

2013 Pediatric Research Retreat

Common Complex Childhood Diseases

Emory+Children's Pediatric Research Center

An Atlanta-based research alliance



Friday, June 28, 2013

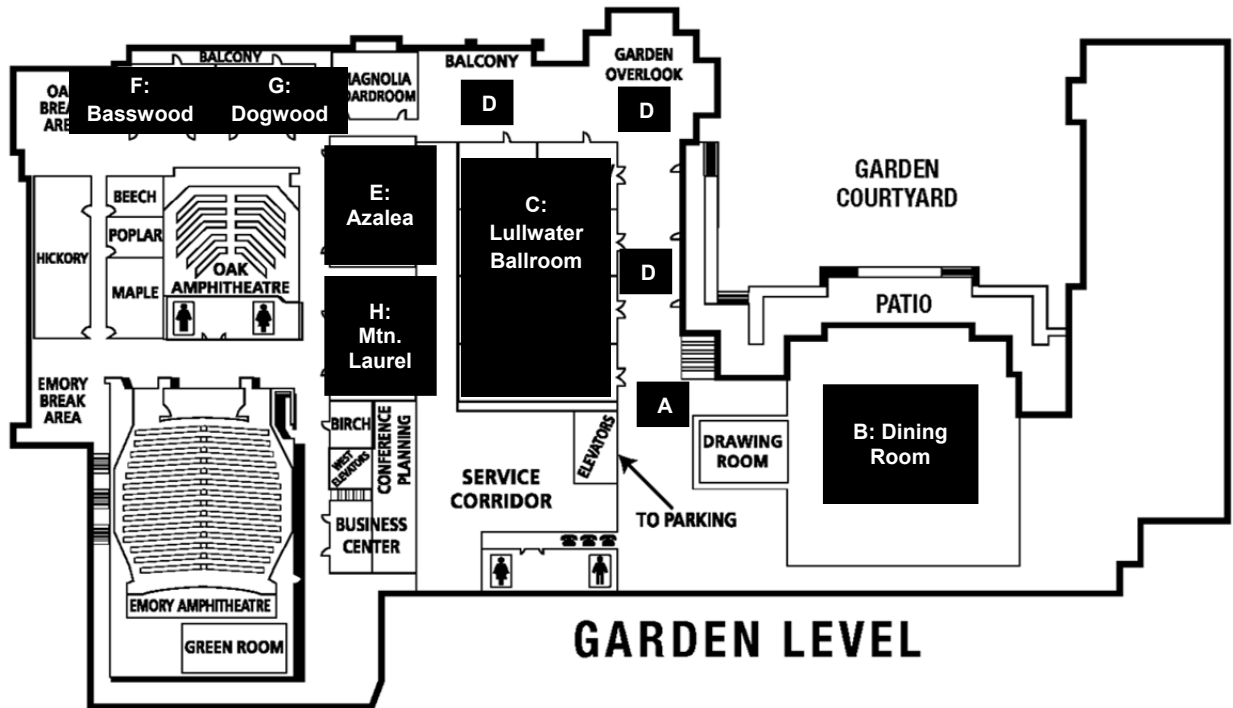
8:00 AM - 5:00 PM

Emory Conference Center

Atlanta, GA



Emory Conference Center Floor Plan



- A Registration and Information Desk
- B Lunch
- C Plenary Sessions
- D Posters 1 – 46
- E Posters 47 – 76
- F Roundtables

Session 1: Methods for Collecting, Processing and Interrogating Pediatric Clinical Samples
 Session 2: Sickle Cell Disease: A Multi-System Disorder

- G Roundtables
 - Session 1: Pediatric Autoimmune Diseases & Innovative Therapies
 - Session 2: Multidisciplinary Orthopedic Research
- H Roundtables
 - Session 1: Core Resources for Basic Science Researchers
 - Session 2: Core Resources for Clinical Researchers

Parking: For complimentary parking, please make sure you pick up a parking voucher at the registration desk. You will need a voucher when exiting the North and South parking decks.

Nursing Room: A nursing room is available behind the concierge desk on the first floor.

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

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How did we do? Provide feedback on today’s event at www.pedsresearch.org – link on home page.

Agenda

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| 7:15 – 8:30 | Registration and Continental Breakfast |
| Morning Session: Molecular and Genomic Aspects of Common Complex Childhood Diseases (Lullwater Ballroom) | |
| 8:00 - 8:10 | Welcome from Retreat Chair Subra Kugathasan, MD |
| 8:10 - 9:00 | Keynote Address: “Harnessing the Power of the Human Microbiome in Health and Disease” |
| | Jonathan Braun, MD, PhD Professor, Pathology and Lab Medicine, UCLA Professor, Department of Molecular and Medical Pharmacology, UCLA Director, Tumor Immunology Program, UCLA Jonsson Comprehensive Cancer Center Chair, Department of Pathology and Laboratory Medicine, UCLA |
| 9:00 - 9:30 | “The Promise of Targeted Pharmacotherapy for Down Syndrome and Fragile X Syndrome” |
| | Jeannie Visotsak, MD, FAAP Associate Professor, Developmental-Behavioral Pediatrics Department of Human Genetics & Pediatrics Emory University |
| 9:30 – 9:40 | Break |
| 9:40 - 10:10 | Short Talks from Selected Abstracts |
| | Moderated by Greg Gibson, PhD and Rabindra Tirouvanziam, PhD |
| | “A 3D Model Recapitulating the Pathological Phenotype of Neutrophils in Cystic Fibrosis Airways” by Marcela Preininger, BSc ; Julie Laval, MSc; Wendy Si Hassen, MSc; Sarah Ingersoll, PhD; and Rabindra Tirouvanziam, PhD |
| | “Variability and Differentially Gene Expression of Craniosynostosis Samples Based on RNA-seq” by Monica Rojas-Peña and Greg Gibson, PhD |
| | “Nanotherapy of Inflammatory Bone Disorders in Sickle Cell Disease” by M. Neale Weitzmann, PhD; Shin-Woo Ha, PhD; Tatyana Vikulina; Susann Roser-Page, MS, DDS; David Archer, PhD ; and George R. Beck Jr., PhD |

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| 10:10 - 10:30 | Rapid-Fire Poster Presentations | |
| | Moderated by Subra Kugathasan, MD | |
| | 106: "Diminished T-Tubule Density in Newborn Human Ventricular Cells is Associated with Heterogeneity of Calcium Transients" by Talib Saafir, PhD; Gitanjali Baroi, BS; Brian Crawford, PhD; Guoliang Ding, MD, PhD; Brain Kogon, MD; Kirk Kanter, MD; Paul M. Kirshbom, MD; and Mary B. Wagner, PhD | |
| | 113: "Effects of Fructose on Cardiovascular Risk in Adolescents with Nonalcoholic Fatty Liver Disease" by Miriam Vos, MD, MSPH ; Ran Jin, MS; Jean Welsh, PhD, MPH, RD; and Ngoc-Anh Le, PhD | |
| | 130: "Curing HIV by Engineered Nuclease Excision of the Integrated HIV Provirus" by Paul Spearman, MD ; Gang Bao, PhD; and TJ Cradick, PhD | |
| | 141: "Arginase-1 and Programmed Death Ligand-1, Potent Inducers of Immune Tolerance, are Upregulated on Airway Neutrophils in Cystic Fibrosis" by Sarah A. Ingersoll, PhD ; Julie Laval, MSc; Marcela Preininger, BSc; Milton Brown, PhD; and Rabindra Tirouvanziam, PhD | |
| 10:30 – 11:30 | Poster Session 1 (Hallways and Azalea Room) | |
| 11:30 – 1:00 Lunch & Roundtables | 11:30 - 12:15 | Roundtable Session 1 <ul style="list-style-type: none"> • Core Resources for Basic Science Researchers (Mountain Laurel) • Methods for Collecting, Processing and Interrogating Pediatric Clinical Samples (Basswood) • Pediatric Autoimmune Diseases & Innovative Therapies (Dogwood) |
| | 12:15 – 1:00 | Roundtable Session 2 <ul style="list-style-type: none"> • Core Resources for Clinical Researchers (Mountain Laurel) • Sickle Cell Disease: A Multi-System Disorder (Basswood) • Multidisciplinary Orthopedic Research (Dogwood) |
| Afternoon Session: Clinical and Translational Applications of Molecular and Genomic Aspects of Common Complex Childhood Diseases (Lullwater Ballroom) | | |
| 1:00 – 1:30 | "Dissecting Complex Traits with Genomic Discoveries: Lessons for Clinicians" | |
| | Sampath Prahalad, MD, MSc Marcus Professor of Pediatric Rheumatology & Chief, Division of Pediatric Rheumatology Associate Professor of Pediatrics and Human Genetics, Emory University School of Medicine Director, Infusion and Laboratory Services, Emory-Children's Center | |
| 1:30 - 2:00 | Short Talks from Selected Abstracts | |
| | Moderated by Warren Jones, PhD and Richard Olney, MD, MPH | |
| | "Longitudinal Profiles of Adaptive Behavior in Children with Autism Spectrum Disorders" by Celine A. Saulnier, PhD and Ami Klin, PhD | |
| | "Tetrahydrobiopterin as a Treatment for Autism Spectrum Disorders: A Double-Blind, Placebo-Controlled Trial" by Cheryl Klaiman, PhD ; Lauren Masaki, BA; Lynne Huffman, MD; Glen R. Elliott, PhD, MD | |
| | "Investigating Factors Associated with Late Detection of Critical Congenital Heart Disease in Newborns" by April Dawson, MPH ; Cynthia H. Cassell, PhD; Tiffany Riehle-Colarusso, MD, MPH; Scott D. Grosse, PhD; Jean Paul Tanner, MPH; Russell S. Kirby, PhD, MS, FACE; Sharon M. Watkins, PhD; Jane A. Correia, BS; and Richard S. Olney, MD, MPH | |

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| 2:00 - 2:20 | Rapid-Fire Poster Presentations | |
| | Moderated by Subra Kugathasan, MD | |
| | 101: "The Impact of Spatial Accessibility on Pediatric Asthma Health Outcomes" by Nicoleta Serban, PhD; Julie Swann, PhD; and Erin Garcia | |
| | 136: "Quantifying Social-Communicative Function in Autism Spectrum Disorder Via a Structured Social Attribution Task" by Rebecca Burger-Caplan, BA ; Warren Jones, PhD; and Ami Klin, PhD | |
| | 118: "Growing Up: Not An Easy Transition. Perspectives and Outcomes of Patients Transferred from the Liver Transplant Clinic" by Sona Chandra; Shannon Luetkemeyer ; Rene Romero, MD; and Nitika Gupta, MD | |
| | 125: "Quantitative Analysis of Phase-Contrast Magnetic Resonance in Pediatric Patients with Chiari Malformation" by Kyle Pate, BS ; Kelsie Riemenschneider, BS; Joshua Chern, MD, PhD; Nilesh Desai, MD; and John Oshinski, MD | |
| 2:20 - 2:30 | Break | |
| 2:30 - 3:15 | Poster Session 2 (Hallways and Azalea Room) | |
| 3:15 - 4:00 | Keynote Address: "Genomics and Personalized Medicine: Present and Future" | |
| | Aravinda Chakravarti, PhD Director, Center for Complex Disease Genomics McKusick - Nathans Institute of Genetic Medicine Johns Hopkins University School of Medicine | |
| 4:00 - 4:15 | Advancing the Pediatric Research Agenda: Emory+Children's Perspective | |
| | Barbara J. Stoll, MD George W. Brumley, Jr. Professor & Chair, Department of Pediatrics, Emory University President & CEO, Emory-Children's Center | Paul Spearman, MD Nahmias-Schinazi Research Professor & Vice Chair for Research, Department of Pediatrics, Emory University Chief Research Officer, Children's Healthcare of Atlanta Director, Children's Center for Immunology and Vaccines |
| 4:15 - 4:20 | Closing and Poster Awards from Retreat Chair Subra Kugathasan, MD | |
| 4:20 - 5:00 | Social (Garden Overlook) | |

Children's Healthcare of Atlanta is accredited by the Medical Association of Georgia to provide continuing education for physicians. Children's designates this live activity for a maximum of 5.5 AMA PRA Category 1 credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Chair and Speaker Biographies



Subra Kugathasan, MD, received his medical degree in Srilanka. He completed his pediatric gastroenterology training at Case Western Reserve University. He joined Emory University in 2008 as a Professor of Pediatrics and Human Genetics and was appointed as Marcus Professor of Pediatric Gastroenterology/Inflammatory Bowel Disease (IBD). He currently also serves as the Medical Director of the IBD program where his clinical focus is on the diagnosis and treatment of IBD. Dr. Kugathasan is a nationally recognized expert in pediatric IBD and provides family-centered care and consultation for children and adolescents with IBD. Dr. Kugathasan also leads nationwide, multi-center research efforts supported by the Crohn's and Colitis Foundation of America (CCFA) and National Institutes of Health (NIH) and funded by CCFA, NIH and FDA. Dr. Kugathasan's principal research focus is on etiopathogenesis of IBD in children, in particular in genetic epidemiology and gene discoveries in childhood IBD. He has published 112 peer-reviewed articles in national scientific journals over the last 17 years.



Jonathan Braun, MD, PhD, is a physician-researcher devoted to the roles of the immune system in resistance and susceptibility to inflammatory bowel disease and cancer. A native of Cleveland, Ohio, Dr. Braun was raised in Los Angeles, where he focused on violin performance. He was an undergraduate at Stanford University (BS, Chemistry and Biology), and did his MD and PhD studies at Harvard Medical School with Emil Unanue. After residency in Pathology at Brigham and Women's Hospital, and a postdoctoral fellowship with David Baltimore at the Whitehead Institute, he joined the faculty at the UCLA School of Medicine in 1985. Through an integrated approach of molecular microbial ecology and metaproteomic and metabolite analysis, and human genetics, his research centers on the biology of mucosal interaction of host immunity with the local microbial community, and its impact on chronic mucosal inflammatory disease and cancer. He has published more than 130 primary research studies, issued 13 patents, and co-founded three biopharma companies. His recent national service includes Chair of the National Scientific Advisory Committee of the Crohn's and Colitis Foundation, and President of the Federation of Clinical Immunology Societies. He still plays violin when possible.



Aravinda Chakravarti, PhD, obtained his PhD at the University of Texas at Houston for developing a theoretical basis for disease prediction in families using genetic linkage. After a fellowship at University of Washington in Seattle he accepted a teaching position at the University of Pittsburgh. The emerging power of recombinant DNA methods at this time prompted his retraining in molecular genetics. He has served on the faculty at University of Pittsburgh and Case Western Reserve University and is currently at Johns Hopkins University where he is Director, Center for Complex Disease Genomics and Professor of Medicine, Pediatrics, Molecular Biology & Genetics, and, Biostatistics at the Johns Hopkins University School of Medicine and the Bloomberg School of Public Health. His research is on experimental and computational methods for discovering and interpreting patterns of human genetic variation and its use in dissecting the molecular basis of human disease. An early enthusiast of the human genome project and its expected profound impact on human medicine, he played an integral role in the Human Genome Project as participant, organizer, Chair of the NIH Third Plan of the U.S. Human Genome Project (1998), the HapMap and 1000Genomes projects, and is one of the founding editors of Genome Research and the Annual Reviews of Genomics & Human Genetics.



Jeannie Visootsak, MD, FAAP, is a developmental and behavioral pediatrician and the Medical Director of the Down Syndrome and Fragile X Syndrome Clinics at Emory University. She is also the Director of the Neurodevelopmental Disorders Clinical Trials Unit at Emory University, Department of Human Genetics. She received a Bachelor's degree in Chemistry from the University of Southern California and MD from UCLA. She completed a pediatrics residency and developmental behavioral pediatrics fellowship at King-Drew University and Cedars-Sinai Medical Center, UCLA, and joined the faculty at Emory University in 2004. Her clinical research projects involve studies of neurodevelopmental outcomes in children with Down syndrome and congenital heart defects, and clinical trials of new promising medications in Down syndrome, Fragile X syndrome, and autism.



Sampath Prahalad, MD, MSc, is a compassionate physician-scientist who has been caring for children with juvenile idiopathic arthritis (JIA) for over 15 years. After receiving his medical training in India and The United Kingdom, he completed his pediatric residency at Hershey Medical Center and rheumatology fellowship at Cincinnati Children's Hospital. Dr. Prahalad joined Emory University in 2009 to pursue his career vision to determine who gets idiopathic arthritis and why. He is presently investigating distant relatives with JIA from multigenerational families for shared genomic regions harboring causal variants. Dr. Prahalad has a proven track record in translational research as evidenced by over 50 publications and enrollment of 3000 subjects for genetic studies, including 1000 cases with JIA. He is a referee for many peer-reviewed journals, and serves on study sections for the NIH and Arthritis Foundation. He regularly volunteers as JIA camp-physician and enjoys mentoring graduate and medical students, and residents.

