD. However, to date, no study has investigated the covariance of the pathological characteristics and gene expression of JOCD. Previous research has focused on retrospective clinical studies. Genomic profiling in combination with contrast based micro-CT imaging could be used to personalize therapy and enhance medical interventions. The overall purpose of this study is to characterize the different stages of JOCD in young individuals in order to gain valuable information about this musculoskeletal disorder, with the long-term objective to develop a bench-to-bedside program to better diagnose and treat this disorder. In this case study, we have investigated human biopsy samples (cartilage and subchondral bone) from the knee joint of 2 JOCD patients, removed during microdrilling surgery. Contrast-enhanced micro-CT (EPIC-µCT) and histology were used to evaluate the morphology and structure of the articular cartilage and bone. The integrity of the articular cartilage was also assessed by its proteoglycan content. Preliminary results showed differences in attenuation within each sample, indicative of proteoglycan loss, in the cartilage portion of the biopsy. The top of the articular cartilage appears to be most severely affected, characterized by a higher attenuation and hence lower proteoglycan content. RNA from cartilage and bone compartments has been isolated and purified and will be used to assess transcript abundance genome-wide. Sequencing of the cartilage and bone in the biopsy samples will be reported, and transcriptome profiling will be performed and correlated with the biopsy morphology and integrity. This study aims to classify JOCD patients by relating their gene expression profile to tissue degenerative changes.

162. Parental Resistance to Treatment of At-Risk Behaviors for Autism Spectrum Disorders in 12-month-old Infants

Celine A. Saulnier, PhD; Elizabeth McGarry, BS; and Kaylee Fiorello, BS

Background: An increasing number of studies are attempting to detect and treat early risk signs for autism spectrum disorder (ASD) prior to full symptom expression in the hopes of altering the course of the disorder. With these attempts, researchers are experiencing parental resistance to treatment when identified concerns precede a confirmed diagnosis. This study investigates if behavioral markers differentiate between treatment-eligible infants whose parents decline consent for treatment from parents who consent to a randomized-controlled treatment protocol (RCT) beginning at 12 months. Methods: Participants include 53 infants enrolled in a prospective study from birth through age 3 (23 High Risk for ASD; 30 Low Risk) and who have aged to their 12-month screening assessment. Assessment measures include the Communication and Symbolic Behavior Scales (CSBS), the Systematic Observation of Red Flags for Autism in Toddlers (SORF), the Early Screening for Autism and Communication Disorders (ESAC), the Mullen Scales of Early Learning, and the Vineland Adaptive Behavior Scales. Of the 18 infants eligible for the RCT, 10 consented to treatment (6 HR; 4 LR) and 8 declined consent (5 HR; 3 LR). Results: 48% of HR infants met eligibly criteria for the RCT but 46% of these parents declined to enroll. Results indicate that infants in the "Declined Consent" sample had higher CSBS Symbolic Standard Scores (MEAN=10; Declined Mean = 7.8; Consented Mean = 6.2); fewer red flags for ASD on the SORF, (Cut-off for eligibility = 8; Declined Mean = 8.6; Consented Mean = 11.8), and lower gross motor scores on the Mullen (MEAN T-Score=50; Declined T-Score = 36; Consented T-Score = 53) and the Vineland (MEAN=100; Declined Motor Mean = 85; Consented Mean = 101) compared to infants in the "Consented" sample. No significant differences were found in Low Risk sample. Conclusions: Results offer a preliminary look at early markers that might impact parental decisions for electing treatment for infants at risk for ASD. Infants whose parents decline treatment show stronger symbolic play skills and less autism symptoms than infants in the consent sample. These infants also exhibit weaker motor abilities, with gross motor skills falling almost 1.5 standard deviations below the mean, which

may detract parents' attention from the identified social communication vulnerabilities. Ethical implications for detecting and treating prodromal ASD will be discussed.

163. Deficits in Adaptive Interpersonal Skills Differentiate Toddlers with ASD from Toddlers with non-ASD Developmental Delays

Celine Saulnier, PhD; Cheryl Klaiman, PhD; and Ami Klin, PhD

Background: Research shows that significant deficits in adaptive skills are evident in children with ASD as young as age 2 (Ventola et al., 2012; Paul, Loomis, & Chawarska, 2014), and that adaptive behavior is associated with positive outcome in adulthood (Farley et al., 2009). Determining profiles of adaptive behavior in the first two years of life can help differentiate ASD from non-ASD developmental delays. Methods: Participants included 130 clinically-referred toddlers (75% male; 60% Caucasian; 22% African American) ages 10-30 months (Mean=22.1m; SD=4.3) that were enrolled in a research study on social cognition. Diagnoses were as follows: 47 children with non-ASD developmental delays (non-ASD/DD) and 83 children with Autism Spectrum Disorders (ASD). Each child was evaluated using the Mullen Scales of Early Learning, the Vineland Adaptive Behavior Scales, Second Edition, Survey Form, and the Autism Diagnostic Observation Schedule, Second Edition, Toddler Module. Results: Children with ASD exhibited significant developmental delays as evidenced by at least 1.5 standard deviations below the mean (50) across all domains of the Mullen, with Mean T-Scores as follows: Visual Reception=32.6(10.4); Fine Motor=35.1(12.7); Receptive Language=24.3(9.2); and Expressive Language=25.5(8.9). Children with non-ASD developmental delays exhibited deficits only in Receptive Language (Mean=30.6; SD=10.2) and Expressive Language (Mean=32.0; SD=10.3). Both groups exhibited significant delays on the Vineland across all domains. The difference between Visual Reception and Vineland Interpersonal Age Equivalent Scores was significantly greater for the ASD group, with a Mean Difference of 9.3 months (5.9) compared to 7.0 months (5.7) for the non-ASD/DD group. Conclusions: Both children with ASD and non-ASD developmental delays exhibit both developmental and adaptive deficits as early as age 2. Thus, it is important to elucidate differences in profiles that can help to make diagnostic differentials at these young ages. Results suggest that in ASD, the gap between conceptual "mental age" and adaptive interpersonal skills is more pronounced than the gap between these abilities in children with non-ASD delays. Results highlight the necessity of assessing adaptive socialization skills when diagnosing young children with and at risk for ASD in order to make accurate differentials between ASD and language and/or developmental delays.

164. Survival in Single Ventricle Heterotaxy: Do Echocardiographic Parameters Inform Outcome?
Brian Schlosser, BS, RDCS; Ritu Sachdeva, MD; Curtis Travers, MPH; William L. Border, MBChB, MPH; Animesh Tandon, MD, MS; Bahaaldin Alsoufi, MD; and Ginnie Abarbanell, MD

Background: Infants with heterotaxy and functional single ventricle have challenging cardiac physiology and known high mortality. Within this group of patients, we sought to identify if there are certain echocardiographic parameters associated with mortality. Methods: Initial echocardiograms in infants with heterotaxy who underwent single ventricle palliation from 2003-2012 were reviewed. Patient demographics, cardiac surgery procedure, and mortality were collected. Echocardiographic parameters collected were: venous abnormalities, atrial isomerism, significant atrioventricular valve regurgitation (≥moderate), ventricular anatomy and dominance, great artery relationships, and outflow obstruction. Results: During the study period, 56 infants with heterotaxy underwent single ventricle palliation, 34 with right atrial isomerism (RAI) and 22 with left atrial isomerism (LAI). Overall mortality was 34% (19 deaths). There was no significant difference in mortality between the RAI and LAI groups (38% and 27%, p=0.57). The median time of death from surgery was 34 days. Median clinical follow-up was 3 years (4.7 months to 5 years). The most common finding was an atrioventricular septal defect, followed by bilateral superior vena cava, d-transposition of the great arteries and double outlet right ventricle. Infants with RAI were more likely to have total anomalous pulmonary venous return ($p < 0.001$) and pulmonary atresia than those with LAI. Interrupted inferior vena cava ($p < 0.001$), partial anomalous pulmonary venous return ($p < 0.001$), and left sided obstruction was present more often in LAI. Atrioventricular regurgitation was present pre-operatively in 20% of infants, and was more common in LAI than RAI ($p = 0.002$). Despite the cardiac complexities within this group, using univariate survival analysis, no echocardiographic parameters were associated with mortality. Conclusions: Mortality in infants with heterotaxy and single ventricle physiology remains high in the current era. Although there are significant anatomic and physiologic differences between RAI and LAI, in this study population there were no specific echocardiographic parameters associated with mortality.