Emory+Children's Pediatric Research Center Website

www.pedsresearch.org

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

Descriptions and leadership of pediatric research centers (summaries below)

Core resources available to basic and clinical scientists

Center membership

Research faculty descriptions

News and calendar for upcoming seminars and events

Pilot grant opportunities and other announcements

Aflac Cancer and Blood Disorders Center

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

Center for Cardiovascular Biology

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

Center for Clinical Outcomes Research and Public Health

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

Center for Cystic Fibrosis Research

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

Center for Developmental Lung Biology

Breathing disorders, such as asthma, are the No.1 reason that children need emergency care. Researchers at this center are working to strengthen and expand our understanding and treatment of these disorders, along with lung development as it relates to very low birth weight newborns and pediatric pulmonary diseases.

Center for Immunology and Vaccines

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

Center for Neurosciences

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

Center for Pediatric Innovation

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

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

Center for Pediatric Nanomedicine

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

Center for Transplantation and Immune-mediated Disorders

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

Marcus Autism Center

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

Children's/GA Tech Partnership

This partnership is setting up synergistic relationships between clinician scientists and investigators with engineers and computer scientists in research and development in:

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

Additional research centers under development:

Center for Clinical and Translational Research

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

Center for Drug Discovery

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

Egleston Pediatric Research Center

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

The Pediatric Research Center (PRC) at Egleston was created to facilitate Children's Healthcare of Atlanta's vision for clinical excellence. Inpatient and outpatient units offer core support facilities (e.g. cardiology) and resources including nursing, pharmacy, laboratory, and bio nutrition. In 2012 & 2013 the PRC studied children with asthma, cardiac disease, hypertension, Crohn's Disease, Type 1 and 2 Diabetes Mellitus, kidney and hepatic disease, Sickle Cell, cystic fibrosis and MRSA. Research studies conducted follow exacting standards for delivering the interventions and collecting the requisite data. To learn more about how the PRC can support your research, please look for our poster at the 2013 Pediatric Research Retreat, call the PRC at 404-785-0400, or email Nancy Ferzola, BSN, MSHS, Nurse Manager, at nancy.ferzola@choa.org.

Short Talk Abstracts

A 3D Model Recapitulating the Pathological Phenotype of Neutrophils in Cystic Fibrosis Airways

Marcela Preininger, BSc; Julie Laval, MSc; Wendy Si Hassen, MSc; Sarah Ingersoll, PhD; and Rabindra Tirouvanziam, PhD

Background: Cystic Fibrosis (CF) lung disease is characterized by an early, massive and persistent recruitment of neutrophils from blood into the lamina propria and lumen of small airways. Activity of neutrophil elastase, released from primary granules into CF airways, is the best predictor of lung function, body mass index, and survival in CF patients. We showed previously that elastase is not released by dead neutrophils, as generally thought, but by live ones, which opens exciting new avenues for therapy. However, the process by which CF airway neutrophils exocytose elastase actively, rather than releasing it into the phagosome, is complex and so far cannot be reproduced in vitro, thus severely hampering research and the development of neutrophil-targeted therapies. **Results:** We used a "waffer" scaffold (Alvetex, Reinnervate, UK) to grow the human bronchiolar H441 cell line at air-liquid interface on a collagen layer. Transmission electron microscopy revealed a polarized monolayer of columnar epithelium with apical microvilli typical of Clara cells and confocal imaging confirmed the presence of the tight junction protein ZO-1 in ring-like pattern around cells. Remarkably, when airway fluid purified from CF sputum was added onto the apical surface, blood neutrophils placed on the basal side migrated through the epithelium and released their primary granules, as measured by flow cytometry analysis. Blood neutrophils placed in CF airway fluid did not exocytose primary granules, suggesting a key inducing role for transmigration. **Conclusions:** Together, these results establish our 3D model as a robust, operative platform for phenocopying CF airway neutrophil dysfunction in a controlled laboratory environment. This new model not only is amenable to the testing of drug candidates, but also provides a superior alternative to conventional Transwell cultures for investigating the complex interactions between migrating leukocytes and bronchiolar epithelial cells. It therefore constitutes a promising tool for developing a greater understanding of CF airway inflammation, and potential new therapies. **Acknowledgments:** Emory Peds Flow & Electron Microscopy Cores, Integrated Cell Imaging Core.

Variability and Differentially Gene Expression of Craniosynostosis Samples Based on RNA-seq

Monica Rojas-Peña and Greg Gibson, PhD

Craniosynostosis is defined as the premature fusion of one or more skull sutures in infants, which occurs in approximately 1 in 3000 infants. Eighty percent of the cases are nonsyndromic craniosynostosis; two common reasons proposed for premature closure are outside compression on the skull or rare genetic abnormalities, presumably inherited as homozygous recessive combinations. Our goal was to perform variance component analysis of total gene expression profiles using RNA-seq, in order to cluster individuals and evaluate association of profiles with types of craniosynostosis. We present evidence that there is no differentiation between region of the skull, but that analysis of gene expression patterns can nevertheless provide a basis for classification of

craniosynostosis. The RNA-seq data from 31 human osteoblasts grown in culture, from craniosynostosis samples collected from 2009 to 2011 representing 23 craniosynostosis patients and 8 normal bone were examined. Cluster analyses shows 4 distinct groups; 1 predominantly normal and 3 craniosynostosis. Groups of differentially expressed genes were identified among the 4 clusters, and annotation of gene function of differentially expressed transcripts strongly implicates physiological differences. Based on our results, we propose craniosynostosis cases can be classified by differences in their gene expression patterns and that these may provide targets for future clinical intervention.

Nanotherapy of Inflammatory Bone Disorders in Sickle Cell Disease

M. Neale Weitzmann, PhD; Shin-Woo Ha, PhD; Tatyana Vikulina, Susann Roser-Page, MS; DDS; David Archer, PhD; George R. Beck Jr., PhD

Sickle Cell Disease (SCD) is a devastating genetic hematological disorder leading to significant morbidity and mortality. A major complication is skeletal malformation in children leading to severe systemic skeletal deterioration (osteoporosis) in the vast majority of adult SCD patients, leading to fracture risk. Bone fractures are associated with significant morbidity and mortality (up to 30% of hip fracture patients die within a year of fracture). Unfortunately, as SCD manifests early in life standard skeletal therapies that are used with good effect in adults can have a very detrimental effect on the forming skeleton of children. Failure to achieve a peak bone mineral density (BMD) in young adulthood further dooms patients to premature development of osteoporosis and early fracture. Our aim was to apply nanotechnology to remedy the inflammatory environment and skeletal aberrations associated with SCD. Towards this end we have previously formulated silica based nanoparticle which suppress NF- κ B signaling, a pro-inflammatory pathway, and stimulate bone formation in healthy mice. Methods: We synthesized 50nm spherical silica-based nanoparticles coupled with polyethylene glycol (PEG) which increases in vivo half-life (NP1-PEG). We treated the Berkeley Sickle mice, a transgenic animal model of SCD, and controls with NP1-PEG (30mg/kg/wk) starting at 4 weeks of age. BMD is being followed prospectively every two weeks. Results: We determined that our murine model of SCD exhibits significantly diminished BMD at the lumbar spine (-21.3%) and Femur (-27.3%) and decreased bone volume, cortical volume and cortical thickness as measured by Micro-computed tomography (μ CT). Gene expression and biochemical markers of bone metabolism revealed an increase in osteoclastogenesis and decrease in osteoblastogenesis. NP1-PEG treatment resulted in increased BMD after 4 weeks relative to control, and BMD remains elevated at 12 weeks. These studies are ongoing. Conclusions: The Berkeley Sickle mouse representative of the bone loss associated with SCD in children and is a consequence of reduced bone formation coupled with elevated bone resorption. Our 50nm engineered bioactive nanoparticles increased BMD in a mouse model of SCD and demonstrates a proof-of-principle that nanotechnology can be used to ameliorate the physical consequences associated with complex childhood diseases.

Longitudinal Profiles of Adaptive Behavior in Children with Autism Spectrum Disorders

Celine A. Saulnier, PhD and Ami Klin, PhD

Background: Research shows a widening gap between IQ & adaptive behavior across age in ASD, with older individuals having more impaired functional skills relative to cognition. Yet, most studies have been cross-sectional and have not included a broad IQ range. Less is known about these profiles within the same sample over time, and the role that level of IQ plays. Objectives: The relationship between IQ and adaptive functioning is investigated in a longitudinal sample of children with ASD at ages 2, 4, and 8. Acquisition of cognitive and adaptive skills over time and the gap between the two are examined. Methods: Participants included 46 children with ASD. Mean age Time 1= 28 months; Time 2=53 months; Time 3=104 months (24% female & 76% male). Results: The Mullen Scales of Early Learning and Differential Ability Scales, Second Edition, were used to assess cognitive ability and the Vineland Adaptive Behavior Scales to assess adaptive functioning. Mean IQ scores (SDs) for the 3 age groups were: Age 2: 68.10 (17.19); Age 4: 86.49 (22.56); Age 8: 88.68 (25.17). A Repeated Measures ANOVA revealed that cognitive skills significantly improved from ages 2 to 4 and 2 to 8, but remained stable between ages 4 and 8 ($F=37.80$, $P<.001$). Significant improvements were noted in Vineland Composite scores between ages 4 and 8 ($F=3.84$, $p=.064$), though scores still fell below age and cognitive expectations. Significant discrepancies were evidenced between mean IQ and Vineland scores at Age 4 ($t=-7.56$, $p<.001$) and Age 8 ($t=-5.96$, $p<.001$), but not at Age 2 ($t=.25$, $p=.81$). The gap between IQ and adaptive skills significantly widened from ages 2 to 4 but remained stable from 4 to 8 ($F=18.96$, $p<.001$). Adaptive skills were higher than cognitive skills in the Low IQ group, and lower than cognitive skills in the High IQ group. Conclusions: Results indicate that despite acquiring cognitive and adaptive skills overtime, children with ASD evidence significant deficits in adaptive functioning as early as age 4 that continue through age 8. Profiles of adaptive functioning were found to differ between individuals with low vs.

high IQs, with overall adaptive functioning being stronger than cognitive ability in the less cognitively able group, and significantly lower than IQ in the more cognitively able group. Given the strong role of adaptive functioning in adult outcome, predictors of adaptive functioning are examined and implications for intervention are discussed.

Tetrahydrobiopterin as a Treatment for Autism Spectrum Disorders: A Double-Blind, Placebo-Controlled Trial

Cheryl Klaiman, PhD; Lauren Masaki, BA; Lynne Huffman, MD; and Glen R. Elliott, PhD, MD

Introduction: Most studies of biological interventions for autism (ASD) focus on symptom reduction, emphasizing behaviors secondary to ASD as opposed to core features. Sapropterin (BH4) is of interest as a possible treatment of ASD. In a pilot study in 6 children ages 3-5 years with ASD 3 mg/kg/day was used for 3 months. Improved social functioning was found in all subjects. In a double-blind placebo-controlled crossover trial with 12 boys, ages 4-7, nonsignificant changes were found at 3 and 6 months in total scores on the CARS, but post-hoc analyses revealed significant improvements in social interactions at 6 months. These and other studies suggest that sapropterin might ameliorate core symptoms of ASD at least in younger subjects. However, the studies had notable limitations. We therefore conducted a double-blind study of sapropterin to evaluate its' efficacy on the core symptoms of ASD in young children. **Methods:** A double-blind, placebo-controlled (RCT), 16-week trial followed by an open-label extension (OLE) was conducted. In the RCT, participants were 46 children (3-6 years) with ASD. The primary outcome measure was the CGI-I; secondary measures assessed social interactions, language, odd behaviors, and side effects. Participants were randomized to 20 mg/kg/day of sapropterin (the approved formulation) or placebo. Behavioral and safety measures were collected at baseline, 8, and 16 weeks. In the OLE, participants were 30 children who successfully completed the double-blind placebo arm of the study. Primary and secondary outcome measures were the same. **Results:** At 16-weeks, the placebo (n=23) and sapropterin (n=23) groups showed similar proportions with a CGI-I of 1 (Very Much Improved) (4.5% vs. 0.0%) and 2 (Much Improved) (9.1% vs. 25.0%). Compared to placebo, sapropterin subjects had significant improvement in social awareness, autism mannerisms, hyperactivity and inappropriate speech. BH4 was well-tolerated with few side effects. OLE data showed continued safety and tolerance of the medication. **Conclusions:** At week 16, the primary outcome measure of global clinical improvement was not different for active treatment vs. placebo; however, analyses of secondary measures yielded statistically significant differences suggesting that BH4 may enhance development in social interaction in young individuals with an autism spectrum disorder and that it is generally well tolerated. The OLE indicated that the drug continued to be well tolerated.

Investigating Factors Associated with Late Detection of Critical Congenital Heart Disease in Newborns

April Dawson, MPH; Cynthia H. Cassell, PhD; Tiffany Riehle-Colarusso, MD, MPH; Scott D. Grosse, PhD; Jean Paul Tanner, MPH; Russell S. Kirby, PhD, MS, FACE; Sharon M. Watkins, PhD; Jane A. Correia, BS; Richard S. Olney, MD, MPH

Background and Objectives: Critical congenital heart disease was recently added to the U.S. Recommended Uniform Screening panel for newborns. This study aimed to assess whether maternal/household and infant characteristics were associated with late detection of critical congenital heart disease. **Methods:** This was a state-wide, population-based, retrospective, observational study of infants with critical congenital heart disease born between 1998 and 2007, identified by the Florida Birth Defects Registry. We examined 12 types of critical congenital heart disease that are primary and secondary targets of newborn critical congenital heart disease screening by pulse oximetry. We used Poisson regression models to analyze associations between selected characteristics (e.g. maternal age, critical congenital heart disease type, and birth hospital nursery level) and late detection of critical congenital heart disease, defined as diagnosis after birth hospitalization. **Results:** Of 3,603 infants with critical congenital heart disease and linked hospitalizations, critical congenital heart disease was not detected during the birth hospitalization for 22.9% (n=825) of infants. The likelihood of late detection varied by type of critical congenital heart disease. Infants born in a birth hospital with a Level I nursery (adjusted prevalence ratio 1.9, 95% confidence interval 1.6-2.2) or Level II nursery (adjusted prevalence ratio 1.5; 95% confidence interval 1.3-1.7) were significantly more likely to have late detected critical congenital heart disease compared to infants born in a birth hospital with a Level III (highest) nursery. No other characteristics were significantly associated with late detection of critical congenital heart disease. **Conclusions:** Controlling for selected characteristics, nursery facility level appears to have an independent association with late detection of critical congenital heart disease. Our results suggest that universal newborn screening for critical congenital heart disease could be beneficial in Levels I and II nurseries and may reduce differences in the frequency of late diagnosis between birth hospital facilities.

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Poster Abstracts

101: The Impact of Spatial Accessibility on Pediatric Asthma Health Outcomes

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There are 4.9 million children (8.4% of children 0-17) in the United States with asthma, making it the most common childhood respiratory disease in the nation. Having asthma impacts their daily lives and activities, and can also lead to severe outcomes of Emergency Department visits or hospitalizations. Such visits are often preventable, but access to non-emergency asthma care is limited. This study investigates the factors that contribute to the occurrence of severe outcomes, focusing on California and Florida because of the structural differences of their health care policies. We answer the questions: Is there a statistically significant association between outcomes and spatial accessibility for pediatric asthma? How does this association vary across different population groups? The outcomes data is extracted from the HCUP SID and SEDD databases for Florida and California. Generalized mixed effects regression models are used to evaluate the impact and significance of multiple factors on these severe outcomes. The factors include spatial access to asthma specialist care, demographic information, socio-economic status, and environmental factors. The measure for spatial access is computed using a centralized assignment optimization model to match children with asthma (grouped by census tract) to asthma specialists, assuming a physician cap on percent of patients that have Medicaid, but equal access otherwise. The optimization model results show the disparities in spatial access to asthma specialist care, with Florida children living no more than 30 miles from their assigned specialists and California children being up to 50 miles away. From the regression models we find that spatial access alone is not a significant predictor for severe outcomes in Florida, where the maximum distance is relatively low, but that it is in California, where the range of distances is much larger. However, the interactions between distance and socioeconomic factors of income and education are significant in both states. This analysis can be used to measure the inequality of access to asthma specialist care locally or at the state or national level. By identifying the significant factors associated to severe pediatric asthma outcomes, we can work to improve these outcomes by developing interventions that will target the geographic areas and specific populations with the greatest need and potential for improvement.

102: Intra-tracheal inoculation of *Pseudomonas aeruginosa* in CFTR ^{-/-} mice induces altered liver gene expression

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Background: Infant mortality was the norm when cystic fibrosis (CF) was initially recognized in 1938, however, current approaches in therapy have led to prolonged life expectancy and better understanding of the extra-pulmonary manifestations of the disease with CF liver disease (CFLD) emerging as the number two cause of mortality and up to 65% of all patients showing some sign of hepatic injury during their lives. Despite improved recognition of CFLD, we still understand little about why fibrosis, and ultimate cirrhosis, occurs in only a select number of patients with a predilection to occur during childhood. Mouse models for CF are available, but have yet to adequately model the clinical patient. Some of the changes seen in CF livers mimic those seen in response to inflammation, yet mechanistic connections between CF pathophysiology in the lung, and those in the liver, remain elusive. We hypothesize that intra-tracheal infection in CFTR^{-/-} mice leads to altered inflammatory signaling in the liver. **Methods:** Gut spared 2 month old CFTR^{-/-} mice [Cftr^{tm1Unc} Tg(FABPCFTR)-1Jaw/J] and wild type (WT) littermates were infected with *Pseudomonas aeruginosa* via an intra-tracheal inoculation at a dose of 75 μ L of 4.9x10⁶cfu/ml, along with observational controls. Livers were collected at 18 hours post infection. RNA was isolated and qRT-PCR performed from tissue to determine hepatic RNA levels of inflammation-sensitive target genes. **Results:** Preliminary data shows a hepatic phenotype after intra-tracheal inoculation of *Pseudomonas aeruginosa*. The expression of sinusoidal bile acid exporter OST- β is up regulated by 48% after intra-tracheal inoculation along with a 50% decrease in expression of the canalicular bile acid exporter BSEP. These changes are similar to those seen in direct hepatic inflammatory models. At baseline, a 26% decrease in expression of apical bile acid transporter ASBT, as well as a 320% increase in OST- β expression, supports an increased inflammatory state as well as increased bile acid concentration in CF mice compared to their WT littermates. **Conclusions:** To our knowledge, this is the first study showing a hepatic phenotype expressed after intra-tracheal infection with an infectious agent and is a model that more closely resembles human clinical patients supporting a role for inflammation in CFLD. Changes in bile salt transporter expression at baseline also suggest a contributory role for bile acid retention in the pathophysiology of CF liver.

103: Likelihood of Looking: Conditional Probabilities in Dynamic Visual Scanning in Children with ASD

Alyna Khan, BA, Ami Klin, PhD, and Warren Jones, PhD

Background: When viewing scenes of naturalistic social interaction, previous studies have demonstrated that individuals with Autism Spectrum Disorders (ASD) allocate their visual attention differently than typically-developing (TD) peers. However, these studies have not examined the temporal sequence of fixations: how the probability of a current fixation location depends on prior fixations. Examining the temporal sequence of fixations may reveal what is learned or missed by children with ASD when viewing scenes of social interaction. **Objectives:** This study has three aims to: (1) identify, within movie scenes of social interaction, onscreen fixation locations that strongly predict future fixation locations in TD children; (2) measure whether fixations on these locations predict the same or different future fixations in children with ASD; and (3) identify fixation locations that strongly predict future fixations in children with ASD. **Methods:** Children with ASD (n=41) and TD children (n=27) were matched on chronological age and verbal IQ (mean age 10.45 years (ASD), 9.49 (TD) and VIQ of 96.28 (ASD), 110.69 (TD)). Children watched videos of age-appropriate social interaction while eye-tracking data were collected. We defined onscreen fixation locations as places where the majority of TD viewers looked at the same place simultaneously. We calculated likelihood ratios (the proportion of viewers who saw locations X and X-1 to those who saw X but not X-1) for all pairs of fixation locations, for both TD and ASD children. **Results:** 60% of the locations fixated by TD children showed higher conditional dependencies than expected by chance alone (p<.05). This indicates that TD children were more likely to fixate on 60% of the locations if they had looked at those earlier locations. After identifying fixation locations of children with ASD, 38% of those locations showed higher conditional dependencies than expected by chance alone, suggesting that fixating on earlier locations did not strongly predict fixations in children with ASD. **Conclusion:** In navigating the social world, current insights depend on past experience. Failure to learn about information conveyed in certain locations may result in later visual fixations that are more divergent from normative viewing patterns. Studies examining the temporal sequence of fixations offer important insights into visual scanning strategies in children with ASD, and the way in which those strategies shape subsequent learning.

104: Effectiveness of Mixed Rotavirus Vaccine Regimens in Preventing Severe Disease

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Introduction: Rotavirus disease is the leading global cause of severe diarrhea in children under 5 years. We examined the association between different rotavirus vaccines (RV) doses and severity of diarrhea. This is the first study to address impact of mixed RV types on disease. Methods: Surveillance of children with acute gastroenteritis (AGE) symptoms was conducted during 2 seasons (January-June) in 2010 and 2011 from 3 pediatric hospitals in Atlanta, Georgia. Enrolled children were tested for rotavirus, using EIA (Rotaclone) and vaccination records were collected from the state immunization registry and healthcare providers. Cases were defined as any enrolled child who tested positive for rotavirus. Each enrolled child was assigned a Vesikari score to assess AGE severity. Results: 63.9% had severe AGE. Cases were more likely to have severe AGE than controls (OR 3.812, 95% CI: 2.242-6.481). Receiving a mixed vaccine regimen had similar protection against severe disease to receiving only RotaTeq® or Rotarix® (Mixed: OR 0.370, 95% CI: 0.191-0.719; RotaTeq®: OR 0.508, 95% CI: 0.269-0.957; Rotarix®: OR 0.379, 95% CI: 0.220-0.653). When controlling for number of vaccine doses, children who received a mixed vaccine dose persisted in having similar protection against severe disease as children who received solely RotaTeq® or Rotarix® (Mixed: OR 0.088, 95% CI: 0.018-0.426; RotaTeq®: OR 0.147, 95% CI: 0.032-0.680; Rotarix®: OR 0.061, 95% CI: 0.012-0.299) (See Table 3). When controlling for number of doses, gender, age, race, and insurance status, children who received only Rotateq®, only Rotarix®, and mixed doses all had similar protection against severe disease (Mixed: OR 0.088, 95% CI: 0.017-0.462; RotaTeq®: OR 0.107, 95% CI: 0.021-0.532; Rotarix®: OR 0.062, 95% CI 0.012-0.321) (See Table 5). Conclusion: Mixed RV type is also effective in preventing severe AGE.

105: Comparative Study of Fluid Balance Accuracies between Pediatric-Specific and Inline Hemofiltration Devices for CRRT during ECMO

Arvind Santhanakrishnan, PhD; Trent Nestle, BS; Tyler Harmon; Brian Moore, MS; Ajit Yoganathan, PhD; Matthew L. Paden, MD

Introduction: Failure of the cardiac or respiratory system is a common problem seen in pediatric and neonatal intensive care units. Extracorporeal membrane oxygenation (ECMO) can provide life-saving temporary heart and lung support in these patients. Children requiring ECMO often have significant fluid overload and renal insufficiency. Continuous renal replacement therapy (CRRT) using an inline hemofilter and two IV pumps is commonly used to provide artificial renal support. However, IV pumps have been previously shown to be inaccurate for CRRT and affected significantly by changing pressure head. Materials and Methods: We have designed a pediatric-specific Kidney Injury and Dysfunction Support (KIDS) CRRT device that can be easily integrated within an ECMO system and is capable of providing accurate fluid balance (FB) across neonatal to pediatric flow rates. Using a mock circuit of ECMO in parallel with CRRT, we compared FB accuracies of 8-hour long continuous operation of KIDS device with a simplified inline hemofilter device that has been implemented at the Pediatric Intensive Care Unit of Children's Healthcare of Atlanta at Egleston (CHOA). In the latter device, the ultrafiltrate (UF) is removed and replacement fluid (RF) is infused using two identical intravenous (IV) pumps. FB accuracy testing was conducted across ECMO flows from 0.2-2 L/min and UF-RF flows from 120-900 ml/hr. Results and Discussion: The results of the study showed that the fluid balance error obtained using our pediatric-specific device ranged from 0.1% to 0.75%, which is over an order of magnitude improvement as compared to the current clinical implementation in CHOA. For some test conditions, the inline hemofiltration device necessitated additional infusion of fluid volume in the bladder of the ECMO circuit during the course of the 8-hour period. Conclusion: The pediatric specific CRRT device with an accurate fluid management system provides significantly improved fluid balance accuracy when used in parallel with an ECMO machine. The accurate performance of KIDS remained unaffected during variations in ECMO circuit pressure.

106: Diminished T-Tubule Density in Newborn Human Ventricular Cells is Associated with Heterogeneity of Calcium Transients

Talib Saafir, PhD; Gitanjali Baroi, BS; Brian Crawford, PhD; Guoliang Ding, MD, PhD; Brain Kogon, MD; Kirk Kanter, MD; Paul M. Kirshbom, MD and Mary B. Wagner, PhD

For children with congenital heart disease (CHD), therapies developed for adults may have different effects on immature myocardium. Thus, to develop therapies for young cardiac patients, it is critical to understand calcium handling in the developing human heart. Methods: Human ventricular cells were isolated from tissue removed as part of the surgical repair for CHDs as well as from rabbits at 5 developmental ages. Changes in t-tubules (membrane invaginations into the cell) were examined in live cells with Di-8 ANEPPS which highlights the cell membrane. We measured the T-index (percent of cell interior occupied by t-tubules), averaged for >3 confocal z-sections per cell. Changes in the spatial organization of calcium transients were measured in cells loaded with Fluo-4. Results: Newborn rabbit myocytes had very few t-tubules and the T-index increased with increasing age (3-5 days: $0.9 \pm 0.1\%$, 11-12 days: $2.6 \pm 0.4\%$, 3 wks: $7.3 \pm 0.6\%*$, 1 mos: $10.5 \pm 0.9\%*$, adult: $17.4 \pm 0.9\%*$, $n=14-42$, $*p < 0.05$). Newborn human myocytes also had a low T-index ($1.3 \pm 0.1\%$, $n=25$) that increased at 2-5 mos to $8.0 \pm 0.5\%$ ($n=78$). Surprisingly, in older infants (>6 mos), the T-index significantly decreased to $5.4 \pm 0.5\%$ ($n=44$). Junctophilin2 (JPH) is a protein that bridges the sarcoplasmic reticulum to t-tubules and is down regulated in heart failure. JPH increased 20 fold in young infant heart compared to newborn heart but decreased in older infant heart. This pattern correlates with the T-index in these patients. In addition, calcium transients from newborn human cells had a 'U' shaped wavefront with calcium first increasing at the outer edge of the cell then propagating toward the center. In contrast, infant cells had a homogenous calcium wavefront. The delay of peak calcium from the edge to center was significantly longer in newborns compared to infants (61.7 ± 8.9 ms, $n=8$ vs. 10.6 ± 1.6 ms, $n=6$, $p < 0.001$). The heterogeneous calcium transient is consistent with a lack of t-tubules in the newborn. We found similar changes in calcium with development in neonatal rabbit cells. Conclusions: Heterogeneous calcium transients in newborn human and rabbit myocytes correspond to a lack of t-tubules. T-tubules increase with age in rabbits, but in samples from children with CHD there is an initial increase in T-index that decreases at older age indicating possible early dysfunction in the older infants. This may suggest that delaying surgical repair for CHD has adverse effects on myocyte development.

107: Nanoparticle Delivery of S100A1 Improves Calcium Handling in Heart Failure

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Survival of children with complex heart defects continues to improve with advancements in surgical repair yet this population shows increasing incidence of heart failure (HF) due to residual abnormal hemodynamics. S100A1 is a small calcium (Ca^{2+}) binding protein that is decreased in heart failure (HF). Viral delivery of S100A1 normalizes Ca^{2+} handling. Nonviral delivery of S100A1 may be a novel therapy for HF. Methods: We have developed a polyketal nanoparticle decorated with N-acetylglucosamine (GlcNAc) which facilitates uptake by cardiomyocytes. We hypothesize that delivery of S100A1 by GlcNAc particles to cardiomyocytes from HF rats will normalize Ca^{2+} handling and function in these cells. Experiments utilizing a cell tracker dye encapsulated in GlcNAc particles confirmed 2 hour incubation was sufficient for robust cellular uptake. We compared HF myocyte contraction (sarcomere shortening) and calcium imaging in three groups: untreated, empty particle (EP) and S100A1 particle (S100-P) treated cells. Results: Sarcomere shortening was significantly increased by both EP and S100-P treatment ($2.2 \pm 0.5\%$ untreated, $3.9 \pm 0.5\%$ S100-P, $4.1 \pm 0.4\%$ EP, $p < 0.05$, $n=7-9$, 2 Hz pacing rate). In addition, there was a significant decrease in baseline Ca^{2+} in S100-P compared to untreated or EP treated cells, although the amplitude of the Ca^{2+} transient was not changed. HF often results in an inability of the heart to increase contractility with faster pacing rates (negative force frequency response, FFR). We found that the untreated cells had a negative FFR as expected. Treatment with S100-P resulted in partial normalization of the FFR. Surprisingly, EP treatment fully normalized the FFR, significantly increasing shortening by 50% at faster pacing. In HF, life threatening arrhythmias are caused by spontaneous Ca^{2+} release (sparks) from intracellular stores. We found that EP treatment significantly decreased the incidence of Ca^{2+} sparks vs. untreated and S100-P treated cells (12.0 ± 2.1 untreated, 11.2 ± 3.7 S100-P vs. $4.6 \pm 1.9*$ sparks/ $\mu m/s$, $p < 0.05$). Spark amplitude was decreased by EP yet increased by S100-P treatment. Spark width and duration was decreased by S100-P and EP treatment. Conclusions: Nanoparticle delivery of S100A1 partially normalizes calcium handling and restores function in HF. Surprisingly, a greater improvement was seen with unloaded GlcNAc particles suggesting that the particles themselves are bioactive and may be a potential therapy for cardiac dysfunction.

108: Decreased Right Ventricular Function in a Novel Model of Pulmonary Insufficiency in Rat

Rong Jiang, MD, PhD; Ming Shen, BS; Paul M. Kirshbom, MD; Guolaing Ding, MD, PhD and Mary B. Wagner, PhD

The population of adult patients with right ventricular (RV) dysfunction is increasing due in part to the increasing number of children with corrected congenital heart defects that now survive to adulthood. We have developed a novel model of pulmonary insufficiency (PI) to investigate the time course of right ventricular failure due to volume loading. Methods: The animal physiology core was utilized for these studies. PI was created in 8 week old rats by disruption of the pulmonary valve using a custom made hook inserted into the valve area through the RV apex and gently moved back and forth several times. In vivo function was assessed by echocardiography (Visualsonics 2100) at 14 weeks followed by sacrifice. Hearts were mounted on a Langendorff perfusion system for measurement of RV pressure. Results: Evidence of PI was noted by regurgitant flow using color doppler. Comparing the PI and sham groups, we found no difference in RV weight or in echo left ventricular measures (ejection fraction, fractional shortening). Tricuspid annular plane systolic excursion (TAPSE) was significantly smaller in the PI group indicating RV dysfunction (3.16 ± 0.13 , $n=5$ vs. 2.46 ± 0.19 , $n=8$, $p<0.05$). Furthermore, RV function measured in isolated hearts was diminished in the PI group. Developed pressure (DP) was significantly smaller in PI compared to sham (25.5 ± 2.7 mmHg, $n=9$ vs. 36.5 ± 3.6 mmHg, $n=5$, $p<0.05$) as was the minimum derivative of pressure (dPmin, -500 ± 46 mmHg/s, $n=9$ vs. -731 ± 81 mmHg/s, $n=5$, $p<0.02$). We separated the PI group into mild and moderate PI based on the degree of regurgitant flow observed by echo. Isolated hearts were perfused with increasing doses of dobutamine to determine RV functional reserve. In the sham group, there was a dose response to increasing dobutamine with respect to DP (36.5 ± 3.6 mmHg vs. 38.0 ± 1.7 mmHg vs. $51.2 \pm 4.1^*$ mmHg for baseline, 100 nM, and 1 μ M dobutamine ($n=5$), $*p<0.05$) with similar results for dPmin and dPmax. In contrast, dobutamine did not significantly increase any of the functional parameters in either the mild-PI or moderate-PI groups. Conclusions: Disruption of the pulmonary valve in a rat model caused mild to moderate PI and RV function in the isolated heart was decreased in the PI group. Response to dobutamine was robust in the sham group and diminished in both mild and moderate PI groups. This is a novel model of PI that can be used to investigate the mechanisms of RV failure in response to volume overload.

109: Hemin-Induced miR-27a Reduces PPAR γ Expression in Sick Cell Disease with Pulmonary Hypertension

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The hallmark of sickle cell disease (SCD) is hemolysis, vaso-occlusion, and oxidative stress. Pulmonary hypertension (PH) is a serious complication of SCD that causes significant morbidity and mortality. We previously demonstrated that: 1) activation of the nuclear hormone receptor, peroxisome proliferator-activated receptor gamma (PPAR γ) attenuated hypoxia-induced Nox4 and endothelin-1 (ET-1) expression and PH in mice and 2) that levels of Nox4 and ET-1 were increased in the lungs of 8-10 week old SCD transgenic mice compared to controls whereas PPAR γ levels were reduced. The current study further examines mechanisms of PH in SCD. Human pulmonary arterial endothelial cells (HPAECs) were treated with the hemolysis product, hemin (5 μ M), for 72 h. Hemin reduced PPAR γ and increased Nox4 and ET-1 expression and HPAEC proliferation. MicroRNA-27a (miR-27a), which negatively regulates PPAR γ , was increased in hemin-treated HPAECs. In contrast, treating HPAECs with the PPAR γ agonist, rosiglitazone (10 μ M) for the final 24 h of hemin exposure attenuated increased HPAEC proliferation and miR-27a levels. These findings suggest that hemin increases miR-27a to reduce PPAR γ and increase Nox4, ET-1, and PAEC proliferation. These results suggest novel pathways for SCD-PH pathogenesis and therapy. Supported by Atlanta VA Merit Review, NIH HL102167, and Emory/Childrens Healthcare CEB F16788-00.