165. Delineating Premature Infants with Bronchopulmonary Dysplasia, Utilizing Retrospective Data from Electronic Health Record (EHR) Systems

Shilpa Vyas-Read, MD and Prabhu RV Shankar, MD, MS

BACKGROUND: Bronchopulmonary dysplasia (BPD) affects approximately 45% of very low birth weight infants. Clinically, BPD is defined as a need for oxygen at 28 days of life, and infants with moderate-to-severe BPD continue to require oxygen/respiratory support at 36 weeks corrected gestational age (cGA). Objective of this study was to determine if very low birth weight infants with BPD could be identified in EHR systems using billing codes for outcome evaluations in future studies. METHODS: The Population Discovery and Clarity databases, available through the Children's Healthcare of Atlanta from 2010–2015, were queried. For clinical BPD definition, the inclusion criteria was Infants who had a weight <1500 grams, and a gestational age <32 weeks at birth. A secondary query was performed for respiratory support: room air, continuous positive airway pressure, oxyhood, tracheostomy tube, high flow nasal cannula, nasal cannula, non-invasive positive pressure ventilation, tracheostomy collar/cap, and ventilator. 36 weeks cGA will be determined by calculating 36 weeks minus gestational age at birth, and this difference will be added to the date of birth to determine the date of BPD assessment. Patients requiring supplemental oxygen or positive-pressure ventilation on the date of 36 weeks cGA will be defined as having moderate-to-severe BPD. The comparison group consisted of infants with diagnosis codes APR-DRG 132 (BPD & Other Chronic Respiratory Diseases arising in Perinatal Period) or ICD 9 code 770.7 (Chronic respiratory disease arising in the perinatal period). RESULTS: There were 407 patients who had a diagnosis code of APR-DRG 132 or ICD 770.7. 5 weeks was the earliest age at which a BPD diagnosis code was assigned (1 infant). Manual curation identified about 626 patients with possible BPD. Further analysis and sub-classification into mild-moderate-severe categories will be performed, and respiratory and clinical variables compared between groups. CONCLUSION: Billing codes may not identify all infants who meet a clinical definition of BPD. Early diagnosis of babies who meet the clinical criteria for BPD, and further categorization, requires Natural Language Processing (NLP) of clinical notes along with billing codes to retrieve all variables, manual curation and secondary mathematical calculations from the retrieved data (cGA). Any future algorithms development for phenotypic characterization of BPD patients need to consider the above mentioned factors.

166. TRANSIT(TM): An Interactive Website to Support Transitioning of Children with Hemophilia

Prabhu RV Shankar, MD, MS; Shanna Mattis, MPH; Deniece Chevannes; Rachelle Willoughby; Tim Morris; and Christine Kempton, MD, MSc

BACKGROUND: Hemophilia is an inherited bleeding disorder, with bleeding into joints which can lead to chronic disability. Children with hemophilia need special attention, to progress through normal developmental stages, while learning to cope with their chronic disease. Patient/family engagement and care coordination among a multi-disciplinary team is required for effective transition through life stages that promotes optimum functioning and quality of life. Coordination of transition services can be challenging and implementing the current National Hemophilia Foundation (NHF) transition guidelines to support care transition from childhood to adulthood has been difficult in the clinical setting. Robust tools are needed to facilitate coordination among providers and also brings into home the many life skills, knowledge and attitudes outlined in the NHF guidelines. METHODS: TRANSITTM, an interactive, secure website brings the transition of care NHF Guideline tasks into focus, with clear information and actionable goals. Each age range (birth to 4, 5-8, 9-12, 13-15, and 16-18 years) will have a module in the website. Each module includes: Social Support & Resources, Health & Lifestyle, Educational Planning, Self-Advocacy & Self-Esteem, Sexual Health and Independent Health Care Behavior, adopted from the NHF Guidelines. Even though website content is mainly directed at patients and parents, treatment center and outreach staff will also be primary users. Patients will be accompanied on their transition journey with resource website links, videos, games, and 'Did you know?' snippets. Evaluation strategy includes preliminary (prior to website development), formative (during development), and summative (following development). RESULTS: After IRB approval, four patients/parents were interviewed to gather user needs/requirements. Based on the user input, TRANSITTM has been developed. Leveraging Twitter Bootstrap Version 3.0, CSS, and JavaScript/JQuery, the website fits a variety of devices. Evaluation is ongoing and pre-post questionnaire has been developed for assessing knowledge acquisition and website usability. CONCLUSION: The pervasive web, with accessibility any time, may provide a rich media to facilitate care coordination and impart self-management skills for successful transition of care in patients with hemophilia. Further evaluation is needed to show improvements in key performance measures, such as therapy adherence, overall health, and quality of life.

167. Automatic Language Translation for Improving Patient Care Management

Prabhu RV Shankar, MD, MS; Cyndie Roberson, RN; Eva K. Lee, PhD; and Harold K. Simon, MD, MBA

BACKGROUND: Language barriers hinder communication between patients and clinicians. Yet, proper communication is critical for optimal patient care and best outcomes. In 2014, Children's Healthcare of Atlanta (CHOA) cared for about 27,000 patients with Limited English proficiency (LEP). To improve patient-provider communication, it is necessary to interpret spoken language and translate discharge (DC) summaries to the patient's primary language of communication. Currently, the gap in the standard of care of LEP patients is not providing the DC summaries in the language they can comprehend. LEP is a risk factor for reduced healthcare accessibility, many quality of care measures and pt. satisfaction. As a pilot, we translated Emergency Department DC summaries using computer-assisted translation and machine translation (MT), from English to 3 commonly spoken other languages. METHODS: We utilize a machine learning environment with Knowledge Discovery (KD) tools, Google Translate, a self-learning translator and a language library. The KD tools process narrative text from de-identified DC summaries and the Google Translate translates English into different languages. Human language experts correct the translated text and the self-learning translator takes in the processed DC text as well as the expert corrected content, learns adaptive from the correction and retains those knowledge in its self-learning translator. As a large corpora is fed, both the self-learning translator and the language library will expand their vocabulary and related content. We will continue to refine and fine tune the MT tools and evaluate the accuracy of language translation from English to other languages, both using computer algorithms and trained human translators. RESULTS: We present the web interface developed for the KD tool and preliminary results of Bilingual Evaluation Understudy algorithm output of translation assessment. The performance of language translators was significantly better for Spanish (0.864 vs 0.293) and Vietnamese (0.568 vs 0.199) with KD tool compared to not using KD tools. CONCLUSION: Automated MT of DC summaries that are validated by a certified translator for potential errors may provide a viable solution to fill the gap in the standard of care, help LEP population better understand DC instructions and quality of care. This project could be generalized across a broad range of clinical settings and patient populations where language barriers are of concern.

168. Preferential Attention to Audiovisual Synchrony in Social Contexts: A Longitudinal Study

Robin Sifre; Sarah Shultz, PhD; Warren Jones, PhD; and Ami Klin, PhD

Background: Preferential attention to biological motion is present in human infants from the first days of life and plays a critical role in social development (Simion et al., 2007). Biological motion contains rich social information and is a source of audio-visual synchrony (AVS). By 24-months, these two features hold different significance for typically-developing (TD) toddlers and toddlers with Autism Spectrum Disorders (ASD): while TD toddlers show a preference for biological motion regardless of underlying AVS, ASD toddlers preferentially attend to AVS, suggesting a preference for physical, rather than social, contingencies (Klin et al., 2009). Little is known, however, about how and when these differences emerge in development, an understanding of which has the potential to inform treatment. Mapping the trajectory of how AVS influences preferential attention in typical development will establish a much needed framework for examining when deviations from this normative trajectory are first observed in ASD and how such deviations impact developmental outcomes. The present study measures the longitudinal change in the association between AVS and attention to biological motion in children at low-risk (LR) and high-risk (HR) for ASD.   Methods: 88 LR and 95 HR infants were shown point-light biological motion animations as in Klin et al. (2009). An upright point-light animation was presented on one half of the screen, with the inverted version playing on the opposite side. Eye-tracking data collected at months 2, 3, 4, 5, 9, 15, and 24, were used to calculate percentage of fixation time during each trial. Levels of AVS were quantified in all animations by measuring synchronous change in motion and sound.   Results: Spearman correlations revealed that preferential attention to AVS was developmentally modulated in LR infants: no association between preferential attention and AVS was seen at months 2, 3, 4, or 24. Significant associations were observed at months 5 ($r=.26$, $p<.001$), 9 ($r=.23$, $p<.05$), and 15 ($r=.36$, $p<.001$). Data from HR infants showed increased variability at all time points.   Conclusion: The present findings reveal a period in typical development when preferential attention is associated with AVS, peaking at 15 months. Future analyses will focus on parsing the heterogeneity of HR infants to better understand the increased variability in their looking patterns, and to determine when and how deviations from the typical development emerge.