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

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Atrioventricular septal defects (AVSD) are a life threatening congenital heart defect (CHD) inflicting substantial social and healthcare costs. Traditional genetic mapping strategies have revealed only a limited, but highly heterogeneous, set of aberrant genes responsible for AVSD, suggesting that many loci remain undiscovered.

Children born with trisomy 21, diagnosed as Down Syndrome (DS), are at a 2000-fold increased risk for AVSD over the general population, resulting in AVSD prevalence in DS of 1 in 5. These data suggest that individuals with trisomy 21 compose a sensitized cohort with respect to AVSD, which can help reveal novel AVSD susceptibility genes. In particular, we hypothesize that copy number variants (CNVs) on chromosome 21 may amplify the risk of AVSD in individuals with DS, and therefore explain the elevated risk for AVSD found in the DS population. To test this, we have performed high-density array comparative genomic hybridization of chromosome 21 in 212 cases (individuals with DS and complete AVSD) and 235 controls (individuals with DS without any CHD). In cases and controls, 621 deletions and 334 duplications were detected using the ADM2 algorithm that identifies a CNV as a region with a mean Log2 score significantly departing from the expectation of Log2 = 0. Duplications ranged in size from 1.9 to 893 kb in cases and from 2.1 kb to 745 kb in controls. Deletions ranged in size from 1.8 kb to 239 kb in cases and 1.8 kb to 422 kb in controls. Initial analyses suggested no statistically significant differences in the overall rate or size of CNVs between our cases and controls. After filtering out common variants found in the Database of Genomic Variants, cases were found to have a significantly greater rate of genes covered by duplications when adjusting for total duplication coverage in each sample (empirical p-value = 0.067). Continuing efforts include: more conservative quality control of questionable samples, evaluating other CNV calling algorithms, testing for specific associations with common versus rare variants, as well as for CNV enrichment over AVSD candidate genes on chromosome 21. Significant CNVs will be validated with Taqman PCR and breakpoint sequencing. At this time, we conclude that the effect of a single or a few common CNVs on chromosome 21 do not account for the 2000-fold increased risk for AVSD in the DS population. Our data bolster arguments that there is a high level of heterogeneity found in the etiology of AVSD.

111: Hospitalizations and Associated Costs in a Population-Based Study of Children with Down Syndrome

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Background and Objective: Healthcare use and costs for children with Down syndrome are significantly greater than those of unaffected children. Information on hospitalizations and costs beyond the first few years of life and by the presence of critical congenital heart defects (CCHDs) is lacking. Our objective was to determine differences in hospital use and associated costs for children with Down syndrome by the presence of other anomalies, including CCHDs. Methods: This was a retrospective, population-based, state-wide study of children with Down syndrome born 1998-2007, identified by the Florida Birth Defects Registry and linked to hospital discharge records for 1-10 years after birth. Descriptive statistics on number of hospitalizations, hospitalized days, and inpatient costs were calculated. Results were stratified by isolated Down syndrome (no other major birth defect present); presence of congenital heart defects (CHDs); and presence of major non-cardiac birth defects. Results for children with Down syndrome and CCHDs were stratified by presence or absence of 12 CCHD types. Results: 2,366 children with Down syndrome had 6,347 inpatient admissions of which 60% occurred during the first year of life. Of these children, 24% (n=560) had isolated Down syndrome, 60% (n=1,414) had a CHD, and 17% (n=392) had non-cardiac birth defects. From infancy through age two, children with CHDs had a greater number of hospitalizations, hospitalized days, and higher total costs than children with isolated Down syndrome or with non-cardiac birth defects. These differences were not significant beyond age two. Among children with CHDs, 14% (n=195) had a CCHD. Mean and median total costs were more than three times higher for infants with CCHDs compared to infants with other CHDs. Infants with CCHDs also had significantly greater number of hospitalizations and twice the number of hospitalized days compared to infants with other CHDs. Conclusions: Results confirm that for children with Down syndrome the presence of other anomalies influences hospital use and costs, and children with CCHDs have greater hospital resource utilization than children with other CHDs. Further examination of demographic and clinical characteristics and the effects of CCHD and Down syndrome on the health care system are warranted. Birth defects registry and hospital discharge data provide useful tools for evaluating patterns of hospital use and associated costs over time.

112: SickleREMOTE: A Two-Way Text Messaging System for Pediatric Sickle Cell Disease Patient

Chihwen Cheng; Clark Brown, MD, PhD; Janani Venugopalan; Todd H. Stokes, PhD; Carlton Dampier, MD; May D. Wang, PhD

Sickle cell disease (SCD) is the most prevalent inherited disease, generally affecting patient lives from early childhood. Effective medical care requires frequent monitoring, such as tracking the frequency, severity, and

duration of painful events. Conventional monitoring requires patients to carry forms, which are easily lost, or laptop computers, which are impractical to scale to a large generally underprivileged population. Text messaging (SMS) has become a favored method of communication in the SCD population. We propose a disease-tailored SMS platform that may resolve several limitations of self-report monitoring. We present the findings of the planned interim "optimization" analysis of an ongoing clinical trial. An automated system, called sickle cell disease REporting and MONitoring TElemedicine (SickleREMOTE), using SMS adaptations of validated clinical tools, is being piloted in adolescent (age 12-18) patients at a comprehensive pediatric SCD program from Children's Healthcare of Atlanta (CHOA). Participants receive training while hospitalized for an acute painful event. After the 27 subjects completed the inpatient protocol, analysis of compliance, accuracy and user-satisfaction was performed on self-reports of pain and quality-of-life (i.e. PROMIS Pediatric Pain Interface Scale) queries. Additional analysis is shown for 14 participants who have completed the 30-day post-hospitalization outpatient protocol. Compliance with at least one daily self-report to an automated pain query was 94.9% (112/118) and 91.1% (327/359) of the inpatient and outpatient days, respectively. Pain response accuracy was 99.2% (970/978), following the predefined short response convention. 33% (7/21) inpatient and 66% (36/54) outpatient PROMIS responses were reported with 98% (50/51) reporting accuracy. All participants expressed high satisfaction with the platform, and expressed intent to use SickleREMOTE to help track pain events. In conclusion, SickleREMOTE promises to be an effective mobile health tool for adolescents with SCD to monitor their disease. The easy-of-use interface allows adolescents to report with a very high compliance. Adolescents can correctly report a variety of disease-related information using the pre-defined text-messaging template. SickleREMOTE can be easily applied to other diseases and health assessments (e.g., Teen Transition Readiness).

113: Effects of Fructose on Cardiovascular Risk in Adolescents with Nonalcoholic Fatty Liver Disease

Miriam Vos, MD, MSPH; Ran Jin, MS; Jean Welsh, PhD, MPH, RD; Ngoc-Anh Le, PhD

Objective: Nonalcoholic fatty liver disease is strongly associated with increased CVD risk. We have previously reported abnormal postprandial TG response after fructose-enriched meals in adolescents with NAFLD suggesting that fructose may contribute to the increased CVD risk. We hypothesized that fructose reduction would improve CVD risk factors in adolescents with NAFLD. Methods: Overweight adolescents who self-reported high consumption of sugar beverages (>24oz/day) were evaluated with a 90 minute fructose tolerance test, fasting labs and hepatic fat screening by MRS. 24 adolescents had high hepatic fat (HHF, $\geq 5\%$) and were randomized to either 4 weeks of fructose reduction (home beverages replaced with 3 glucose study provided beverages per day) or 4 weeks of continued high fructose (home beverages replaced with 3 fructose study provided beverages per day). MRS, fasting labs, and anthropometrics were repeated at baseline and after 4 weeks. Results: Subjects with HHF had increase size of VLDL particles, increase number of small atherogenic LDL and increased dyslipidemic response to fructose over 90 minutes. After reduction of fructose for 4 weeks, compared to those continuing fructose, subjects had improvement of insulin resistance (adipose IR, $p=0.034$), inflammation (CRP $p=0.026$), atherogenic oxidized LDL ($p=0.056$), and oxidative stress (TBARS, $p<0.05$). Subjects who continued on fructose had worsening of VLDL size in response to the 90 minute fructose tolerance test ($p<0.05$). No change was seen in body weight, and hepatic fat. Conclusion: Reduction of fructose containing beverages for 4 weeks improved CVD risk profile in adolescents with HHF despite a lack of change in hepatic fat. This suggests that decreasing sugar sweetened beverages may be an important component of the treatment for NAFLD and should be tested in longer clinical trials.

114: Making a definitive diagnosis and therapeutics decision from genome sequencing: Putting it all together.

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Inflammatory bowel disease (IBD) is heritable and early onset IBD has distinct clinical phenotype and is associated with differential diagnoses for common presenting symptoms. Loss of function gene variants can result in both common and complex diseases like IBD. We ascertained a five-member family of European ancestry that includes mother and 3 sons presenting with atypical IBD. The proband was diagnosed with Crohn's colitis at the age of 6. At enrollment in this study, he was 14, refractory to all therapies, growth retarded, delayed puberty and had a deep venous thrombosis from the leg to the atrium. One of his brothers has T1D, and another one has psoriasis. His

mother had a colectomy for refractory colitis, and wears an ostomy bag. His uncle died of medical complications while treated for Crohn's disease (aplastic anemia induced by immunosuppressants). We perform whole exome sequencing (WES) of all family members to correlate genotype to phenotype. After mapping, annotation and stringent filtering criteria, we identified a novel hemizygous damaging missense variant in exon 6 of the FOXP3 gene on the X chromosome. The c.694A>C substitution in FOXP3, shared by mother and 3 sons, results in a Cysteine to Glycine amino acid (AA) change at a position 232 found to be conserved among all vertebrates. The mutation did not impair FOXP3 protein expression but significantly reduced the ability of T regulatory cells (Tregs) to suppress inappropriate autoimmune response. Substitution of Cysteine 232 disrupts the dimerization of the FOXP3 protein and interferes with its normal assembly. Our study represents a successful elucidation of a dominant Mendelian disorder using whole exome sequencing for reverse phenotyping. Loss of function mutations at FOXP3 cause the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. FOXP3 controls the development of Tregs, which help prevent autoimmune disease and deficiency of which cause autoimmunity. Typical IPEX is a rare disorder characterized by the clinical triad of enteropathy, dermatitis and endocrinopathies that result in lethality at a very early age. The atypical presentations in this family represent manifestation of atypical IPEX. The proband was recommended for allogeneic bone marrow transplantation and is being evaluated for it. Our study has important implications for IPEX biology and directed therapeutic development.

115: Derivation of Multiple Induced Pluripotent Stem Cell Lines to Model Muscular Dystrophy-Associated Cardiomyopathy

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Cardiomyopathy is the major cause of death in Duchenne muscular dystrophy (DMD), the most common and severe childhood disease of skeletal muscle. DMD results from mutations in the dystrophin gene, leading to the progressive loss of muscle mass and function and, through mechanism(s) that remain incompletely understood, cardiomyocyte (CM) dysfunction and subsequent heart failure. To investigate the cellular and molecular processes underlying dystrophic CMs, we are in the process of generating induced pluripotent stem cells (iPSCs) through reprogramming dermal fibroblasts from DMD patients and unaffected controls. For each of the four controls, we have created at least two iPSC-like lineages that carried markers associated with pluripotency. Other cellular and molecular characteristics of these lines, including karyotype, teratoma formation and in vitro differentiation, are currently being assessed. We have recently induced differentiation of one of these lines into CMs. These iPSCs-derived CMs beat, featured structure of striated muscle, and were stained positive for a cardiomyocyte-associated protein α -actinin. We have also employed suspension cultures to engineer these CMs into three-dimensional cardiac tissue constructs, enriching the CM populations to over 90%. We expect to obtain iPSC lines from DMD patients and plan to compare molecular and cellular properties of the iPSC-derived CMs from patients and controls. Ultimately, we will validate if these dystrophin-deficient iPSC-derived CMs can serve as an in vitro cell system model of cardiomyopathy in DMD.

116: Microbiota-Dependent Th17 and Foxp3+ Regulatory T Cell Differentiation in the Intestine

Duke Geem, Oscar Medina-Contreras, Benoit Chassaing, Andrew T. Gewirtz, and Timothy L. Denning

Introduction: The microbiota promotes tolerogenic innate and adaptive immune responses in the intestines of healthy individuals. This tolerance is broken during pediatric inflammatory bowel disease resulting in pro-inflammatory immune reactivity toward the microbiota. Specific components of the microbiota, such as segmented filamentous bacteria (SFB) and Clostridium species, can induce the differentiation of tolerogenic CD4+ T cells (Foxp3+ Treg) and pro-inflammatory CD4+ T cells (Th17/Th1), yet the mechanism of microbiota-induced CD4+ T cell differentiation remains incompletely understood and is currently believed to take place predominantly in the mesenteric lymph nodes (mLN). Thus, the objective of this study was to define how specific components of the microbiota regulate intestinal CD4+ T cell differentiation in the intestine and mesenteric lymph nodes (mLN). **Materials and Methods:** Intestinal CD4+ T cell differentiation and the influence of the microbiota on this process were examined 1) using mice deficient in mLN (lymphotoxin- α deficient) reconstituted with defined microbiota and 2) in adoptive transfer studies using SFB+ or SFB-recipient mice in order to characterize CD4+ T cell differentiation in the intestine via multi-color flow cytometry. **Results and Discussion:** Our data demonstrate that mature CD4+CD8- thymocytes adoptively transferred into recipient mice were capable of rapidly migrating to the intestine.

Consistent with these observations, naïve CD4+ T cells were abundant in the intestines of both adult germ-free mice and early postnatal conventionally-housed mice. Bacterial colonization of either group induced differentiation of Foxp3+ Treg cells. Additionally, oral gavage of SFB-containing microbiota into SFB-free mice was also sufficient to drive Th17 cells in mice void of mLN. Conclusions: Collectively, these data suggest that specific components of the microbiota are capable of inducing the development of effector and regulatory T cell subsets directly in the intestine and not exclusively in the mLN, as previously believed. Impact: These findings provide a foundation for future studies directed towards understanding how the microbiota and specific intestinal antigen presenting cell subsets regulate the differentiation of pro-inflammatory and regulatory CD4+ T cells, which will enable the discovery of novel cellular and molecular targets for the treatment of pediatric inflammatory bowel disease.

117: Genome- wide Analysis of Copy Number Variants Associated with AtrioVentricular Septal Defects in children with Down Syndrome

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Our project is focused on identifying genetic variants contributing to congenital heart defects (CHD), especially atrioventricular septal defects (AVSD) among individuals with Down Syndrome (DS). Non-syndromic AVSDs occur in approximately 1 in 10,000 births in the general population. However, among infants with DS nearly 20% have an AVSD, representing a 2000-fold increased risk compared to the general population. We hypothesize that in the presence of extra chromosome 21, otherwise benign copy number variants (CNVs) become susceptibility alleles and hence could explain the increased prevalence of DS-associated AVSD. We used the Affymetrix SNP 6.0 genotyping platform to comprehensively characterize the CNVs in 819 samples consisting of 235 DS cases (complete AVSD, DS+AVSD), 264 DS controls (no CHD, DS-CHD) and 320 DS case parents. Our analysis pipeline had strict quality control filters, which required each CNV call to be made by at least 2 out of the 3 algorithms (GLAD, GADA, BEAST) used. Upon excluding CNVs overlapping centromeres and those reported in Database of Genomic Variants (DGV), we identified 1,991 deletions in DS+AVSD cases and 2,442 deletions in DS-CHD controls. Using the same filtering, we identified 1,434 duplications in DS+AVSD cases and 1,802 duplications in DS-AVSD controls. Standard burden tests using PLINK did not identify statistically significant differences between cases and controls in the number or size of the CNVs. Association analyses uncovered a ~40kb deletion within the SGSM2 gene on chromosome 17 with a nominal significance of $p < 0.003$, and after permutation correction for multiple testing, was nearly genome-wide significant ($p < 0.07$). Interestingly, a meta-analysis of GWAS data on cardiac structure and function identified multiple SNPs in three adjacent genes associated with aortic root diameter in this same region with genome-wide significant p-values. Additionally, we have identified large rare CNVs overlapping genes previously associated with CHD, including CRELD1 and GATA5. Validation of CNVs in these regions is currently underway. In summary, our study has identified genetic variations that appear to contribute to the high prevalence of AVSD in this sensitized DS population.

118: Growing up: not an easy transition. Perspectives and outcomes of patients transferred from the liver transplant clinic.

Sona Chandra, Shannon Luetkemeyer, Rene Romero MD, Nitika Gupta MD

Background: Transition from the pediatric to the adult care is an area of intense investigation. Children with chronic illness are unable to maneuver the demands of adult medical care, sustaining high morbidity and mortality in the process. Aim: The aim of this study was to assess patient perspectives regarding the transition process with the ultimate goal of improving patient services and ensuring good outcome. Methodology: A phone survey of the patients who had been transferred to the adult services over the past 3 years from hepatology and liver transplant clinic was conducted from Jan 2011 to Jan 2012. Demographic information regarding their follow up with adult services was obtained and feedback was sought regarding teen clinic services and opportunities for improvement. Results: A total of 31 surveys were conducted. Of these, 22 were patients/parents of children who had received a liver transplant and 9 were those with end stage liver disease. Diagnoses were varied across the group. Majority of the patients surveyed were female (70%). Mean age of the patients at transfer was 19.81 years (18-21). The majority were Caucasians (57%) with 33% being African American and 10% Hispanic. Majority of the patients (70%) were transferred to Emory and the rest to different places within GA. Almost half the patients (47%) were not seen at the new facility until 2-6 months after leaving CHOA and 20% were not seen until between 6-12 months,

even though half the patients (54%) had scheduled a visit at the new facility prior to leaving CHOA. Though majority of the patients were seen in clinic, 20% had their first contact with adult services through an ER visit. Most of the patients (21/31; 68%) reported that they did not run out of medication with 19% (6/31) reporting being out of medication. Four patients were not taking their medication at all. Of the transplanted patients, 19% were being evaluated for a re-transplant. The single factor deemed as being critical to a smooth transition was education of the children. The majority (82%) felt that institution of peer support groups for the children with 'letting go' by parents and providers would be helpful. Conclusions: Transition from pediatric to adult care requires an organized effort, which should be directed towards education and empowerment of the patients. Since these results, a mentoring program has been instituted and a concerted effort towards education and independent clinic visits is being made.

119: The dynamic role of PD1 in ischemia reperfusion injury of a steatotic liver

Nitika Gupta MD; Vasantha Kolachala PhD; Rong Jiang MD; Carlos Abramowsky MD; Allan Kirk MD PhD

Introduction: Steatotic livers undergo increased hepatocellular death when exposed to ischemia reperfusion injury (IRI). Though the role of PD1, as a critical inhibitory member of the CD28 family is emerging in various clinical scenarios such as transplant tolerance, sepsis, viral hepatitis and autoimmunity it not well studied in IRI of a steatotic liver. This understanding could lead to development of novel therapeutic targets to alleviate this injury. Aim: To determine the role of PD1 in IRI of a steatotic liver. Methods: Male C57BL/6 mice were fed a high fat diet (HFD) for 12 weeks and subjected to IRI with reperfusion for 6, 24 and 72 hours. Hepatic and splenic T cells were isolated and subjected to flow cytometry for CD45, CD3, CD4, CD8, CD4+PD1+ and CD8+PD1+. Serum ALT was measured and H&E performed. Ligands of PD1: B7 H1 and B7DC were assessed by western blot, IF and RTPCR. PD1 KO mice were fed a HFD and exposed to IRI followed by histology and serum ALT. Results: HFD fed mice showed increased body weight (42.16 ± 1.28 vs 24.6 ± 0.65 grams * $p < 0.0001$) and presence of hepatic steatosis. After IRI they showed increased necrosis and higher serum ALT as compared to their lean littermates (700 ± 43 vs 401 ± 46 IU/ml * $p < 0.009$). At 72 hours of reperfusion, PD 1 was upregulated on CD4+ hepatic T cells of HFD fed mice (HFD IRI: 61.63 ± 5.2 vs lean IRI: 36.08 ± 3.6 * $p < 0.009$). There was no significant difference at baseline (HFD: 41.05 ± 15.55 vs lean: 30.40 ± 11.01 $p < 0.57$). Similar findings were seen in splenic T cells after IRI in HFD fed mice vs lean mice (44.43 ± 3.8 vs 28.16 ± 3.6 %, * $p < 0.01$). Lean mice did not show significant difference after IRI (28.61 ± 3.6 vs 19.98 ± 3.57 $p < 0.15$). No difference in CD8+PD1+ T cells was seen. Additionally, PD1 KO mice were protected from IRI, showing decreased necrosis and lower serum ALT (127 ± 28 vs 700 ± 43 * $p < 0.0001$). PD1 ligand, B7H1 was decreased in HFD mice undergoing IRI. Conclusions: Along with increased cell death, there is an increase in CD4+PD1+ hepatic and splenic T cells after IRI of a steatotic liver, with concomitantly decreased ligand, leading to loss of inhibitory effect of PD1, with resultant activation. This profiles a unique signature, which can be targeted for therapeutic intervention for mitigating hepatocellular injury in a steatotic liver.

120: Liver Transplant Transition Clinic 101(I Own It): Role of a Patient Navigator

Shannon Luetkemeyer, Amy Hauser, Nitika Gupta MD

Background: There is increased morbidity and mortality during the process of transition from pediatric to adult services. The young adult with chronic illness is unable to handle this process and this invariably leads to graft loss in a solid organ transplant recipient. Aim: The aim of the study was to institute a new role of a patient navigator for the liver transplant teen clinic with focus on education and empowerment. Methodology: A systematic approach to the liver transplant teen transition clinic was adopted. Consistency was maintained with one MD providing care. A new position of a patient navigator was instituted who acted as the liaison between the healthcare providers and the patients. The role of the navigator was to provide one on one education, assessment and support to the teen patient. Reminders for lab and clinic visits, and tours to the adult clinic were provided. A personalized binder was created for each patient, which consisted of operative reports, latest lab and other significant findings. Additionally, information about local support groups was provided. A home visit was conducted to the patients at the highest risk. Long-term complications were monitored and high- risk behaviors screened. Results: There was increased emphasis by the caregivers to the education and empowerment of the teen patients. Patients > 14 years old were enrolled in the teen clinic. Between 14-16 they were seen with parent, between 16-18 the parent was asked to step out once and > 18 years they were seen alone, simulating the adult model. Reminders resulted in very low no-show rates in clinic. The written information in the binders was not well received so paper was abolished and information was placed on a USB presented to the teens. Home visits resulted in increased education and support for the teen who confided about social concerns during that time instead of a clinic visit. A mentoring program was instituted.

Universal screening resulted in detection of STDs in patients who denied being sexually active, and of drug users, which lead to early treatment. Conclusion: Institution of a dedicated teen clinic with consistency in the care providers with goals of education and empowerment are the cornerstones of a successful transition, which should be started at an early age. A patient navigator can provide the much needed support and liason between the caregivers and aid the teen during this difficult period of transition.

121: c-Abl Tyrosine Kinase's Role in Increasing Catalase Activity in the Catalase-Dysregulated Newborn Rabbit Heart Following Ischemia-Reperfusion

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Pediatric patients undergoing corrective cardiothoracic surgery numbered in the tens of thousands annually and therefore it is necessary that pre- and post-operative strategies be employed to limit ischemia-reperfusion (IR) injury. We have found differences in the way the newborn (versus the adult) heart responds to IR injury. In the adult, catalase activity increases appropriately with increasing levels of hydrogen peroxide (H₂O₂), conferring cardioprotection. This effect however does not occur in the newborn. One proposed reason for this observed dysfunctional response to increasing H₂O₂ levels is due to post-translational modification of catalase; rendering it inactive and unable to function in the same way it does in the adult heart. Following IR, catalase undergoes phosphorylation mediated by the tyrosine kinase c-Abl, which activates catalase and allows it to function as a scavenger of H₂O₂. Following hypoxia, we measured the ratio of phosphorylated to total catalase and c-Abl by densitometric analysis in isolated rat myocytes and found that levels in the newborn did not increase and were significantly lower (1.92- and 6.21-fold, respectively) than their adult counterparts. In addition, ubiquitination of catalase was also increased 1.27-fold in the newborn. Pre-treatment with 200 μ M MG132, a ubiquitin inhibitor caused a 4.12-fold decrease in the ubiquitination of catalase but activity and phosphorylation levels remained unchanged. Interestingly, when 200 μ M DPH, an activator of c-Abl was administered one hour prior to hypoxia, not only was catalase activity significantly increased 6.28-fold, but phosphorylation levels were also altered. Finally, direct injection of DPH (0.4 ml, 200 μ M), a c-Abl activator, into the right ventricle of an isolated rabbit newborn heart using Langendorff perfusion method caused a significant improvement in recovery of developed pressure (from 49.53 \pm 5.42% to 125.5 \pm 15.5%) after IR. Catalase activity in these same hearts increased 2.92-fold. This suggests that in the newborn, phosphorylation of catalase causes its activation and this appears to be mediated by c-Abl, a tyrosine kinase with potential therapeutic applications in protecting the newborn heart against oxidative injury.

122: Behavioral Topographies that Adversely Impact Dynamic Visual Scanning in Adolescents with ASD

Eugene Kim, BA; Warren Jones, PhD; and Ami Klin, PhD

Background: Adaptive social behavior relies heavily on our ability to effectively orient attention to socially relevant information while ignoring potential distractors. Previous research measuring dynamic visual scanning during viewing of naturalistic social situations revealed moments when typically developing (TD) individuals allocated their visual resources in a spatially and temporally locked manner. For viewers diagnosed with autism spectrum disorder (ASD), convergence of visual resources on socially relevant events was markedly diminished, demonstrating that behaviorally salient events for TD individuals did not receive the same visual scrutiny by those with ASD. The current study examines the specific factors that guide, fail to guide, or disrupt the deployment of preferential attention in adolescents with ASD. Methods: Eye-tracking data were collected from adolescents with ASD (mean age = 16.67 (3.92) years; n = 21) and TD controls matched on age and verbal function (mean age = 16.86 (4.5); n = 17) while viewing video scenes of realistic social interactions. We used kernel density estimation to quantify the level of convergence of visual scanning at each moment in time in order to obtain measures of relative salience. Ethograms were constructed for each video, where a frame-by-frame characterization of specific events allowed us to examine relationships between discrete event categories and moments where significant group-differences emerged. Findings: Between-group differences in visual scanning were greatest when multiple actors were onscreen, during which individuals with ASD exhibited considerably diminished convergence on faces that were salient to TD individuals. When the ASD group did display convergent visual scanning, it was on faces that occupied greater total screen area or actors who made sudden vocalizations or body motions. However, convergence on faces by the ASD group indicated a stronger preference for the mouth and body regions than the eyes. When viewing dynamic social interactions, individuals with ASD may rely more heavily on non-social physical

cues to allocate their attention, being at their greatest disadvantage when the perceived environment encompasses more competing stimuli.

123: A Structured Indirect Assessment of Problem Behavior Severity

Faith Cawthon, M.Ed., BCBA; Natalie A. Parks, PhD, BCBA; Daniel Conine, BCaBA; Briana R. Lopez, BS

The severity of problem behavior is a key factor in triage and placement decisions for programs that serve children with autism who exhibit severe problem behaviors. Without an appropriate method to identify which services would be most appropriate, individuals are at risk for being placed within a program that is either not equipped to treat the problematic behavior or resources are spent on treating behaviors that could have been decreased with less intensive services. Currently, there are only a few standardized rating scales that provide information about the severity of problem behavior; however, they are not ideally suited to evaluate individuals with autism who exhibit severe problem behavior. Absent such a standardized assessment, clinicians must rely on the reports of caregivers, which are often unreliable, or expend precious resources on other in vivo observations or functional assessments. A standardized assessment would not only provide an objective measure of severity of problem behavior, but would decrease the amount of resources required to make objective decisions regarding program placement. The Problem Behavior Severity Scale (PBSS) was developed to provide an objective measure of the severity of problem behavior as it relates to injury to self or others, property destruction, and the level of intervention or staff required to safely intervene. A scale was developed based upon scores on the PBSS to determine the most appropriate level of intervention according to the score on the PBSS. Clinician referrals and PBSS ratings were completed with 285 individuals. Clinician referrals and PBSS ratings were compared. The clinician ratings and PBSS produced the same recommendation for 87% of the individuals. Disagreements were analyzed to determine which recommendation (PBSS or clinician) was more appropriate, as determined by successful completion of one program or a referral to a different program. Recommendations from the clinicians were more appropriate for 6%, where as the severity score from the PBSS was more appropriate for 1%. The quantification of problem behavior exhibited by individuals with autism is important for ensuring individuals receive the most appropriate treatments. This behavior is often difficult to measure without expending vast resources. The PBSS appears to be an adequate instrument for satisfying this need.

124: Markovian Dynamics of Visual Scanning Behavior in Toddlers with ASD

Gordon Ramsay, PhD; David Lin, MD; Warren Jones, PhD; Ami Klin, PhD

INTRODUCTION: Research has shown that children with autism exhibit atypical patterns of visual attention to social scenes relative to typically developing peers. In studies involving audiovisual stimuli comprising faces and shapes synchronized with speech and tones, we showed that ASD infants are insensitive to social contingencies afforded by talking faces, focusing instead on physical contingencies between light and sound. In those studies, measures of visual attention were derived from summary statistics comparing fixation durations on different parts of the screen. These do not capture patterns of temporal correlation, which may contain information about behavioral responses specific to ASD. The goal of this research is to develop a mathematical model for parameterizing the dynamics of visual scanning, and determine whether temporal dynamics distinguish ASD from TD children.

METHODS: Drawing on our research with stochastic models of goal-directed actions, we constructed a hidden Markov process to model the temporal structure of our data, including discrete looking events, event timing, visual targets and oculomotor dynamics. We derived parameter estimation algorithms to recover the Markov transition kernel from training data, and state estimation algorithms that allow the hidden states of the model to be recovered for any given eyetracking trajectory. We derived likelihood-ratio tests to determine which of a set of trained models is most consistent with any observed test set of eyetracking trajectories. The result is a complete system for automatically quantifying and classifying the full spatiotemporal dynamics of visual scanning behavior. We applied the model to eyetracking data for 20 ASD and TD toddlers from our previous experiments, training models for each diagnostic group and stimulus type, and testing for significant differences in each model parameter. **RESULTS:** We found differences in Markov parameters across diagnostic groups reflecting temporal sequencing of saccades and fixations, which depended on the social nature of the stimulus. These differences cannot show up in our summary statistics. **CONCLUSIONS:** Significant differences in visual scanning behavior exist between ASD and TD children that cannot be fully quantified without characterizing the detailed temporal unfolding of individual looking patterns. **IMPACT:** Our research suggests biomarkers for mechanisms of attention that may be crucial in identifying children at risk of autism.

125: Quantitative Analysis of Phase-Contrast Magnetic Resonance in Pediatric Patients with Chiari Malformation

Kyle Pate BS, Kelsie Riemenschneider BS, Joshua Chern MD, PhD, Nilesh Desai MD, John Oshinski MD

Introduction: Chiari I malformation is defined as a tonsillar ectopia of greater than 5 mm below the foramen magnum. A CSF-filled cyst in the center of the spinal cord (syrinx) often develops as the disease progresses and is an indication for surgical decompression. Previously, cardiac-gated magnetic resonance imaging (MRI) scans in the sagittal midline view have been used to qualitatively assess flow in patients undergoing. However, these scans have yet to yield quantitative criteria useful for selecting patients best suited for surgery. We propose an alternative approach, using cardiac-gated, phase-contrast magnetic resonance (PCMR) to quantitatively evaluate CSF flow values acquired in the transverse plane. We have focused our study on a pediatric population to determine if the presence of a syrinx can be linked to quantitative changes in pre-surgery patients. Materials and Methods A standard clinical MRI protocol was followed with two cardiac-gated, transverse PCMR series, the first at the level of the foramen magnum and the second at C6. 17 patients were included in the study (age: 10.6 ± 4.3). Studies were performed on a Siemens 3.0T MRI scanner and analyzed using flow quantification software. Regions of interest (ROI's) were defined to isolate the CSF flow from the spinal cord. The study patients were divided into groups based on the presence or absence of a syrinx at the time of the scan. Results and Discussion PCMR analysis showed that the maximum cranial flow value at C6 was significantly lower in those patients that presented with a syrinx when compared to those without a syrinx (1.38 ± 0.55 ml/s vs. 2.19 ± 0.53 ml/s, $p=0.01$). A small, but non-significant decrease in flow was observed at the foramen magnum (2.07 ± 0.91 ml/s vs. 2.93 ± 1.50 ml/s, $p=0.19$). These results may indicate a de-compensation in flow in response to decreased volume of the subarachnoid space. Conclusions PCMR analysis of the transverse plane at C6 showed a significant reduction in maximum cranial CSF flow in CM patients with a syrinx. Quantitative measures may be helpful in analysis of an inherently complex and subjective condition as Chiari malformation. Future analysis of PCMR will concentrate on how differences in flow translate to improved response to surgery.