169. Evaluating Hospice and Palliative Medicine Education in Pediatric Sub-Specialty Training Programs

Arun L. Singh, MD; Jeffrey Klick, MD; Courtney E. McCracken, PhD; and Kiran Hebbar, MD, FCCM

Background: Hospice and Palliative Medicine (HPM) competencies are a growing area of importance in the training of other pediatric subspecialties. In 2009, the Accreditation Council for Graduate Medical Education (ACGME) provided further emphasis, stating that pediatric trainees should understand the impact of chronic disease, terminal conditions and death on patients and their families. Despite this emphasis, there may still be a continued deficit of formal HPM training in other pediatric sub-specialties. RESEARCH OBJECTIVES: To identify the presence, teaching methods, and attitudes toward training opportunities in HPM competencies in pediatric sub-specialty training. METHODS: A Research Electronic Data Capture survey was sent via e-mail to all 287 ACGME accredited pediatric training program directors (PDs) in cardiology, critical care medicine (CCM), hematology-oncology (Heme/Onc) and neonatology (NICU) to assess demographics & HPM attitudes and education practices. RESULTS: The total response rate was 35.5% (102/287) with 17.6% Cardiology, 31.3% CCM, 22.5% Heme/Onc and 28.4% NICU. Of these programs, 46% offer formal HPM training; Heme/Onc (55%) the highest. HPM training commonly included conferences, HPM consultations and bedside teaching. 93.3% (14) Cardiology, 82.8% (24) CCM, 40.9% (9) Heme/Onc and 75% (21) NICU programs do not offer a formal HPM rotation. 73% of programs felt that HPM curriculum would improve trainees ability to care for patients. Most [Cardiology (77%), CCM (82%) and Heme/Onc (95%] agree that a HPM rotation would enhance trainees' education, except for NICU PDs (55%) (p < 0.05 for all comparisons). CONCLUSION: Despite most programs reporting benefit from a formal HPM training, there remains a paucity of opportunities for pediatric subspecialty trainees. While there is differing aspiration for new training methods, there is significant opportunity to further emphasize HPM in other pediatric specialty training. IMPLICATIONS FOR RESEARCH, POLICY OR PRACTICE: Further investigation is needed into the barriers to implementing training in HPM competencies, as well as into the impact on the trainees in other pediatric subspecialties.

170. Production and Characterization of Candidate Ebola Virus VLP Vaccines

Karnail Singh, PhD; Xuemin Chen, PhD; Jaang-Jiun Wang, PhD; and Paul Spearman, MD

Ebola virus is a highly infectious pathogen that causes severe hemorrhagic fever resulting in high rates of mortality. Knowledge of immune responses to this virus is limited because of lack of infrastructure needed to perform research with this virus. Currently there is no vaccine in use that affords protection against this deadly virus. Expression of Ebola virus antigens in non-infectious virus-like particles (VLPs) provides a means of presenting antigens in native conformation in a safe and practical format. Here we report the development of two production systems to produce VLPs that express high levels of Ebola Zaire glycoprotein (GP) on either Ebola matrix protein VP40 or HIV Gag core. Though VLPs produced by both the systems expressed high levels of Ebola Zaire glycoprotein, density gradient analysis studies suggested that the particles produced with Ebola virus VP40 were slightly lighter in buoyant density. Negative-staining electron microscopic analysis revealed that VLPs with an immature HIV Gag core were spherical in shape and were densely covered with GP on their surface. VLPs with Ebola virus VP40 core were filamentous in shape, and also demonstrated a high level of Ebola GP incorporation. The striking abundance of the Ebola Zaire glycoprotein trimers on these VLPs suggests that they may serve as effective products for eliciting GP-specific immune responses.

171. Approaches to Account for the Influence of Inflammation on Nutrient Biomarkers in Children

Parminder S. Suchdev, MD, MPH; Sorrel Namaste, DrPH; Yaw Addo, PhD; Leila Larson, MPH; and Kevin Sullivan, PhD: On behalf of the BRINDA working group

Background: Inflammation is known to affect many biomarkers used to assess micronutrient status and can thus lead to incorrect diagnosis of individuals, as well as over- or under-estimation of the prevalence of deficiency in a population.Methods: In 2012, the Centers for Disease Control & Prevention (CDC), National Institutes of Health and Global Alliance for Improved Nutrition formed a collaborative research group called Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA) to examine the relationship between inflammation and nutrient biomarkers. We pooled data from 16 cross-sectional nutrition surveys conducted in the last 10 years that included 27,335 children 6-59 months of age and measured the following biomarkers: inflammation [defined as elevated C-reactive protein (CRP)> 5mg/L or alpha-1-acid glycoprotein (AGP) >1g/L]; anemia [hemoglobin (Hb)<

11g/dL); iron deficiency (ferritin <12ug/L); and vitamin A deficiency (retinol binding protein (RBP) <0.7mmol/L). Linear regression was used to assess the relationship between inflammation and nutrient biomarkers. Results: Prevalence of elevated CRP and AGP ranged from 6% (USA) to 40% (Cote D'Ivoire) and 21% (Philippines) to 64% (Cote D'Ivoire), respectively. Both CRP and AGP were significantly positively correlated with ferritin, and negatively correlated with Hb and RBP across all countries. Ignoring inflammation would result in an underestimation of iron deficiency prevalence of 9 percentage points (range 1-19%) and an overestimation of anemia prevalence of 16 percentage points (0.3-30%) and vitamin A deficiency prevalence of 19 percentage points (7-29%). Conclusions: Biomarkers of inflammation (CRP and AGP) should be measured concurrently with biomarkers of anemia, iron and vitamin A, and adjustments should be made to appropriately interpret status of both populations and individuals. Results from this project will inform WHO/CDC guidelines on the assessment of anemia and micronutrient status in populations with high levels of inflammation. Findings will also guide the development of a research agenda for future longitudinal studies in clinical settings.

172. Improved High-Resolution Pediatric Vascular Imaging with a Novel Gadofosveset-Enhanced 3D Respiratory Navigated IR GRE Sequence

Animesh Tandon, MD, MS; W. J. Parks, MD; Sassan Hashemi, MD; Denver Sallee, MD; and Timothy C. Slesnick, MD

Background: Improved delineation of vascular structures, including coronary arteries and pulmonary veins, is a common indication for CMR imaging in children and requires high spatial resolution. Currently, pre-contrast 3D, respiratory navigated, T2 prepared, fat saturated imaging with a bSSFP readout (3D bSSFP) is used; however, these images can have limitations including blood pool inhomogeneity and exaggeration of metal artifact. We sought to compare the standard 3D bSSFP sequence to imaging after administration of the blood pool contrast agent, gadofosveset trisodium (GT), with a novel 3D, respiratory navigated, inversion recovery prepared sequence with a gradient echo readout (3D IR GRE). Methods: For both sequences, VCG triggering was used with acquisition during a quiescent period of the cardiac cycle. 3D bSSFP imaging was performed pre-contrast, and 3D IR GRE imaging was performed 5 minutes after GT administration. We devised a vascular imaging quality score (VIQS) with scores for coronary arteries, pulmonary arteries and veins, blood pool homogeneity, and metal artifact. Scoring was performed on axial reconstructions of isotropic datasets by two independent readers and differences were adjudicated. Imaging scores were compared using Wilcoxon signed-rank tests, tests of symmetry, and the Brown-Forsythe test, with $p<0.05$ considered significant. Results: 35 patients had both 3D bSSFP and 3D IR GRE imaging performed and were included in the analysis. 3D IR GRE imaging showed improved overall vascular imaging compared to 3D bSSFP for all patients when comparing non-metal VIQS scores (median 14 (IQR 11-15), vs 6 (4-10), $p<0.0001$). Sub-analysis of patients with intrathoracic metal (n=17) showed 3D IR GRE again had improved VIQS (16 (14-17) vs. 5 (2-9), $p<0.0001$). 3D IR GRE showed significantly improved VIQS scores for imaging the RCA, pulmonary arteries, and pulmonary veins (all $p<0.05$). In addition, 3D IR GRE imaging showed reduced variability in scores compared to 3D bSSFP for both nonmetal and metal scores (both $p<0.05$). Conclusion: Imaging with the novel respiratory navigated 3D IR GRE sequence after administration of GT provides improved vascular imaging in pediatric patients compared to pre-contrast 3D bSSFP imaging, especially in those patients with intrathoracic metal. It is an attractive alternative in this challenging patient population when high spatial resolution vascular imaging is needed.

173. Promoting Quiet NICU Soundscapes

Jonathan Weber, BS; Erica E. Ryherd, PhD; Ashley Darcy Mahoney, RN, PhD; Heather Cooper, BSN, RN; Myra Rolfes, MN, BSN, RNC; and Brooke Cherven, MPH, RN, CPON

A healthy sound environment or soundscape is a crucial component in the hospital setting to promote healing for patients and to provide a healthy workplace for staff. Difficulty arises in intensive care units, such as Neonatal Intensive Care Units (NICUs), as the patients' conditions tend to increase in severity and variability. As more equipment and staff are required to care for patients, noise tends to rise and counteracts the health-promoting environment. Standards have been set by the American Academy of Pediatrics (AAP) to limit noise levels in the NICU. However, previous studies consistently show units exceeding these standards. This project focuses on characterizing the soundscape of two local NICUs before and after the implementation of a Quiet Time (QT) evidence-based practice change. Two-hour periods in the afternoon and night were set in which detailed protocol was encouraged to reduce noise generated by people in the unit. Detailed acoustic measurements were taken

before and after QT implementation. Results show noise levels consistently above standards, but trends toward decreased levels after QT implementation. Comparing QT hours to non-QT hours showed the greatest decrease in sound levels after six months, pointing toward the necessity of a habituation period. Spectral data across 1/3 octave bands showed significant decrease in levels across the vocal frequency range, which could improve communication among staff. Implications for future research will be discussed.