126: Magnetic Immuno-separation and Detection of Pediatric Brain Tumor Cells in CSF Samples

Run Lin, Hui Wu, Hongyin Zhang, James Provenzale, Tobey MacDonald and Hui Mao

Introduction: Medulloblastomas (MBs) are the most common primitive neuroectodermal tumors of the pediatric central nervous system (CNS). Early detection of metastases is important in improving outcome. This study is to develop a nanotechnology approach to detect metastatic tumor cells in cerebral spinal fluid (CSF) samples collected in pediatric brain tumor patients. Although micrometer sized magnetic particles are traditionally used for cell separation applications, we attempted to use magnetic nanoparticles coated with anti-fouling "stealth" polymers and functionalized with antibodies targeting MB biomarkers, EphB1 or transferrin receptor, to reduce off-target pick up and improve the specificity and sensitivity of cancer cell capture and detection in CSF samples. Methods and Materials: Magnetic nanoparticles with various sizes (5 -25 nm) and magnetic susceptibility were prepared and then coated with polysiloxane diblock copolymer. Targeting antibodies, anti-transferrin receptor (Trf) were conjugated on the nanoparticles through amine-thiol interaction to obtain MB cell targeted Trf-IONP, which can be labeled with FITC for optical detection. The Bradford method were used to measure the number of antibody on each nanoparticle to estimate the number of antibodies conjugated on each nanoparticle based on the BSA standard curve. Macrophage (RAW264.7) was used to test the nonspecific uptake of developed Trf-IONP. Human medulloblastoma cell (D556) was used to test targeting and cell separation with Trf-IONP. Cells were incubated with Trf-IONP with a concentration of 0.1mg/ml (Fe) for 3 hours. Prussian blue staining for iron or confocal microscopy were used to examine cell binding of Trf-IONP. A hand-hold magnetic separation magnet was used to test the separation of MB cells bound with Trf-IONP from cells without over expression of transferrin receptors. Results: First, anti-fouling "stealth" polysiloxane diblock copolymer developed in the study can substantially lower the non-specific binding of non-targeted cells comparing particles coated with conventional polymers such as PEG. With reduced off-target effect, prepared Trf-IONP exhibited excellent targeting and binding to MB cells (D556) with over expressed transferrin receptors as evidenced by both Prussian blue staining and confocal microscopic images. Using small hand-hold low field magnet, MB cells bound with Trf-IONP can be separated from those cells without over expression of transferrin receptors.

127: An Engineered GM-CSF-CCL2 Fusokine Suppress Medulloblastoma Cell Growth in a Xeno-graft Mouse Model

Jingbo Liu, MPH, Jiusheng Deng, PhD, Shala Yuan, Jacques Galipeau, MD, Tobey MacDonald, MD

Medulloblastoma is the most common malignant brain tumor in children. Although recent advance in the clinical management of this disease, the majority of survivors still suffer from long-term side effects of radiation treatment. Chemokine CCL2 and its receptor CCR2 expression are associated with the proliferation and metastasis of several tumors including medulloblastoma. Thus, inhibiting CCL2/CCR2 axis provide an important target for anticancer drug development. We have generated a mouse GM-CSF-based fusion protein GMME1 which enclose a N-truncated CCL2 (6-76) and explored its anti-medulloblastoma therapeutic effect. Our in vitro study demonstrated that GMME1 caused a dose-dependent inhibition in growth of medulloblastoma cells, including human cell line Daoy and the mouse cell line PS125 derived from the SmoA1 transgenic mouse model of medulloblastoma. To test the responsiveness of medulloblastoma to GMME1 in vivo, we created a xeno-graft mouse tumor model by subcutaneously injecting PS125 cells into low flank of 10 week-old C57BL/6 mice. Tumor appearance and volume were monitored. One week later, the tumor bearing mice were randomly divided into 3 groups. Mouse mesenchymal stromal (MSC) cells were engineered to express GMME1 in vivo to serve as a robust recombinant GMME1 biofactories. The mice in the first group (n=10) received i.p. injection of 2×10^6 MSC-GMME1 cells suspended in 200ul PBS as a treatment group. The second group of mice (n=10) received the same amount of MSC cells without GMME1 expression as a MSC control. The third group mice (n=3) received 200ul of PBS as another control. The mouse body weight and the tumor progression were monitored every other day. The results showed that the tumor volume increased significantly in the two control groups compared with MSC-GMME1 treatment group ($P < 0.02$). And there is no difference in tumor volume increase between the two control groups ($P > 0.05$). The GMME1 expression levels in the mice circulation were negatively correlation with the tumor size, the Pearson correlation coefficient is -0.735 ($p < 0.01$). In conclusion, the MSC-GMME1 is an effective treatment in suppression of mouse medulloblastoma in vivo. It can significantly delay the tumor progression. The results provide valuable data in supporting the further study for MSC-GMME1 as a potential anti-cancer agent in the treatment of medulloblastoma.

128: Molecular Components Of The Insulin/Insulin-Like Growth Factor-1 Signaling Pathway Are Highly Expressed By Airway Neutrophils In Cystic Fibrosis And Cystic Fibrosis-Related Diabetes

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Background: Insulin and insulin growth factor-1 (IGF-1) are potent hormones, which, by binding to surface receptors and activating a common signaling intermediate (insulin-receptor substrate-1, or IRS-1), trigger anabolic signaling in the liver, pancreas, muscle and bone. Both hormones have also been found to modulate inflammatory cell function. In cystic fibrosis (CF) and its adult complication, CF-related diabetes (CFRD), insulin and IGF-1 levels in the systemic compartment are respectively low and very low, consistent with the poor metabolic status of these patients. Interestingly, airway epithelial cells can release IGF-1 and we recently found that CF airway neutrophils undergo anabolic reprogramming, suggesting a potential role for insulin / IGF-1 signaling in this compartment.

Methods: We used flow cytometry to characterize surface insulin and insulin-like growth factor-1 receptors (IR and IGF-1R, respectively) and intracellular IRS-1 levels in blood and airway neutrophils from CF and CFRD patients (N=6 and N=7, respectively), as well as in blood neutrophils from healthy controls (HC, N=8). CF and CFRD patients were assessed at steady-state (SS) and during acute pulmonary exacerbations (APE). In addition, blood neutrophils from HC, CF and CFRD subjects were activated by various agents promoting degranulation, to investigate whether IR and IGF-1R are integral components of neutrophil secretory vesicles or granules.

Results: There was no difference in surface IR, surface IGF-1R and intracellular IRS-1 levels in blood neutrophils from HC, CF and CFRD groups (the latter two, at either SS or APE). By contrast, all three components of the insulin/IGF-1 signaling pathway were markedly increased in airway neutrophils when compared to their blood counterparts, in both CF and CFRD patients (at either SS or APE). In vitro activation data suggest that surface IR and IGF-1R levels are not dependent upon exocytosis of secretory vesicles or granules (a hallmark of CF airway neutrophils), but via another mechanism.

Conclusions: Our results suggest a potential role for insulin/IGF-1 signaling in the anabolic reprogramming of CF and CFRD airway neutrophils, which may be amenable to therapeutic modulation by drugs commonly used in patients with diabetes or metabolic syndrome.

129: Fetal Loss Rates, Maternal Age Dynamics and Optimal Risk Cutoff Values for Prenatal Screening Strategies for Down Syndrome

Turgay Ayer, PhD; Pinar Keskinocak, PhD; Jia Yan, MS

Introduction: Down syndrome (DS) is the most common type of chromosomal abnormality. While numerous screening strategies are available, there exists no consensus on the optimal strategies. Moreover, detection and false-positive rates of a given screening strategy significantly depend on the risk cutoff values. Risk cutoff values are selected based on the tradeoff between undetected DS pregnancies and fetal losses of normal babies. We explored the impacts of changing procedure-related fetal loss rate of diagnostic tests and maternal age distribution on optimal risk cutoff values. **Materials and Methods:** We formulated a constrained nonlinear optimization model over 100,000 singleton pregnancies and solved for optimal risk cutoff values of integrated screening strategy. In particular, the optimal risk cutoff values were chosen to maximize the number of detected DS pregnancies minus the number of normal fetal losses due to diagnostic tests. Our model considered procedure-related fetal loss rate, changing maternal age distributions over years and age specific prevalence. The measured outputs included DS detection rates, false positive rates, number of false negatives and number of procedure-related normal fetal losses. **Results and Discussion:** Our results showed that procedure-related fetal loss rate and age distribution had significant impacts in determining the optimal risk cutoff values of prenatal screening strategies for DS. As procedure-related fetal loss rate decreased from 1.5% to 0.5%, optimal risk cutoff value decreased from 1/85 to 1/202 (years 2008-2010). In addition, considering the maternal age distributions in 1999 and 2008-2010, the optimal risk cutoff value increased from 1/119 (year 1999) to 1/116 (years 2008-2010). **Conclusion:** Population dynamics change recently and advanced age pregnancies become more common. In addition, procedure-related fetal loss rate has been decreasing over years due to advances in medical technology. When designing prenatal screening processes, decision makers need to take these trends into account. Our research provides a modeling framework to choose best risk cutoff values. Our findings suggest that the optimal risk cutoff values of prenatal screening strategies need to be adjusted based on changes in procedure-related fetal loss rates and maternal age.

130: Curing HIV by Engineered Nuclease Excision of the Integrated HIV Provirus

Paul Spearman, MD; Gang Bao, PhD; and TJ Cradick, PhD

INTRODUCTION: There is a great need to develop curative therapies for HIV. Worldwide, 3.4 million children are living with HIV, with 390,000 children are newly infected each year. For each infected child, HIV represents a lifelong illness requiring continuous treatment with antiretroviral drugs, unless a cure can be found. Conventional approaches to curing HIV typically rely on the identification, activation, and clearance of infected target cell populations. These efforts are quite promising, but require the death of each infected cell. **MATERIALS AND METHODS:** We are developing a paradigm-shifting approach to treat HIV using gene targeting with TAL effector nucleases (TALENs) to cure infected cells. Binding of a TALEN pair to a specific region of the HIV viral genome generates a DNA double-strand break (DSB). Mis-repair of the DSB leads to the destruction of the function of the HIV sequence. TALEN pairs targeting sites in the pair of HIV LTRs (Long Terminal Repeats) can cleave the target sites in each LTR, leading to excision the proviral DNA. Our approach seeks to completely excise the DNA provirus from infected cells, resulting in a cure at the cellular level instead of the death of each infected cell. The challenges are to develop the specific nucleases to remove or inactivate integrated HIV proviruses, and delivery to the appropriate target cells. HIV sequences were aligned to determine relatively conserved regions of the HIV LTR regions that are the optimal TALEN target sites. We engineered and characterized an LTR-specific TALEN pair. **RESULTS AND DISCUSSION:** Artificial plasmid targets were constructed and used for nuclease validation experiments. Bioinformatic techniques were employed to identify putative off-target sites that will be assayed for cleavage and mis-repair in cultured cells that express the TALENs. The left and right members of the TALEN pair were engineered, cloned and verified. The TALEN pair cleaved their target sites with high activity in the single-strand annealing assay in cultured HEK293 cells. Constructs are now being generated with the flanking proviral DNA replaced by reporter DNA that facilitates detection of the cells that have had DSB at two LTR sequences, and tested in cell culture assays. **CONCLUSIONS:** Cure of HIV may require a number of approaches. We have developed TALENs that can cleave out the integrated provirus, and are adapting this technology for application in animal models and future studies in humans.

131: Whole Exome Sequencing Uncovers Rare Variants Within a GWAS Loci In Two Different Ethnic Groups With Early-Onset IBD

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Inflammatory Bowel Disease (IBD) is a chronic disorder with significant morbidity. IBD is heritable in large part and genome-wide association studies (GWAS) have identified ~163 susceptibility loci for IBD, containing at least 301 genes of interest. However, the effect sizes of nearly all of these loci are relatively small, with odds ratios <1.5 and accounting for only ~20% of the estimated heritability. This lead us to hypothesize that, rare variants with moderate to large effect contribute to IBD susceptibility. We predicted that the genes within the ~163 IBD associated loci may be enriched for rare variants at evolutionarily conserved sites. To test this hypothesis, we performed whole-exome sequencing (WES) on 73 European ancestry (EA) and 29 African ancestry (AA) individuals with very early-onset IBD. The WES data was very high quality, with greater than 100X of average sequence coverage. WES analysis of 73 EA IBD cases identified 34,228 replacement single nucleotide variants (SNVs) and 2,291 exonic indels. Quality filtering and annotation with SeqAnt revealed that 6,005 exonic SNVs were novel (not present in dbSNP137). To orthogonally replicate IBD GWAS findings, we focused our analysis on the 301 key genes reported within the 163 IBD associated loci. Within these 301 genes, we observed 484 exonic SNVs, 97 of which were novel. By selecting SNVs at evolutionarily conserved sites and predicted to be damaging by in silico algorithms, we shortlisted 17 candidate variants (15 missense and 2 nonsense SNVs). Among these of most significant importance was a nonsense mutation at the FUT2 locus (Q166*), a gene previously identified in a IBD GWAS. WES analysis of 29 AA IBD cases identified a total of 33,787 replacement SNVs and 4,399 exonic indels. Using the same selection criteria as stated above, we found a total of 13 candidate variants (8 missense, 4 nonsense and 1 stop loss SNV). Surprisingly, in this population also we discovered another nonsense mutant in the gene FUT2 (R231*). Thus, our discovery of a two rare nonsense mutations in the FUT2 gene provides an orthogonal replication of the IBD GWAS finding. Furthermore, the FUT2 locus now becomes a far more interesting candidate for functional assays and will be followed up in future collaborative studies.

132: Early Vocal Development in Infants At Risk of Autism: Prosodic Development, Social Interaction, and Outcome

Kristin Muench; Shweta Ghai, Ph.D.; Ami Klin, Ph.D.; Gordon Ramsay, Ph.D.

Introduction: Autism is a neurodevelopmental disorder of early onset defined by core deficits in social communication and restricted repetitive behaviors. Deficits in receptive and expressive prosody are key symptoms of autism, but the origin and nature of these deficits remain unknown. Prosodic interactions between infant and caregiver help scaffold spoken language acquisition in the first year of life, so early derailment of the production and perception of prosody in autism may impact typical language development. The goal of this study is to explore the potential of prospective longitudinal measures of early vocal behavior to inform clinical diagnosis of autism. We test the hypothesis that abnormal development of intonational interactions is predictive of later outcome. **Materials and Methods:** Using a miniature recording device (LENA Foundation), we collected day-long audio recordings from infants in their home environment at monthly intervals from 2 to 24 months of age. We then collected a battery of clinical assessment measures from each child at age two to establish clinical diagnosis. At each time point, we calculated three measures of prosodic development for sequences of utterances: the fundamental frequency contour, utterance duration, and relative timing between infant and caregiver vocalizations. Using Functional Data Analysis, we compared developmental trajectories for these measures with differences in clinical outcome measures. **Results and Discussion:** Our final sample consisted of 4 typically developing children (TD), 2 children diagnosed with a language delay (LD), and 2 children diagnosed with broader autism phenotype (BAP). Group differences in prosodic measures predicted categorization into TD and non-TD groups as determined by clinicians. However, prosodic measures alone were not sufficient to distinguish between LD and BAP subgroups in our present sample. **Conclusions:** Preliminary results suggest that TD and non-TD infants differ in acoustic measures of prosodic development. However, these measures alone appear insufficient to discriminate between children with language delay and children with broader autism phenotype. **Impact:** This work describes how prosodic measures, by indexing social attunement between infant and caregiver prior to age two, could improve clinical evaluation of developmental disorders. This work is supported by NIMH (P50MH100029), Simons Foundation, Marcus Foundation, and the Whitehead Foundation.

133: Efficient Strategies for Teaching Receptive Language to Students with Autism: Observational Learning and Incidental Teaching

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Over the past 30 years autism related research has become increasingly more focused on observational learning. One-on-one instruction is often the prescribed teaching model for children with developmental disabilities. However, this arrangement is not always feasible. As the prevalence of autism is on the rise, there is an increasing need for efficient teaching strategies that capitalize on available resources. The present study investigated if receptive language targets were acquired by way of three instruction methods used in a dyad teaching arrangement. For the purposes of this study instructive feedback was defined as nontarget information presented consistently following instructional trials. Observational learning was defined as learning that occurred as a result of observing, retaining, and replicating another's behavior. In this study two young boys with developmental disabilities participated in structured teaching sessions that incorporated observational learning opportunities and instructive feedback. The participants were explicitly taught separate receptive identification targets in dyad style teaching sessions. Additional information regarding features, the function, or class of the target was provided through instructive feedback but not explicitly taught. Probes were conducted prior to each teaching session to assess acquisition of the explicitly taught targets, the information provided through instructional feedback and the other participant's targets. Both participants acquired 100% of the targets that were taught through explicit teaching, and 100% of the information provided through instructional feedback and observational learning. Results suggest that observational learning and instructive feedback can be effective strategies for teaching novel receptive language skills. Incorporation of these teaching strategies in clinical and classroom settings may increase the efficiency of existing teaching methods for both typically developing children and children with developmental disabilities.

134: Efficient Strategies for Teaching Students with Autism: Observational Learning and Incidental

Hannah Robinson, BS; Caitlin H. Delfs, PhD, BCBA-D; Daniel Conine, BCaBA

Observational learning within the autism population has been a focus of research for over 30 years (Varni, Lovaas, Koegel, & Everett, 1979; Egel, Tryon & Kean, 1986). Previous research has shown that students diagnosed with developmental disabilities can acquire new skills through observation of peer learning (Schuster, Gast, & Wolery, 1988). One-on-one instruction is commonly recommended for children with autism, but does not provide opportunities for learning from peers. Incidental learning is the acquisition of nontarget information for which there are no programmed contingencies to aid in acquisition (Stevenson, 1972). Incorporating such information into structure teaching strategies constitutes another potentially efficient teaching strategy. The current study examined whether listener and tact object identification responses were acquired via four methods of instruction within a small group format: direct constant time delay teaching, observational learning, incidental teaching, and observation of incidental teaching. Participants include four children diagnosed with autism, ages five, eight, nine, and sixteen. Current results indicate varied rates of acquisition across participants and across the four teaching methods evaluated. For one participant, verbal instruction to attend to peer responding mediated acquisition of peer targets. Implications for clinicians and educators, as well as areas of future research, are also included.