174. Uremic Cardiomyopathy is Associated with Inflammatory Gene Signature in a Mouse Model of Chronic Kidney Disease

Pamela D. Winterberg, MD; Gregory Tharp, MS; Rong Jiang, MD,PhD; Sonal Harbaran; Ming Shen; and Mary B. Wagner, PhD

Introduction: The underlying mechanisms contributing to uremic cardiomyopathy during chronic kidney disease (CKD) are poorly understood, limiting treatment options.   Hypothesis: We aimed to uncover novel pathways involved in the development of diastolic dysfunction and cardiac hypertrophy (uremic cardiomyopathy) in a mouse model of CKD.   Methods: CKD was induced in male 129X1/SvJ mice through five-sixths nephrectomy in a two-stage surgery (n=5). Age-matched mice underwent bilateral sham surgeries (n=5). Transthoracic echocardiography including mitral valve velocity measurements (Vevo2100, VisualSonics) was performed at 8 weeks post-CKD to assess heart structure and function. Hearts were then harvested and preserved in RNAlater. A sample of left ventricle tissue was processed for total RNA isolation and cDNA libraries were constructed using standard methods based on the Illumina TruSeq platform. Libraries were validated by microelectrophoresis, quantified, pooled and clustered on Illumina TruSeq v3 flowcells, and sequenced on an Illumina HiSeq 1000 in 100-base single-read reactions. Messenger RNA sequencing reads were aligned to the mm10 (UCSC) mouse reference assembly and annotation using the STAR RNA-seq aligner (version 2.4.0f1). Transcript assembly, abundance estimates, and differential expression analysis was performed using Cufflinks v2.1.1 and Cuffdiff. Significant differential expression was determined using a BH corrected FDR<0.05. Pathway analysis was performed using Ingenuity Pathway Analysis (IPA) software (Qiagen). The significance of the pathways was determined based on the ratio of differentially expressed genes within each pathway and Fischer's exact test (p<0.05). Two-tailed t-test was performed to compare echocardiography parameters between the groups. Results: CKD mice developed left ventricular hypertrophy (LVAW;d 1.42 ± 0.08 vs 1.06 ± 0.07 mm; p<0.0001) and diastolic dysfunction (E/A ratio 1.16 ± 0.11 vs 1.64 ± 0.20; p=0.02) compared to control mice. A total of 1,105 genes were found to be differentially expressed in CKD hearts compared to controls. Ten of the top 20 ingenuity canonical pathways were involved in inflammation and immune system function. Additional significant pathways included extracellular matrix remodeling and fibrosis, cardiac hypertrophy, and calcium signaling. Conclusions: Mice with uremic cardiomyopathy have gene expression changes enriched in inflammatory pathways that may represent novel therapeutic targets.

175. Validation of Temporally-Sensitive Eye-Tracking Indices of Social Disability as Treatment Endpoints in School-Age Children with ASD

Alaina Wrencher; Jennifer Moriuchi; Ami Klin, PhD; Sarah Shultz, PhD; and Warren Jones, PhD

Improving the quality of life of individuals with autism spectrum disorder (ASD) requires that methods of informing appropriate treatments be validated. Both the inherent social nature and the heterogeneous manifestation of ASD complicate this task. The core social deficit of ASD makes the disorder difficult to quantify; its heterogeneity renders individualized treatment approaches. Two important questions present themselves: How do we best quantify the degree of social disability at the core of autism? And how do we best measure whether a treatment for social disability has been effective? We investigate whether looking to the appropriate region of interest (ROI) at the appropriate time can serve as both an accurate indicator of social disability and as a successful endpoint for the assessment of new treatments. Objective: To assess the reliability and validity of relative salience measures to be used as treatment endpoints in school-age children with ASD. Methods: We assessed the use of eye-tracking measures in terms of their interpretability and general appropriateness to the condition; their content, construct, and convergent validity; and their reliability, precision, and internal consistency. To assess the range and distribution of scores found in the general population, we collected eye-tracking data from typically developing children (TD, mean age=9.61 years, N=42, FSIQ: 73-140) and then also collected comparison values in a heterogeneous sample of children with ASD (mean age=10.12 years, N=128, FSIQ: 32-149). Results: Reliability measures indicate high test-retest correlations for looking at each of our ROIs: all ICC > 0.5, all p < 0.001 for ASD; all ICC ≥ 0.4, all p < 0.05 for TD. Correlations for looking at the right ROI at the right time were also strong: ICC= 0.719, 0.001 < p < 0.140 for

ASD; ICC= 0.420, all p < 0.001 for TD. Preliminary analyses show promising convergent validity of ASD individuals' median salience values with their calibrated severity scores on the Autism Diagnostic Observation Schedule (ADOS): r= -0.357, p < 0.001. Conclusions: Eye-tracking measures of visual scanning can serve as effective and valid quantifiers of social disability. In the current analyses, we focused on relative salience measures of both social and non-social ROIs. Future analyses will explore whether splitting our heterogeneous ASD sample based on clinical characteristics might improve the convergent validity of our eye-tracking measures with the ADOS.

176. The Echo Dashboard: It's Value in Monitoring and Managing Echocardiography Laboratory Efficiency

Bonnie Wright; Nathan Woods; Ritu Sachdeva; and William L. Border

Background: Accurate and timely assessment of lab productivity and staffing is critical to ensuring operational efficiency and success. We sought to develop an echo dashboard that could help us track key operational metrics such as procedure volumes, sonographer and physician productivity, and trends in patient load on a daily basis.Methods: Qlikview (Qlik; Lund, Sweden) business intelligence software was used to aggregate and present the data graphically. The source data was derived from three applications: an echocardiography picture archiving and communication system, a cardiovascular imaging and information system, and the electronic medical record. Using Qlikview's native scripting language one can query for and pull the desired data and present it as charts, graphs, and tables. The system automatically updates every morning.   The graphic displays make this dashboard easy to navigate and analyze the laboratory data. A quick selection of tabs and parameter options provides instantaneous, up-to-date information. Results: Graphic representation of our procedures can be shown as a total or by echo modality. Data can be sorted by the desired time period: yearly, quarterly, monthly, weekly, daily or hourly using the pivot tool function (Fig A, B); These data have been utilized in preparing and presenting operational reports and that easily incorporating powerful visuals. Individual sonographer productivity can be monitored and inequitable work distribution can be detected (C). This feature has been used to modify sonographer assignments aiming at an even workload distribution (D).   Similarly physician productivity can be analyzed. The dashboard is also being used for fellowship record-keeping. Additional tabs can be added to include a variety of information, such as quality assurance data and customer service scores. Conclusions: The echo dashboard is a powerful tool that provides a rapid, real-time and accurate overview of lab data and can be significantly useful in optimizing lab operations. It helps to improve the efficiency of staffing, and provides readily available data for presentations and justifications to senior leadership.

177. Human B cell Responses to Vibrio cholerae Infection and Vaccination

R. Kauffman, PhD; J. Trost; T. Bhuiyan, PhD; L. Mayo-Smith; F. Qadri, MD; J. Harris, MD; and J. Wrammert, PhD

Vibrio cholerae causes 3 to 5 million cases of cholera and over 100,000 deaths annually, and the incidence of cholera has increased by approximately 25% over the past decade. The ongoing epidemic in Haiti illustrates the organism's continued global reach. More than a billion people lack access to safe drinking water and remain vulnerable to cholera. The increasing burden of cholera, the inability to achieve benchmarks for sanitation and safe water, and the emergence of more virulent strains of V. cholerae suggest that more aggressive approaches to preventing cholera, including vaccination programs, are needed. A reason that current cholera vaccines are not widely used is that they have significant immunologic limitations. Current cholera vaccines are administered in two or three doses given two to four weeks apart, vaccine induced immunity wanes rapidly after administration, and provides only partial protection, especially in children younger than five years. This is critical, as children two to five years of age represent the population most affected by cholera in endemic regions. In contrast, infection with V. cholerae induces 90-100% protection against re-infection that lasts for up to10 years in adults and children. We have characterized the V. cholerae-specific gut-homing plasmablast responses observed in infected patients at the ICDDRb, in Dhaka, Bangladesh. Using state of the art single cell technologies developed by us we have been able to study both the repertoire of the infection induced B cell responses, and generate a large panel of human monoclonal antibodies against V. cholerae. This panel of antibodies provides an unprecedented level of insight into the antibody responses raised against infection, at a single cell level, with respect to antigens targeted, affinity maturation and repertoire breadth against this complex bacterial antigen, both in the context of infection and vaccination. These antibodies may lead to identification of novel vaccine candidates, and development of rapid diagnostic tests or even novel approaches to passive immunization. As cholera is non-invasive, it also represents an excellent model for the study of immunity at the mucosal surface. Mucosal biopsy samples from the infected patients will allow us to determine how migration of plasma cells to this site is orchestrated and how the longevity of the mucosal plasma cells is regulated.