135: Social Determinants of Community Associated Methicillin Resistant Staphylococcus aureus (CA-MRSA) Infections in Children

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Background: CA-MRSA infections continue to increase in children. Population based studies suggest health disparities may exist for invasive MRSA infections. Household crowding has been suggested as a risk factor for CA-MRSA infections. Geographic information system (GIS) tools and geo-spatial modeling are effective ways to map disease conditions. Purpose: To determine if socio- environmental factors such as housing conditions and household crowding are associated with Community Associated Methicillin Resistant Staphylococcus aureus (CA-MRSA) and non resistant CA-Staphylococcus aureus (CA-MSSA) infections in children using geographic information system (GIS) tools. Design Methods: Case control study identifying children who had S. aureus infections from two pediatric hospitals. Patients' addresses were geocoded and then clustering and spatial patterns were determined between CA-MRSA (cases) and CA-MSSA (controls) using ArcGIS10 software. Data on social

determinants such as income, race, and housing conditions were obtained from the US Census. Primary data collected included demographic, medical, and laboratory information. Results: From 1,029,355 *S. aureus* cultures, 6,206 unique patients were identified of which the addresses of 5,554 were successfully geo-coded. The number of MRSA infections has increased in children from 2002-2006, with CA-MRSA increasing at a more dramatic rate. Black children were 2.38 times more likely to have CA-MRSA infections compared to White. Race, previous hospital visits, history of chronic illness, and public insurance were associated with CA-MRSA infections, $p < 0.01$. Clusters of cases were seen for both, but were more intense for MRSA compared to MSSA controls. Poverty, determined using income data, was significantly associated with CA-MRSA infections. Conclusion: CA-MRSA infections have continually increased in Atlanta from 2002-2006. Socio-economic factors affect the risk of MRSA infection in children seeking care from pediatric hospitals in Atlanta. Racial disparities also exist in the risk associated with MRSA. Spatial analysis, using GIS is an effective way of looking at social determinants related to MRSA infections.

136: Quantifying Social-Communicative Function in ASD Via a Structured Social Attribution Task

Rebecca Burger-Caplan, BA; Warren Jones, PhD; Ami Klin, PhD

BACKGROUND: With coming changes to the DSM characterization of Autism Spectrum Disorders (ASD), there is renewed need for clinically valid quantification measures of the disability. Individuals with ASD exhibit great difficulty in social cognitive tasks that require intuitive social understanding of ambiguous stimuli. Capitalizing on Heider & Simmel's (1944) classic animation, in which geometric shapes enact a social story, we previously quantified spontaneous narratives given after viewing the cartoon. High-functioning adolescents with ASD demonstrated significant social attribution deficits, not apparent in more traditional, explicit tests of social and mental state attribution, relative to matched controls (Klin, 2000). However, this procedure required laborious coding and was impractical for more expansive usage. In this study, we tested the clinical utility of a simplified procedure, the Social Attribution Task–Multiple Choice (SAT-MC), in which multiple-choice questions are presented following viewing of the animation, to assess differential predictive power of this task relative to social-communicative adaptive function, independent of verbal skill. **METHODS:** The task was administered to children with ASD, characterized by standardized diagnostic procedures ($N=23$; Age 4.5 to 12 years; VIQ 62 to 146), and to typically developing (TD) children, matched on chronological age and Verbal IQ ($N= 57$). Adaptive skills were assessed with the Vineland Adaptive Behavior Scales. Correct answers on 19 items yielded a global SAT-MC score. **RESULTS:** SAT-MC performance differed significantly between ASD and TD groups. Task scores positively correlated with age ($r=0.47$) and were not related to VIQ ($r=0.24$), indicating a developmental process and independence from verbal ability. SAT-MC scores strongly correlated with Vineland Communication ($r=0.46$) and Socialization ($r=0.48$) standard scores but not with Vineland Daily Living ($r=0.12$). The strong correlation with social adaptive skills suggests differential predictive utility of the measure, relative to the unrelated construct of Daily Living Skills. **CONCLUSIONS:** The SAT-MC discriminated a heterogeneous group of children with ASD from matched controls, and differentially predicted social adaptive skills independently from verbal ability. This initial study corroborates previously demonstrated deficits in social attribution and holds promise for quantification of skills essential for successful adaption in real life.

137: Disposition Index detects abnormal glucose homeostasis earlier than Oral Glucose Tolerance testing in Cystic Fibrosis.

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Background: The gold standard for diagnosis of cystic fibrosis related diabetes (CFRD) is oral glucose tolerance testing (OGTT). There is evidence that abnormalities in glucose homeostasis in cystic fibrosis (CF) start before detection by OGTT. The disposition index (DI) is a measure of pancreatic Beta cell function (insulin secretion) adjusted for insulin sensitivity. In one study done in healthy adults, DI was shown to be abnormal well before the OGTT became abnormal in those who later developed type 2 diabetes. We hypothesized that the DI would be abnormal in CF patients with a normal OGTT, indicating subtle beta cell dysfunction. Furthermore, the DI would worsen with progression from CF with normal glucose status to CFRD. In order to test this hypothesis, we first had to assess the validity of the DI by demonstrating that a hyperbolic relationship existed between insulin sensitivity and insulin secretion. **Methods:** 39 CF patients (14 Normal glucose tolerance (NGT), 20 impaired glucose tolerance (IGT), 5 CFRD) and 21 healthy controls (Con) (14 NGT, 7 IGT) underwent OGTT. Insulin and glucose levels were measured before, 30 min and 2 hrs after glucose ingestion. Insulin sensitivity was estimated as $1/\text{fasting insulin}$.

Insulin secretion was estimated as the ratio of change in insulin to change in glucose from 0 to 30 min ($\Delta I_{0-30}/\Delta G_{0-30}$). DI was calculated as $1/\text{fasting insulin}$ multiplied by ($\Delta I_{0-30}/\Delta G_{0-30}$). Results: There was a hyperbolic relationship between insulin sensitivity and insulin secretion in all groups except the CFRD group (presumably due to the small sample size). Median (interquartile range) DI was: Con-NGT 3.63 (3.7); Con-IGT 2.69 (1.32); CF-NGT 1.34 (1.68); CF-IGT 0.96 (0.91); CFRD 0.33 (0.73). DI was significantly lower in CF-NGT compared to Con-NGT ($p=0.0035$), supporting our hypothesis that DI is abnormal in CF despite normal glucose values. DI was lower in CFRD compared to CF-NGT ($p=0.025$) indicating that DI worsens with progression of the disease. There was no correlation in the CF groups between DI and age, gender, percent body fat and lung function. Conclusion: This is the first study to evaluate DI in CF and we found that it can detect abnormalities in glucose homeostasis well before the OGTT. If confirmed in larger studies, earlier detection of those abnormalities through DI would allow earlier intervention and prevention of morbidities and possibly prevention of CFRD.

138: The Effect of Hypocalcaemia on the Risk of Autism Symptoms in Patients with 22q11 Deletion Syndrome

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Background: The importance of copy number variants (CNV) in complex pediatric disorders is of growing interest. 22q11 deletion syndrome (22q11DS) is a CNV disorder that has a diverse clinical presentation including congenital heart defects, palatal abnormality, immunodeficiency, hypocalcaemia, language and learning disabilities, and psychiatric disorders. Many patients with 22q11DS present with signs of Autism Spectrum Disorders (ASD), which manifest as impairments in social interaction and communication, repetitive behaviors, and idiosyncratic interests. The physiological mechanisms that link 22qDS with ASD are unknown. This study explores the influence of hypocalcaemia in 22q11DS on the risk and severity of social communication delays, which can be associated with ASD. Methods: In a retrospective cohort study testing the association of physiological variables with social and communication abilities in infants and toddlers from Children's Healthcare of Atlanta 22q11 clinic, we abstracted medical and laboratory records for the earliest and lowest serum albumin-adjusted calcium level ($n=151$). The Communication and Symbolic Behavior Scales- Developmental Profile (CSBS) was used to evaluate communication in a subset of these children ($n=37$, 6-24 months). The models controlled for age at assessment, age at calcium draw, and gender. Results and Discussion: On average, the calcium level was taken contemporaneously with CSBS. There was a significant relationship between the lowest calcium value and CSBS Social Score ($R^2=0.25$, $p=0.05$), CSBS Speech Score ($R^2=0.32$, $p=0.04$), CSBS Symbolic Score ($R^2=0.31$, $p=0.02$), and overall CSBS Total Score ($R^2=0.28$, $p=0.04$). This relationship between low calcium and deficits in CSBS was also seen at the trend level in models using the earliest calcium value ($p=0.08$ - $p=0.11$). Conclusions: Lower calcium level associates with impaired social communication development in patients with 22q11DS. Impact: Early peripheral risk factors such as hypocalcaemia may impact neuropsychological outcomes in 22q11DS patients. Calcium dysregulation affects neuroplasticity, and studies are needed to explore the influence of hypocalcaemia, and the role of calcium management, on early and later neurodevelopmental and psychiatric outcomes. Support: Emory Neuroscience Initiative, Autism Foundation of Georgia, Tal Senior, RN, (CHOA).

139: An Eye-tracking Based Diagnostic Screener for Autism Spectrum Disorders in 18- to 42-month-old Children

M. Valente; M. Ly; A. Klin; and W. Jones

Background: Mean age of diagnosis for an autism spectrum disorder (ASD) in the United States is currently later than five years of age. This late age marks the loss of a potentially critical opportunity for improving treatment efficacy and associated outcome. In addition, gold standard diagnostic evaluations usually require multiple tests proctored by an experienced clinician at specialized centers. These are not often available in either rural or disadvantaged communities, and primary care providers are hesitant to recommend such tests without being certain of initial concerns. In order to improve the efficacy of early screening, new tools yielding objective, performance-based measures of risk for autism would be highly advantageous. Past research using eye-tracking has shown evidence of strong between-group differences when comparing children with ASD to their typically-developing (TD) peers. In some cases, the eye-tracking measures have demonstrated predictive utility for measuring individual levels of social-communicative disability. In the current research, we tested the utility of eye-

tracking as a screener for ASD in 18- to 42-month-old children. Objectives: The objective of this research is to test the extent to which patterns of dynamic visual scanning in 18- to 42-month-old children, measured by eye-tracking, can serve as a screening tool, with sensitivity and specificity values above the accepted range for first-level screeners (>80% per Meisels, 1989). Methods: Eye-tracking data were collected from a large cohort of children, N = 170, 18 to 42 months of age, while they watched naturalistic video scenes of peer social interaction. Standardized clinical assessment measures (ADOS, ADI, cognitive and language testing) confirmed diagnostic status for ASD and TD children within the cohort. The first 50 consecutive referrals in the ASD group (ASD-1) were used for comparison against the TD group; these children provided a training set with which to develop a model of expected differences between ASD and TD visual scanning. We then tested the remaining ASD children (ASD-2) as an external validation sample. Receiver operating characteristic (ROC) curves were created to analyze sensitivity and specificity. Results: Preliminary results indicate robust between-group differences in visual scanning between TD and ASD-1 groups. Using this model, the remaining ASD-2 children were classified with sensitivity of 85% and specificity of 77.9%.

140: The activity of neutralizing antibodies targeting HIV-1 gp41 pre-hairpin intermediates is strongly enhanced by sub-inhibitory doses of human α -defensin in the presence of serum

Lusine Demirkhanyan, PhD, Mariana Marin, PhD, Wuyuan Lu, PhD, and Gregory B. Melikian, PhD

Human neutrophil peptide 1 (HNP-1) blocks HIV-1 entry and fusion in the absence of serum while in the presence of serum it displays attenuated anti-viral activity. This implies that HNP-1 is unlikely to directly inhibit HIV-1 infection in the bloodstream. Here, we have examined the effect of sub-inhibitory concentrations of HNP-1 on the kinetics of early steps of HIV-1 fusion with target cells in the presence of serum. Our results show that, in spite of the marginal effect on the extent of fusion under these conditions, HNP-1 can strongly enhance the activity of neutralizing antibodies and peptide inhibitors targeting transient intermediate conformations of HIV-1 gp41. Studies of the fusion kinetics combined with live cell imaging of virus uptake revealed that HNP-1 exerts this effect by slowing down the virus uptake and thereby prolonging the exposure of gp41 intermediates on the cell surface. The increased longevity of gp41 intermediates correlated with the marked enhancement of the virus' sensitivity to anti-gp41 antibodies, whereas the activity of antibodies to gp120 was not affected. Moreover, sub-inhibitory concentrations of HNP-1 sensitized the virus to neutralizing antibodies and HIV-1 immune serum in fusion experiments involving peripheral blood mononuclear cells. Thus, sub-inhibitory doses of HNP-1 potently enhance the activity of anti-gp41 antibodies and peptide inhibitors, apparently by prolonging the lifetime of gp41 intermediates. Our findings strongly suggest that HIV-1 neutralization is kinetically restricted and reveal an important role of α -defensin in enhancing adaptive immune responses to infection. This work was supported by the NIH R21 AI087453 and R01 GM054787 grants to GBM.

141: Arginase-1 and Programmed Death Ligand-1, Potent Inducers of Immune Tolerance, are Upregulated on Airway Neutrophils in Cystic Fibrosis

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Introduction: A long-standing paradox in cystic fibrosis is the chronic presence of viruses, bacteria and fungi in conjunction with high numbers of live neutrophils in the lung. We hypothesized that CF airway neutrophils may express molecules that induce tolerance and dampen the immune response to airway pathogens. Therefore, in the current study, we determined the expression of potential immunomodulating markers on CF airway neutrophils in order to better understand the role of neutrophils in CF disease pathology. Methods: Levels of arginase-1, indoleamine 2,3-deoxygenase (IDO) and programmed death ligand-1 (PDL-1) were quantified on live neutrophils from blood and sputum of CF patients using flow cytometry. Additionally, an ELISA specific for soluble PDL-1 was used to quantify PDL-1 levels in plasma and airway fluid from CF patients and healthy control plasma. Results: We found that arginase-1 and PDL-1 levels were significantly increased on the surface of airway neutrophils compared to blood neutrophils. IDO was not detectable in neutrophils from either the blood or sputum. We observed two distinct populations of PDL-1 expressing neutrophils; one subset expressed high levels of PDL-1, while the other subset expressed lower levels of PDL-1. We hypothesized that PDL-1 may be cleaved from the surface of airway neutrophils by proteases present in the CF airway fluid; therefore, we compared levels of soluble PDL-1 in plasma and airway fluid. We found that soluble PDL-1 levels in the plasma were not significantly different in CF patients compared to healthy controls; however, soluble PDL-1 was significantly increased in airway fluid

compared to plasma in CF patients. Conclusions: Our results suggest that upon entering CF airways, neutrophils upregulate molecules that may induce tolerance, either directly through cell-cell contact or remotely through mediators released in the extracellular fluid. Thus, the persistence of pathogens in CF airways may stem from active tolerance by live neutrophils rather than neutrophil death as once believed, which is an important consideration for the development of targeted CF treatments.

142: Emotional and Behavioral Symptoms of Children and Adolescents with 22q11 Deletion Syndrome

A. Nichole Evans, BA and Opal Ousley, PhD

Background: 22q11 deletion syndrome (22q11DS), also known as DiGeorge Syndrome or velocardiofacial syndrome, occurs in approximately 1/4000 live births, and results in a diverse range of medical, cognitive, behavioral and social impairments (Bassett et al., 2011). Although 22q11DS is known to associate with adverse mental health adult outcomes, including schizophrenia, we do not fully understand the childhood manifestations of this disorder. This study investigated parental report of a broad range of psychological symptoms in children with 22q11DS recruited from the Children's Healthcare of Atlanta. We predicted that these children would manifest clinically significant social, thought, and attention problems. **Methods:** We examined the emotional and behavioral symptoms for 23 children with 22q11DS (age range = 6.2 to 11.9 years; M = 9.64, SD = 1.92). 22q11DS status was confirmed by fluorescent in situ hybridization (FISH). The study group was comprised of 48% (n = 11) females and 52% (n=12) males, with five racial/ethnic groups represented. Parents completed the Child Behavior Checklist (CBCL), which yields factor-analytically derived symptom scores, internalizing, externalizing, and total problems summary scores, and DSM-related domain scores. **Findings:** Fifty percent (50%) of the children met or exceeded borderline clinical T-scores for total problems and DSM-affective problems; between 30% and 49% met or exceeded borderline clinical T-scores for thought, attention, internalizing, externalizing, DSM-anxiety, DSM-ADHD, and DSM-conduct problems; and between 10% and 29% met or exceeded borderline clinical T-scores for anxious/depressed, withdrawn/depressed, somatic complaints, rule-breaking and aggressive, DSM-somatic, and DSM-oppositional defiant problems. No CBCL subscale had fewer than 10% of our participants scoring at the borderline clinical level. We also identified a subgroup of children with elevated thought problem scores. **Conclusions:** Overall, our results reveal that clinically significant symptoms are present in school-age children with 22q11DS, especially for the CBCL total problems and the DSM-affective problems domains, and, possibly, a subgroup of children with emerging thought problems can be identified based on parent report. By tracking these symptoms across time we may be able to identify those children with 22q11DS who are at increased risk for psychopathology, especially schizophrenia-related disorders.