Participant Directory

Shelly Abramowicz, DMD, MPH
Assistant Professor, Oral and
Maxillofacial Surgery and Pediatrics,
Emory University, Children's
Healthcare of Atlanta
sabram5@emory.edu

Anna Aceituno, MSPH
Supervisor, Research Project
Coordinator, Emory University
anna.aceituno@emory.edu

Udit Agarwal, MD, PhD
Cardiology Fellow
Emory School of Medicine
uagarw2@emory.edu

Hyunhee Ahn, PhD
Senior Research Associate,
Department of Orthopaedics
Emory University
hyunhee.ahn@emory.edu

Bolanle Akinsola, MD
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
bakinso@emory.edu

Eme Anderson, CRA
Sr. Sponsored Program Analyst,
Children's Healthcare of Atlanta
eme.anderson@choa.org

Larry Anderson, MD
Professor, Pediatric Infectious
Diseases, Children's Healthcare of
Atlanta, Emory Department of
Pediatrics
larry.anderson@emory.edu

Sheila Angeles-Han, MD, MSc
Assistant Professor of Pediatrics
Ophthalmology, Emory University
School of Medicine
sangele@emory.edu

Ananyaveena Anilkumar
Undergraduate Student,
Georgia Tech
aanilkumar3@gatech.edu

Qiana L. Ayana, MA, CPPB
Children's Healthcare of Atlanta
qiana.ayana@choa.org

Nnamdi I. Azih
Morehouse School of Medicine
ndazih3@gmail.com

Haylee Bachman
Georgia Tech
hbachman6@gatech.edu

Faith Barron
Emory Department of Pediatrics
faith.barron@emory.edu

Amy Baxter, MD
Director of Emergency Research,
Pediatric Emergency Medicine
Associates, Children's Healthcare of
Atlanta
abaxter@mmjlabs.com

Torria Beasley
Clinical Research Coordinator,
Killian Owen Curing Kids Cancer
Clinical Research Office, Aflac
Cancer & Blood Disorders Center,
Children's Healthcare of Atlanta at
Egleston
Torria.beasley@choa.org

Zoe Beato
zoe.beato1@gmail.com

Timothy Beaty, MD, MS
Assistant Professor Emory
Department of Pediatrics
tbeaty2@emory.edu

Ajay Bhatia, MD, PhD
Fellow, Pediatric Cardiology,
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
bhatiaa@kidsheart.com

Siddhartha K. Bhaumik, PhD
Research Associate, Emory
Department of Pediatrics
sbhaumi@emory.edu

Hunter Blair
chiblair10@gmail.com

Felicia Bornes-Agyekum
Children's Healthcare of Atlanta -
Hughes Spalding
feliciaagyekum1212@gmail.com

Dawn Boughton
Children's Healthcare of Atlanta -
Egleston
dawn.boughton@choa.org

James Bowen
Emory Department of Pediatrics
jbowen6@emory.edu

Michael Brewington
Michael.Brewington@Outlook.com

Ashley Brown, PhD
Research Scientist
Georgia Institute of Technology
ac287@gatech.edu

Kelly Brown, BS, CCRC
Senior Research Coordinator-
Cardiothoracic Surgery, Children's
Healthcare of Atlanta
kelly.brown@choa.org

Lou Ann S Brown, PhD
Professor of Pediatrics Emory
University
lbrow03@emory.edu

Tracy Brown
Children's Healthcare of Atlanta -
Egleston
tracy.brown@choa.com

Alice Bruce, BS
Clinical Research Coordinator,
Emory Department of Pediatrics
alice.bruce@emory.edu

Corinthian Bryant, BS, CCRC
Clinical Research Coordinator IV
Emory University
Corinthian.bryant@emory.edu

Erin Buckley, PhD
Research Scientist, Georgia Tech,
Emory University
erin.buckley@bme.gatech.edu

Rachel M. Burke, MPH
PhD Candidate, Department of
Epidemiology, Rollins School of
Public Health, Emory University
rmburke@emory.edu

David P. Carlton, MD
Marcus Professor of Pediatrics
Division Director Neonatal-Perinatal
Medicine, Emory University School
of Medicine
dpcarlt@emory.edu

Ann Chahroudi
Achahro@emory.edu

Anusha Challa, BA
Research Specialist - Marcus
Autism Center, Children's
Healthcare of Atlanta
schall3@emory.edu

Denise Chauvet, RN, BSN
Children's Healthcare of Atlanta-
Hughes Spalding
denise.chauvet@choa.org

Albert Cheng
Georgia Tech
acbert@gatech.edu

Chih-Wen Cheng, PhD
Postdoctoral Fellow, Biomedical
Engineering, Georgia Institute of
Technology
cwcheng83@gmail.com

Alice Cho
Emory Department of Pediatrics
ahcho@emory.edu

Hannah (Mi Hyun) Choi
Undergraduate student: Emory
University/
Undergraduate researcher:
Department of Pediatrics at Emory
University/
Volunteer: Children's Healthcare of
Atlanta, Egleston
mchoi39@emory.edu

Junghwa Choi
PhD student, IMP, Emory University
jchoi30@emory.edu

Victoria Churchilll, MPH
Program Manager, Pediatrics
Clinical Research Center
Morehouse School of Medicine
vchurchill@msm.edu

Carrie Ciccotello
Undergraduate Researcher, Emory
University
cciccot@emory.edu

Rebecca Cleeton, MPH, CCRP
Clinical Research Coordinator IV
Emory University School of
Medicine
rcleeto@emory.edu

Lindsay Collin
lindsay.jane.collin@emory.edu

Amanda Cook
Director of Clinical Research
Services, Emory Department of
Pediatrics
amcook@emory.edu

Kristen Criado, PhD
Assistant Professor of Pediatrics,
Emory University School of
Medicine, Marcus Autism Center
kristen.criado@emory.edu

Aomeng Cui
acui2@emory.edu

Guiying Cui
Emory Department of Pediatrics
gcui2@emory.edu

Pauline Daniels, RN, BSN
Staff Nurse Collegue, Children's
Healthcare of Atlanta
pauline.daniels@choa.org

Mike Davis, PhD
Director, Children's Heart Research
and Outcomes Center Associate
Professor of Biomedical Engineering
& Cardiology
Wallace H. Coulter Department of
Biomedical Engineering Emory
University and Georgia Institute of
Technology
michael.davis@bme.gatech.edu

Tarsha Davis, RN
Staff Nurse/Resource Nurse
Children's Healthcare of Atlanta -
Hughes Spalding
tarsha.davis@choa.org

Ton de Grauw, MD, PhD
Chief of Neurosciences, Children's
Healthcare of Atlanta, Division
Director, Pediatric Neurology, Emory
School of Medicine
ton.degrauw@choa.org

Liezl de la Cruz, CCRC
Lead Research Coordinator,
Transplant/Hepatology, Children's
Healthcare of Atlanta - Egleston
liezl.delacruz-tracy@choa.org

Megan Denham, MAEd, EDAC
Research Faculty, SimTigrate
Design Lab, Georgia Tech, College
of Architecture
megan.denham@coa.gatech.edu

Shriprasad Deshpande, MD, MS
Assistant Professor of Pediatrics,
Pediatric Cardiology, Emory
University, Medical Director,
Mechanical Circulatory System
Program, Children's Healthcare of
Atlanta
deshpandes@kidsheart.com

Abhinav Dey, PhD
Postdoctoral Fellow, Emory
Department of Pediatrics
abhinav.dey@emory.edu

Ronyiah Douglas
Ronyiahdouglas318@yahoo.com

Shaneka Douglas, BS, CRC
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
sdougl5@emory.edu

Jennifer DuBose, MS, LEED AP,
EDAC
Managing Director (interim), Center
for Transforming Pediatric
Healthcare Delivery, Associate
Director, SimTigrate Design Lab,
Senior Research Associate, Georgia
Tech
jennifer.dubose@coa.gatech.edu

Angie Duprey, MEd
Development Officer, Children's
Healthcare of Atlanta
angie.duprey@choa.org

Stella Fagbemi
Georgia Tech
sfagbem@emory.edu

Sherry Farrugia
Managing Director, Health Research
Partnerships, Director, Georgia
Tech, Children's Healthcare of
Atlanta Partnership, Health IT
Strategic Partners Officer
sherry.farrugia@gatech.edu

Jan Fernandez, BS, RRT-NPS,
CCRC
Senior Research Coordinator,
Cardiothoracic Surgery, Children's
Healthcare of Atlanta
janet.fernandez@choa.org

MK Findley, BSN, MS, RN
PhD Student, Emory University, Nell
Hodgson Woodruff School of
Nursing
mk.findley@emory.edu

M. G. Finn, PhD
Professor and Chair, School of
Chemistry and Biochemistry, School
of Biology, Director, Center for
Pediatric Nanomedicine, Georgia
Tech
mgfinn@gatech.edu

Anne Fitzpatrick, PhD, APRN
Director, Asthma Clinical Research
Program, Director, ACTSI Pediatric
Research Unit, Associate Director,
Children's Center for Cystic Fibrosis
and Airways Disease Research
anne.fitzpatrick@emory.edu

Julie Kozarsky Flores, BA
Clinical Research Coordinator,
Emory University Department of
Pediatrics
julie.flores@emory.edu

Maxine Forbes, RN, BSN, CPN
Staff Nurse, Children's Healthcare of
Atlanta
Maxdon16@aol.com

Osric Forrest
Emory University
osricforrest@gmail.com

Patrick Frias, MD
Chief Operating Officer at Children's
Healthcare of Atlanta
Pat.Frias@choa.org

Heather Friedman, MPH, CCRP
Senior Clinical Research
Coordinator, Cardiac Imaging
Research Core, Children's
Healthcare of Atlanta
heather.friedman@choa.org

D. D. Fritch-Levens, MSN, MHA, RN
Director of Contact Center,
Childrens Healthcare of Atlanta -
Nurse Advice Line, One Point of
Contact, Telemedicine
d.d.fritch-levens@choa.org

Jacques Galipeau, MD
Professor
jgalipe@emory.edu

Beatrice Gee, MD, FAAP
Professor of Pediatrics; Director,
Sickle Cell Program, Children's
Healthcare of Atlanta, Morehouse
School of Medicine
bgee@msm.edu

David B. Goldstein, PhD
Director, Institute for Genomic
Medicine Columbia University
dg2875@columbia.edu

Patty Gregory
Children's Healthcare of Atlanta
patty.gregory@choa.org

Teresa Gross
tesasgross@gmail.com

Bob Guldberg, PhD
Professor
Director, Institute for Bioengineering
and Bioscience
School of Mechanical Engineering
Georgia Institute of Technology
robert.guldberg@me.gatech.edu

Chris Gunter, PhD
Associate Director of Research,
Marcus Autism Center, Children's
Healthcare of Atlanta, Emory
Department of Pediatrics
chris.gunter@emory.edu

Nitika Gupta, MD, DCH, DNB,
MRCPCH
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
narorag@emory.edu

Jakob Habib
Emory Department of Pediatrics
jghabib@emory.edu

Claire Hailey
Children's Healthcare of Atlanta -
Egleston, Emory Department of
Pediatrics
ceunder@emory.edu

Megan Hamling, MPH
Laboratory Research Coordinator,
Children's Healthcare of Atlanta
megan.hamling@choa.org

Teresa Hammarback, MS, RN, CPN
Nurse Researcher, EBP
Coordinator, Children's Healthcare
of Atlanta
teresa.hammarback@choa.org

Jason E. Hammonds, PhD
Assistant Professor, Emory
University, Department of Pediatrics
jason.hammonds@emory.edu

Cheri M. Hampton, PhD
Postdoctoral fellow Emory University
Cmhampt@emory.edu

Jingjia Han, PhD
Emory Department of Pediatrics,
Children's Healthcare of Atlanta,
Georgia Tech
jingjia.han@emory.edu

Caroline Hansen
Georgia Tech
caroline.hansen@gatech.edu

Sonal Harbaran, BS
Lead Research Specialist,
Children's Healthcare of Atlanta
Center, Emory Department of
Pediatrics
sonal.harbaran@emory.edu

Frank Harris
Emory Department of Pediatrics
fharris@emory.edu

Brooke Hartwell
Senior Application Analyst
Children's Healthcare of Atlanta
bhhartw@emory.edu

Sassan Hashemi, MD
Image Processing Scientist
Children's Healthcare of Atlanta
sassan.hashemi@choa.org

Lauren M. Head, BSN, RN
PhD student Emory University
School of Nursing
lmhead@emory.edu

Stacy Heilman, PhD
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
sheilma@emory.edu

Kristen Herzegh
Program Coordinator, Children's
Healthcare of Atlanta
kcoshau@emory.edu

Peter Hesketh, PhD
Professor, School of Mechanical
Engineering, Georgia Tech
peter.hesketh@me.gatech.edu

Marian Hettiaratchi
Wallace H. Coulter Department of
Biomedical Engineering, Georgia
Tech and Emory University
mhettiaratchi3@gatech.edu

Eric Hoar, RRT, CCRP
Lead Research Coordinator,
Children's Healthcare of Atlanta
Healthcare
eric.hoar@choa.org

Ryan Hoffman
Graduate Student, Georgia Tech &
Emory University
rhoffman12@gatech.edu

Scott Hollister, PhD
Professor, University of Michigan
scottho@umich.edu

Donna Hyland
President and Chief Executive
Officer
Children's Healthcare of Atlanta
Donna.hyland@choa.org

Sarah Ingersoll, PhD
Postdoctoral Fellow, Emory
University
iggyredbac@gmail.com

Kesmic Jackson, PhD
Biorepository Coordinator
Children's Healthcare of Atlanta
Kesmic.jackson@choa.org

Dov Jacobson
Studio Director, GamesThatWork
Dov@GamesThatWork.com

Kirsten Jenkins
kirsten.jenkins@choa.org

Rajneesh Jha, PhD
Postdoctoral Fellow, Emory
University
rajneesh.jha@emory.edu

54

Rong Jiang, MD, PhD
Technical Director, Animal
Physiology Core
rjiang2@emory.edu

Ran Jin
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
rjin@emory.edu

Jonathan Johnson
Children's Healthcare of Atlanta
jonathan.johnson8@gmail.com

Juna Konomi Johnson, PhD
Post Doctoral Fellow
Department of Pediatrics,
Gastroenterology
Emory University School of
Medicine
junakonomi@emory.edu

Christopher Jones, PhD
Associate Vice President for
Research
Georgia Institute of Technology
christopher.jones@chbe.gatech.edu

Rheinallt Jones, PhD
Assistant Professor
Division of Gastroenterology,
Hepatology and Nutrition
Department of Pediatrics
Emory University School of
Medicine
rjones5@emory.edu

Warren Jones, PhD
Director of Research, Marcus
Autism Center
warren.jones@emory.edu

Harish C. Joshi, PhD
Assoc. Professor, Emory
Department of Pediatrics
harish.joshi@emory.edu

Zunlong Ke
Graduate Student
Georgia Tech
Emory Dept. of Pediatrics
zunlongke@gatech.edu

Karen Kennedy, PhD
Program Coordinator, Children's
Healthcare of Atlanta
kmurra5@emory.edu

Barbara Kilbourne, RN, MPH
Manager, Business Operations,
Children's Healthcare of Atlanta
bkilbou@emory.edu

Hyunmi Kim, MD, PhD, MPH
Emory Department of Pediatrics
hyunmi.kim@emory.edu

Baek Kim
Director of Center for Drug
Discovery, Professor, Emory
Department of Pediatrics
baek.kim@emory.edu

Jen King
Project Manager, Children's
Healthcare of Atlanta
jen.king@choa.org

Erin Kirshtein
Georgia Tech
erin.kirshtein@bme.gatech.edu

Ami Klin, PhD
Director, Marcus Autism Center,
Children's Healthcare of Atlanta
Georgia Research Alliance Eminent
Scholar
Professor & Chief, Division of
Autism and Related Disorders
Department of Pediatrics, Emory
University School of Medicine
Center for Translational Social
Neuroscience, Emory University
Ami.klin@choa.org

Brett Klosterhoff
Graduate Research Assistant,
Parker H. Petit Institute for
Bioengineering and Bioscience,
Georgia Tech
brett.klosterhoff@gatech.edu

Lazaros Kochilas, MD
Associate Professor, Emory
University School of Medicine
kochilasl@kidsheart.com

James J. Kohler, PhD
Assistant Professor, Assistant
Director for Emory CFAR Scientific
Working Group for Viral Eradication,
Emory University
jjkohle@emory.edu

Holly Korschun
Executive Director, Research
Communications and Media
Relations, Emory University,
Woodruff Health Sciences Center
hkorsch@emory.edu

Subra Kugathasan, MD
Marcus Professor of Pediatric
Gastroenterology / Inflammatory
Bowel Diseases
Professor of Human Genetics
Scientific Director of Pediatric IBD
program / Children's Healthcare of
Atlanta
Director, Children's Center for
Transplantation and Immune
mediated Disorders
skugath@emory.edu

Elham Laghaie, MS
Clinical Research Coordinator,
Morehouse School of Medicine,
Childrens Healthcare of Atlanta
elham.laghaie@choa.org

Leila Larson, MPH
PhD Candidate, Nutrition and Health
Sciences Program, Emory
University
leila.larson@emory.edu

Nari Lee
Georgia Tech
nlee46@emory.edu

Jake Lehman
jrlehman@usc.edu

Juan Leon, PhD, MPH
Assistant Professor, Emory
University
juan.leon@emory.edu

Traci Leong
Emory Department of Pediatrics
tleong@emory.edu

Rebecca Levit, MD
Assistant Professor, Cardiology,
Emory University
rlevit@emory.edu

Helen Li
yli2333@emory.edu

Karen Lindsley, RN, MSN, CDE,
CCRC
Research Supervisor, Emory
Department of Pediatrics
klindsl@emory.edu

Kiah Lofland
Children's Healthcare of Atlanta -
Hughes Spalding
Kiah.Lofland@choa.org

Daphne Ma, PhD
Postdoctoral Research Fellow,
Emory Department of Pediatrics
daphne.ma@emory.edu

Kevin Maher, MD
Associate Director, Center for
Pediatric Nanomedicine
Director, Pediatric Cardiac
Nanomedicine
Associate Director, Atlanta Pediatric
Device Consortium
Director, Cardiac Intensive Care
Unit
Children's Healthcare of Atlanta
Associate Professor of Pediatrics
Emory University
maherk@kidsheart.com

Anshu Malhotra, PhD
Post Doctoral Fellow, Emory
University
anshu.malhotra@emory.edu

Aneeq Malik, BS
Children's Healthcare of Atlanta,
Morehouse Schoold of Medicine
aneeq.malik@gmail.com

Manisha Malik, MD
Pediatric Neurology Resident,
Children's Healthcare of Atlanta
mmalik3@emory.edu

Punam Malik, MD
Cincinnati Children's Hospital
Medical Center, Marjory J. Johnson
Chair of Gene and Cell Therapy,
Professor of Pediatrics
punam.malik@cchmc.org

Maret Maliniak, MPH
Clinical Research Coordinator,
Emory+Children's Center
maret.lee.maliniak@emory.edu

Urko M. Marigorta, PhD
Postdoctoral Fellow, Gibson Lab,
Center of Integrative Genomics,
Georgia Tech
urkotxapela@gmail.com

Bernadette Martineau, MS, RD, LD
Clinical Nutritionist and Clinical Data
Coordinator
Children's Healthcare of Atlanta
bernadette.martineau@choa.org

Shanna Mattis, MPH
Public Health Associate & Social
Worker, Comprehensive Bleeding
Disorders Center, Emory University
and Children's Healthcare of Atlanta
slmatti@emory.edu

Maud Mavigner, PhD
Post Doctoral Fellow, Emory
Department of Pediatrics
mmavign@emory.edu
Victor Maximov, PhD
Postdoctoral Fellow Emory
University
victor.maximov@emory.edu

Joshua Maxwell, PhD
Postdoctoral Fellow Emory
University
joshua.t.maxwell@emory.edu

Nael A. McCarty, PhD
Director, Center for CF and Airways
Disease Research, Emory
Department of Pediatrics
namccar@emory.edu

Heather McDonald
Children's Healthcare of Atlanta
heather.mcdonald@choa.org

Courtney A. McWhorter
2nd Year Medical Student
Morehouse School of Medicine
cmcwhorter@msm.edu

Laura Mee
Children's Healthcare of Atlanta -
Egleston, Emory University
laura.mee@choa.org

Yash Mehta
yashmehta31@gmail.com

Stephanie Meisner, RN, BSN,
CCRP
Clinical Research Manager,
Pediatric Research Center,
Children's Healthcare of Atlanta,
Atlanta Clinical Translational
Science Institute (ACTSI), KIDS
Georgia
stephanie.meisner@choa.org

Stephen Milhollin, MPH
Clinical Research Coordinator,
Children's Healthcare of Atlanta
stephen.milhollin@choa.org

Sameer Mishra
smishra39@gatech.edu

Anaam Mohammed, MPH, CCRC
Clinical Research Coordinator,
Pediatric Emergency Medicine
Associates, LLC, Children's
Healthcare of Atlanta
anaam.mohammed@choa.org

Kajari Mondal, PhD
kmondal@emory.edu

E. Clark Montague, DO
Neonatal-Perinatal Medicine Fellow,
Emory Department of Pediatrics
emonta2@emory.edu

Martin Moore, PhD
Assistant Professor of Pediatrics
Co-Director, Center for Childhood
Infections and Vaccines (CCIV)
martin.moore@emory.edu
Amy Moore, PhD
Director of Research Programs,
Georgia Research Alliance
amoore@gra.org

Kira Moresco
kira.moresco@emory.edu

Emilie Morris
emiliec.morris@gmail.com

Natasha Morris, MS
Clinical Research Coordinator, Aflac
Cancer and Blood Disorder Center,
Children's Healthcare of Atlanta
natasha.morris@choa.org

Claudia R. Morris MD
Associate Professor, Emory
Department of Pediatrics
claudia.r.morris@emory.edu

Gemma Morrow, RDCS
Pediatric Cardiac Sonographer
Children's Healthcare of Atlanta
gemma.morrow@choa.org

Beth Mynatt, PhD
Professor, GA Tech
Director, Center for Transforming
Pediatric Healthcare Delivery
mynatt@cc.gatech.edu

Karthik Nathan
Biomedical Engineering,
Georgia Tech
karthik.nathan3@gmail.com

Kira Newman
MD/PhD Candidate, Emory
University
kira.newman@emory.edu

Janice Newman, MBA, CCRC
Children's Healthcare of Atlanta
Janice.newman@choa.org

John Nicosia
Graduate Student, Georgia Tech
jnicosia3@gatech.edu

Aidan O'Connor, MPH
Clinical Research Coordinator,
Children's Healthcare of Atlanta
aidan.oconnor@choa.org

Lindsay Olson, BA
Pre-doctoral Research Fellow,
Marcus Autism Center, Emory
Department of Pediatrics
lolson4@emory.edu

Matthew Oster, MD, MPH
Assistant Professor of Pediatrics,
Emory University School of
Medicine; Assistant Professor of
Epidemiology, Emory University
School of Public Health
osterm@kidsheart.com

Mitali Pakvasa, MD
Neonatology Fellow, Children's
Healthcare of Atlanta, Emory
Department of Pediatrics
mitali.atul.pakvasa@emory.edu

Sirish Palle, MD
Fellow in Pediatric
Gastroenetrology, Hepatology and
Nutrition, Emory University
sirish.palle@emory.edu

Lauren Pascarella, MA
Research Coordinator, Children's
Healthcare of Atlanta - Marcus
Autism Center
lauren.pascarella@choa.org

Virginia Pascual, MD
Investigator & Director, Center for
Inflammation and Autoimmune
Diseases; Center for Personalized
Medicine, Baylor Institute for
Immunology Research
virginip@baylorhealth.edu

Brad D. Pearce, PhD
Research Associate Professor and
Graduate Training Faculty,
Department of Epidemiology, Rollins
School of Public Health, Emory
University
bpearce@emory.edu

Lori Ponder
laponde@emory.edu

Sampath Prahalad, MD, MSc
Marcus Professor of Pediatric
Rheumatology
Chief, Division of Pediatric
Rheumatology
Professor of Pediatrics & Human
Genetics
sprahal@emory.edu

Mahadev Prasad
Emory Department of Pediatrics
mprasa3@emory.edu

Marcela Preininger
Lead Research Technologist,
Wallace H. Coulter Department of
Biomedical Engineering, Georgia
Tech
mpreininger@gmail.com

Jarod Prince
Biorepository Manager, Emory
Department of Pediatrics
jjprinc@emory.edu

Lalita Priyamvada
Graduate Student, Emory
Department of Pediatrics
lpriyam@emory.edu
Ximei Qian, PhD
Research Assistant Professor
xqian2@emory.edu

Todd Quartiere
The Emory Clinic
EM-ProLEAD Summer Intern
todd.quartiere@emoryhealthcare.org

Kendra Quicke
Graduate Student, Emory University
kquicke@emory.edu

Senthil Ramamurthy, MS
Image Processing Scientist,
Children's Healthcare of Atlanta
senthil.ramamurthy@gmail.com

Tiana Raphel
The Emory Clinic
EM-ProLEAD Summer Intern
tiana.raphel@emoryhealthcare.org

Elizabeth Record, DNP, CPNP
Aflac Cancer and Blood Disorders
Center, Children's Healthcare of
Atlanta, Cancer Survivor Program:
Clinical Program Manager
betsy.record@choa.org

Bonney Reed-Knight, PhD
GI Psychologist, Emory Department
of Pediatrics
bonney.reed-knight@emory.edu

Linda Riley, PhD, RN
Director, Nursing Research & EBP
Children's Healthcare of Atlanta
linda.riley@choa.org

Cyndie Roberson, MSN, RN, CEN
Vice President, Ambulatory Nursing
and Physician Practice
Operations,Children's Healthcare of
Atlanta
cyndie.roberson@choa.org

Rana Roberts, RN, MBA
Director Clinical Operations,
Physician Practice, Children's
Healthcare of Atlanta
rana.roberts@choa.org

Hope Robinson
mhrobin@emory.edu

Kelli Robinson
kyrobinson@msm.edu

Beverly B. Rogers, MD
Chief of Pathology, Children's
Healthcare of Atlanta, Adjunct
Professor of Pathology and
Pediatrics, Emory University School
of Medicine
beverly.rogers@choa.org

Kris Rogers
Director, Research and Academic
Administration, Children's
Healthcare of Atlanta
Kris.rogers@choa.org

Monica L. Rojas-Pena
PhD Candidate, Georgia Tech
Schlumberger (STEM) Faculty for
the Future Fellow
monica.rojas@gatech.edu

Myra Rolfes, MN, BSN, RNC-NIC
Staff Nurse, Clinical Leader,
Children's Healthcare of Atlanta -
Egleston
myra.rolfes@choa.org

Sheri Russell
Program and Operations Manager,
Georgia Tech & Children's
Healthcare of Atlanta Partnership
sheri.russell@gtri.gatech.edu

Guliana Salazar-Naratto
Georgia Tech
giuliana.sn@gatech.edu

Celine A. Saulnier, PhD
Clinical Director for Research,
Marcus Autism Center, Associate
Professor, Emory University School
of Medicine
celine.saulnier@emory.edu

Leane Shilling
Children's Healthcare of Atlanta
leann.schilling@choa.org

Brian A. Schlosser, BS, RDCS,
RDMS, FASE
Senior Pediatric Sonographer,
Children's Healthcare of Atlanta
brian.schlosser@choa.org

Elisha Segrist
esegrist@drury.edu

Sachin Shah
sshah57@emory.edu

Todd Sharp, MSci, MBA
Head, Research IT, Manager,
Business Itelligence, Children's
Healthcare of Atlanta
todd-sharp@choa.org

William Sharp, PhD
Director
Feeding Disorders Program
Assistant Professor
Emory University
william.sharp@choa.org

Ming Shen, BS
Lead, research specialist
Emory University/SOM/Department
of Pediatrics
mshen@emory.edu

Robin Sifre
Predoctoral Research Fellow,
Developmental Social Neuroscience
Lab, Emory University School of
Medicine, Children's Healthcare of
Atlanta, Marcus Autism Center
robin.sifre@choa.org

Erin Singer
Children's Healthcare of Atlanta
erin.singer@choa.org

Monalisa Singh, MD, PhD
Emory Department of Pediatrics
monalisa.singh@emory.edu

Arun L. Singh, MD
Pediatric Critical Care Medicine
Fellow, Emory University School of
Medicine
arun.singh@choa.org

Karnail Singh, PhD
Instructor, Division of Pediatrics
Infectious Diseases, Emory
Department of Pediatrics
ksingh6@emory.edu

Tim Slesnick, MD
Director, Cardiac MRI, Assistant
Professor, Children's Healthcare of
Atlanta, Emory University School of
Medicine, Sibley Heart Center
slesnickt@sibleyheart.com

Jackie Smith, MBA, CCRP
Research Manager, Children's
Healthcare of Atlanta
jaclyn.smith@choa.org

Leslie Smitley, RN, MSN
Lead Research Nurse
Children's Healthcare of Atlanta
leslie.smitley@choa.org

Emily Smotherman
Children's Healthcare of Atlanta
emily.smotherman@choa.org

Jie Song, PhD
Postdoc Fellow,
Georgia Institute of Technology and
Emory University
jschem10@gmail.com

Gail D. Spatt, CRA
Program Manager, Office of the
Executive Vice President for
Research, Georgia Tech
spatt@gatech.edu

Paul Spearman, MD
Nahmias-Schinazi Professor and
Vice Chair for Research, Emory
Department of Pediatrics, Chief
Research Officer, Children's
Healthcare of Atlanta, Chief,
Pediatric ID, Emory University
paul.spearman@emory.edu

Diane Spencer
Children's Healthcare of Atlanta -
Egleston
diane.spencer@choa.org

Victoria Stefanelli
Georgia Tech, Emory University
vstefanelli@gatech.edu

David Stephens, MD
Vice President for Research,
Woodruff Health Sciences Center
Chair, Department of Medicine
Chief of Medicine, Emory
Healthcare

Hazel Stevens
Research Scientist, Georgia Tech
hazel.stevens@me.gatech.edu

Kay Stewart-Huey
Vice President, Cardiac Services,
Children's Healthcare of Atlanta
Kay.stewart-huey@choa.org

Barbara J. Stoll, MD
Chair, Department of Pediatrics,
Emory University School of
Medicine, President, The Emory
Children's Center, Director, The
Pediatric Center
bstoll@emory.edu

Cheryl Stone, RN, CCRP
Senior Research Nurse, Critical
Care Medicine, Egleston
cheryll.stone@choa.org

Joshua Strauss
Joshua.d.straus@emory.edu

Jill Strickland
SVP, Physician Practices
Administration, Children's
Healthcare of Atlanta
jill.strickland@choa.org

Daneka Stryker
dstryke@emory.edu

Parmi Suchdev, MD, MPH
Associate Professor of Pediatrics
and Global Health, Medical
Epidemiologist, CDC
psuchde@emory.edu

Cynthia Sundell, PhD
Director, Life Science Industry
Collaboration, Georgia Tech
Cynthia.sundell@gmail.com

Sushruta Surappa
Georgia Tech
sushsurappa@gmail.com

Mehul S. Suthar, PhD
Assistant Professor, Emory
Department of Pediatrics, Emory
Vaccine Center
msuthar@emory.edu

Animesh (Aashoo) Tandon, MD, MS
Advanced Imaging Fellow, Sibley
Heart Center Cardiology, Children's
Healthcare of Atlanta, Emory
University
tandon.animesh@gmail.com

Rachel Tanos, PhD
Emory Department of Pediatrics
rtanos@emory.edu

Keiko Tarquinio, MD, FAAP
Assistant Professor of Pediatrics
Emory University
Attending Physician for Pediatric
Critical Care Medicine
Children's Healthcare of Atlanta
keiko.tarquinio@emory.edu

Rian Thornton, BS, RN, CCRC
Clinical Research Nurse,
Orthopaedics and Rehabilitation
Medicine, Children's Healthcare of
Atlanta
rian.thornton@choa.org

Erika Tyburski
Children's Healthcare of Atlanta,
Georgia Tech, Emory Department of
Pediatrics
etyburski3@gmail.com

Yasmin Tyler-Hill, MD
Chair, Department of Pediatrics,
Morehouse School of Medicine,
Medical Director, Children's
Healthcare of Atlanta
ytyler-hill@msm.edu

Karan Uppal, MS, PhD candidate
Graduate student, Georgia Tech
and
Senior Application Developer,
Emory University
kuppal3@mail.gatech.edu

Kristen Vangile, MPH, CCRP
Applications Analyst, Children's
Healthcare of Atlanta
kristen.vangile@choa.org

Arthi Vasantharoopan, MS
Emory Department of Pediatrics
arthivroopan@emory.edu

Janani Venugopalan
jvenugopalan3@gatech.edu

Jennifer Villaseñor
Lead Program Coordinator,
Children's Healthcare of Atlanta
jkenny2@emory.edu

Miriam Vos, MD, MPH
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
mvos@emory.edu

Shilpa Vyas-Read, MD
Assistant Professor
Emory University
svyasre@emory.edu

Mary B. Wagner, PhD
Assistant Professor of Pediatric,
Emory University
mary.wagner@emory.edu

Yan Wang, DDS, PhD
Emory University
ywang61@emory.edu

Janine Ward
Children's Healthcare of Atlanta,
Emory Department of Pediatrics
janine.ward@emory.edu

Amanda Watt
Clinical Research Coordinator, Aflac
Cancer and Blood Disorder Center,
Children's Healthcare of Atlanta
Amanda.Watt@choa.org

Jonathan Weber, BS
Woodruff School of Mechanical
Engineering Georgia Tech
jweber35@gatech.edu

Allison Wellons, RN, BS, CCRC
Clinical Research Manager,
Children's Healthcare of Atlanta
allison.wellons@choa.org

Christina Wessels
Business Operations Coordinator,
Marcus Autism Center, Children's
Healthcare of Atlanta
christina.wessels@choa.org

Leanne West, MS
Chief Engineer, Pediatric
Technologies, Principal Research
Scientist, Georgia Tech
leanne.west@gtri.gatech.edu

Cynthia Wetmore, MD, PhD
Director, Center for Clinical and
Translational Research, Emory
Department of Pediatrics, Director,
Innovative Therapy Program, Aflac
Cancer and Blood Disorders Center,
Children's Healthcare of Atlanta

Nick Willett, PhD
Assistant Professor
Emory University
nick.willett@emory.edu

Martha Willis, MS
Program Manager, APDC,
Children's Healthcare of Atlanta
martha.willis@gatech.edu

Pamela Winterberg, MD
Assistant Professor of Pediatrics,
Emory University School of
Medicine, Children's Healthcare of
Atlanta
pdwinte@emory.edu

Nathan Woods
Senior Applications Analyst, Cardiac
Services, Children's Healthcare of
Atlanta
nathan.woods@choa.org

William Woods, MD
Professor & Director, Aflac Cancer
and Blood Disorders Center,
Children's Healthcare of Atlanta
william.woods@choa.org

Jens Wrammert, PhD
Assistant Professor, Department of
Pediatric Infectious Diseases,
Department of Hematology and
Oncology, Emory Vaccine Center,
Emory University
jwramme@emory.edu

Alaina Wrencher
Children's Healthcare of Atlanta –
Marcus Autism Center
alaina.wrencher@choa.org

Royalle Lydia Wright
Children's Healthcare of Atlanta -
Marcus Autism Center
royalle.wright@choa.org

Bonnie Wright, BS, RDCS, FASE
Children's Healthcare of Atlanta
Manager, Non-Invasive Cardiology
bonnie.wright@choa.org

Qingling Wu, MS
Georgia Tech, Emory Department of
Pediatrics
qwu26@emory.edu

Aline Yonezawa
Graduate Student, Emory University
ayonezawa3@emory.edu

Shan Ping Yu, MD, PhD
Department of Anesthesiology,
Emory University School of
Medicine
spyu@emory.edu

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