143: Antagonism of Innate Immunity by the Respiratory Syncytial Virus Nucleoprotein

Lifland, AW; Jung, J; Alonas, E; and Santangelo, PJ

Introduction: Human respiratory syncytial virus (hRSV) is the most important etiologic agent of pediatric viral respiratory disease. Currently, there are few drugs for hRSV infections, and a vaccine is not currently available. Our overall hypothesis is that through the investigation of the spatial biology of hRSV, we will identify virus-specific drug or vaccine targets. To date, few studies have explored the changes in localization of innate immune molecules in response to hRSV. Therefore, our working hypothesis is that during an hRSV infection, the creation of subcellular viral structures will alter the localization of innate immune components in order to antagonize the interferon response. **Results:** In this investigation, we found that both RIG-I and MDA5 colocalized with viral genomic RNA and the nucleoprotein (N) as early as 6 hpi. By 12 hpi, MDA5 and MAVS were observed within large viral inclusion bodies (IB). Using proximity ligation assays and immunoprecipitation, we determined that the N was in close proximity to MDA5 and MAVS in IBs during the infection and even when only N and P were coexpressed. Additionally, we found that the localization of MDA5 and MAVS in IBs inhibited interferon β mRNA expression 27-fold following NDV infection. From this, we concluded that the N likely interacts with MDA5, is in close proximity to MAVS, and localizes these molecules within IBs to attenuate the interferon response (Lifland et al, JVI, 2012). **Materials and Methods:** Virus: human RSV A2 and NDV LaSota. RNA imaging probes: MTRIPS delivered with SLO to identify viral genomic RNA. Cells: A549, HEp-2, Vero, and HeLa cells. Proximity ligation assays (PLA). PLA detection was used to detect hRSV N interactions with RIG-I, MDA5, and MAVS in situ. Immunostaining, IP and Western blotting: standard procedures. Imaging: widefield and confocal fluorescence imaging were performed. **Conclusions and Impact:** To our knowledge, this is the first report of hRSV IBs and the N protein as a modulator of interferon. This discovery coupled with the identification of the protein-protein interface between N and MDA5,

could lead to the development of small molecule inhibitors that assist in the rescue of interferon, preventing severe disease. In addition, if recombinant vaccine strains are to be developed, identifying nucleoprotein sequences that allow for virus rescue, but lack the ability to antagonize MDA5, will be vital to tuning the immune response of a vaccine strain.

144: Quantifying Post-Transcriptional Gene Regulation in situ during Cancer Pathogenesis

Jeenah Jung; Aaron W. Lifland; Chiara Zurla, PhD; and Philip J. Santangelo, PhD

Introduction: Deregulation of gene expression contributes to cancer pathogenesis. Alterations in trans-acting factor binding to mRNA affect the stability and translational efficiency of mRNAs encoding proto-oncogenes, cytokines, and other regulatory proteins to promote tumorigenesis, cancer progression, and chemotherapy resistance. Therefore our overall hypothesis is that by developing methods to identify aberrant RNA-protein interactions: 1) new interventions can be developed to prevent these complexes from forming, and 2) these methods can be used to identify drug-resistant tumors from biopsies prior to drug selection. Our working hypothesis is that by combining modified single RNA sensitive imaging probes and proximity ligation assays (PLA), we can detect RNA-protein interactions with single molecule sensitivity within the cellular milieu (Jung et al., *Nucleic Acids Research*, 2013). **Results:** To visualize and quantify RNA-protein interactions in situ, we developed a PLA that combined FLAG peptide-modified, multiply-labeled tetravalent RNA imaging probes (MTRIPs), targeted to sequences near RBP binding sites, with proximity ligation and rolling circle amplification (RCA). Using this method, we detected and quantified, with single-interaction sensitivity, the interactions of HuR with native β -actin mRNA, native poly(A)+ mRNA, and plasmid-derived GFP-myc mRNA at both native and increased HuR expression levels and under the effects of actinomycin D. HuR was interrogated because it effects the expression of many important cancer related genes, such as Myc, Fos, COX2, VEGF, and cyclins, as well as being implicated in hematopoietic malignancies (Baou et al., *Blood*, 2011). **Materials and Methods:** mRNA probes: tetravalent chimera antisense RNA imaging probes modified with Flag peptide against polyA+, β -actin, and GFP-myc mRNA. Plasmids: Drugs: Actinomycin D (Sigma). Cells: HeLa cells. Proximity ligation assays (PLA). PLA detection was used to detect polyA+, β -actin, and GFP-myc mRNA interacting with HuR in situ. Imaging: fluorescence microscopy. **Conclusions and Impact:** Using this technology, we are able to characterize RNA regulation events in cellular models of tumor progression, and in the future, within clinical biopsy samples. From this characterization we hope to identify new targets for therapeutic development and possibly gain insight into mechanisms that may make tumor cells refractory to chemo and radiation therapy.

145: Characterizing Adhesion Protein Expressions and Conformations On Site-Derived Neutrophils in Cystic Fibrosis Patients

Prithviraj Jothikumar; Sergey Pryshchep, PhD; Rabindra Tirouvanziam, PhD; Nael McCarty, PhD; and Cheng Zhu, PhD

INTRO Cystic Fibrosis (CF) is the most common life-shortening recessive genetic disorder among Caucasians in the United States. These patients are most susceptible to respiratory failure following progression of lung disease. There are indications of a defective innate immune system as seen by the ineffective clearance of pathogens, more specifically, impaired activity of neutrophils in the lung. The mechanism as to why neutrophils fail to effectively clear pathogens is not yet known. The present study focuses on characterizing site-derived neutrophils from CF patients by observing a panel of surface adhesion proteins involved in neutrophil rolling and extravasation. **MATERIALS & METHODS** We analyzed neutrophils by multi-color flow cytometry using a panel of antibodies directed against key adhesion proteins (L-selectin, Mac-1, and LFA-1). In addition to observing the total expression of LFA-1, we also analyzed the different conformations of β 2 integrins (bent vs. extended, hybrid domain in vs. out, α A domain with low vs. high affinity states). Neutrophils were purified from the peripheral blood of both non-CF and CF human subjects. In addition, neutrophils of CF subjects were purified from bronchoalveolar lavage (BAL) fluid. **RESULTS & DISCUSSION** We found no significant differences of the expression level of all the key adhesion proteins on neutrophils purified from peripheral blood between non-CF and CF subjects. We observed significance when comparing neutrophils obtained from BAL to blood in CF subjects. We saw ~1.5-fold increase in the expression level of LFA-1 using monoclonal antibody TS1/22 on neutrophils from the BAL when compared to blood. In addition, the expression level of LFA-1 in the bent state was found to be less and the expression level of LFA-1 in the extended state was found to be high on neutrophils from the BAL when compared to blood. This was not reported before in CF as it physiologically important for the LFA-1 to be at an extended state, indicating higher

affinity to bind to its ligand, thus enabling neutrophils to be recruited at the site of infection. Low expression of L-selectin and high expression of Mac-1 was found on neutrophils from BAL compared to blood, indicating neutrophil activation upon entering the site of infection. **CONCLUSION** In summary, the current study characterizes the different states of LFA-1 and the total expression of various adhesion proteins found on neutrophils derived from different sites in CF patients.

146: Functional Interaction of Hereditary Spastic Paraplegia-Linked Protein Complexes

Pearl V. Ryder; Rachel Vistein; Avanti Gokhale, PhD; Matthew N. Seaman, PhD; Manojkumar Puthenveedu, PhD; and Victor Faundez, MD, PhD

Introduction: Neuromuscular diseases are a leading cause of disability in children. The hereditary spastic paraplegias (HSP) are one cause of neuromuscular dysfunction in pediatric and adult populations. HSP arises from degeneration of axons projecting to the spinal cord from the brain motor cortex. More than 50 genetic loci are linked to the disease in humans and within an HSP subtype, age of onset and symptoms are highly variable, suggesting complex pathogenic mechanisms. We hypothesized that at least some of the gene products of HSP loci would form protein networks and participate in the same biological pathways. To test this hypothesis, we focused on a protein disrupted in a mouse model of HSP, the membrane lipid kinase PI4KII α . PI4KII α interacts with and regulates the BLOC-1 and AP-3 complexes, which are vesicular coat complexes that traffic cargo from early endosomes to lysosomes, lysosome-related organelles, and synaptic vesicles. **Methods:** We immunoaffinity purified PI4KII α from isotope-labeled cell lysates, which allowed for the quantitative identification of interactors by mass spectrometry. We validated several interactors by independent purifications followed by immunoblotting. We then characterized a functional interaction by biochemical fractionations, high-resolution deconvolution microscopy, live cell spinning disc confocal microscopy, and cell surface labeling and pulldown. **Results:** Strikingly, PI4KII α isolation co-enriched proteins that are genetically linked to peripheral motor nerve degeneration (Charcot-Marie Tooth disease, dynamin-2; distal motor neuropathy, ATP7A) and central motor nerve degeneration, including proteins linked with infantile-onset (alsin) and adult-onset hereditary spastic paraplegia (strumpellin). We focused on characterizing interactions between PI4KII α , the BLOC-1 complex, and strumpellin, a component of an Arp2/3 activator known as the WASH complex. Strumpellin depletion led to changes in PI4KII α endosomal morphology and mis-localization of the BLOC-1-sensitive cargoes PI4KII α , ATP7A, and VAMP7. **Conclusions:** We conclude that PI4KII α and strumpellin, two proteins independently implicated in the pathogenesis of hereditary neurodegeneration, interact and regulate the BLOC-1 vesicular trafficking pathway. Importantly, this pathway delivers components to the nerve terminal, suggesting that disruption of this delivery mechanism may contribute to the pathogenesis of hereditary spastic paraplegia.

147: Cancer SurvivorLink(TM): Predictors of Successful Web Based Storage and Sharing of Healthcare Documents

Rebecca Williamson, MPH; Lillian Meacham, MD; Brooke Oakley-Cherven, RN, MPH; Paula Edwards, PhD; and Ann Mertens, PhD

INTRODUCTION: Early detection and treatment of late effects among pediatric cancer survivors requires life-long surveillance by a team of primary and specialty providers. Cancer SurvivorLinkTM (CSL), www.cancersurvivorlink.org, is a secure website where survivors can electronically store and share documents with their healthcare providers. This analysis determined the predictors of successful storage and sharing of documents using CSL. **MATERIAL AND METHODS:** All survivors who registered between October 2010 and January 2013 were included. A registration wizard was added in June 2012 to improve usability. Metrics obtained from CSL include: registrant date and type (parent vs. survivor), storage of a document in an e-Chart, and sharing the e-Chart with a provider. Recruitment method (mail, community event, clinic or other) was tracked. Demographic information was obtained from survivors who have attended survivor clinic. Logistic regression was used to determine if recruitment method, registrant type, clinic attendance, survivor's race/ethnicity and use of the wizard predicted storage and sharing of healthcare documents. **RESULTS AND DISCUSSION:** Of the 275 registrants, 66.9% created an e-chart and 30.5% stored a health document. Those recruited from clinic were more likely to have a document uploaded (48.5%) compared to recruitment by mailing (14.3%; $p=0.005$), community event (30.4%; $p=0.50$), or other method (17.5%; $p=0.46$). Document storage was more likely for those who had attended clinic (38.5% vs. 3.2%, $p=0.001$), used the wizard (42.7% vs. 25.4%, $p=0.04$) and whites as compared to blacks (41.9% vs. 24.0%; $p=0.05$). There was no difference between registrant types. Of those who stored a document, 21.4%

have shared with a provider. Survivors who registered prior to the wizard were more likely to have shared (28.6% vs. 11.4%, $p=0.04$), likely because they have been registered longer (15.3 ± 6.8 months vs. 11.6 ± 6.8 months; $p=0.05$). Survivors as compared to parent registrants (32.0% vs. 16.9%; $p=0.12$) and those ever having been to clinic (22.0% vs. 0.0%; $p=0.99$) have also shared more. There was no difference among recruitment types and race/ethnicity. **CONCLUSIONS AND IMPACT:** Survivors who attended clinic are more likely to store and share health documents via CSL. Many survivors must advocate for their survivorship care and educate their providers about their health risks. CSL helps to increase awareness and communication, improving coordinated care.

148: Microinjection-Based Delivery of β -Globin-Targeting TALENs Into K562 Cells for Gene Modification

R.N. Cottle; D. Archer, PhD; and G. Bao, PhD

Introduction: Sickle cell disease (SCD) is a major cause of global mortality and health disparities. Bone marrow transplantation is the only cure for SCD, but has limited clinical applicability. A novel approach to treating SCD involves the simultaneous delivery of transcription activator-like effector nucleases (TALEN) specifically targeting the mutant β -globin gene and a donor template DNA to induce correction of the sickle cell mutation in hematopoietic stem cells (HSC). Subsequent engraftment of gene corrected HSCs will replace sickled cells with healthy RBCs. Previous studies use lentivirus and nucleofection to deliver multiple vectors into cells; these approaches have significant drawbacks. An alternative approach for delivering β -globin-targeting TALENs and donor template DNA into HSCs is microinjection. As proof-of-concept, the focus of this work is to quantify viability and TALEN induced on- and off-target activity in K562 cells microinjected with β -globin targeting TALENs. **Methods:** K562 cells, a hematopoietic cell line, are microinjected with different amounts of β -globin targeting TALEN DNA, mRNA, and purified protein on a recombinant fibronectin matrix. Microinjected K562 cells are seeded at a limiting dilution in 96-well plates and expanded into large colonies of cells with TALEN induced β -globin gene disruptions. The genomic DNA is extracted from colonies and subjected to the Cel-I assay to quantify NHEJ activity in the β - and δ -globin gene loci. **Results:** We show that microinjection lowers K562 cell survival and delays proliferation. The cell doubling time is 20 and 30 hours for control and cells injected with dextran respectively during the first 48 hours in culture. K562 cells injected with TALENs are capable of expansion into large colonies from a single cell, albeit a lower frequency compared to control cells. In initial experiments, 37.6% of K562 cells injected with TALEN encoding plasmids compared to 53.1% of control cells formed colonies from single cells in a 14-day culture. The results suggest dose dependent toxicity of TALEN DNA plasmids in injected cells. We also find a correlation between the frequency of TALEN induced NHEJ and the plasmid DNA concentration injected. On-going work will investigate the frequency of NHEJ in K562 cells injected with different amounts of TALEN mRNA and protein. The results from the completed study will inform the concentration and form of TALENs to inject into cells for gene correction.

149: HLA Associations in Oligo- and Polyarticular RF (-) JIA-associated Uveitis

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Purpose. Juvenile idiopathic arthritis-associated uveitis (JIA-U) can lead to complications such as cataracts and glaucoma, and increase risk for vision loss and blindness. Studies show an association between polymorphisms of HLA class II genes and JIA-U, especially in females with oligoarticular JIA and early disease. While HLA-DR11 and HLA-DR13 alleles increase susceptibility to disease, HLA-DR1 is protective. Most studies have not included children with polyarticular rheumatoid factor (RF) (-) JIA-U nor examined the effect of carriage of two risk alleles. Our objective is to validate previously reported HLA associations and investigate the association between HLA-DRB1 in oligo- and polyarticular RF (-) JIA-U. **Methods.** Thirty children of European ancestry with oligo- or polyarticular JIA-U were followed in rheumatology and ophthalmology clinics. Chart reviews confirmed the diagnoses. Controls were 100 healthy adults screened for common autoimmune disorders. Cases and controls were matched for ethnicity. High resolution sequence based typing was performed to determine HLA-DRB1 genotypes. Statistical analysis was performed using chi-square or Fisher's exact test for odds ratio (OR). **Results.** Of 30 subjects, 43.3% were females, 76.7% were ANA (+), 83.3% had oligo JIA and 16.7% had RF (-) poly JIA. Mean age of JIA diagnosis was 3.0 years (SD 2.4). Of 10 subjects, mean age of JIA-U diagnosis was 3.4 years (SD 2.5) with a mean of 20 months (SD 28.5) of arthritis before uveitis onset. In our cohort, we found the following DR13 alleles – *0101 (n=9), *1302 (n=2), and *1303 (n=2), and the following DR11 alleles- *1101 (n=7), and *1103 (n=3). There was a significant association between JIA-U and DRB1*13 (OR 2.18, $p=0.08$), and DRB1*11 (OR

6.71, $p=0.0003$), and between carriage of either DRB1*11 or DRB1*13 (OR 3.25, $P=0.005$). There was a very strong association between JIA-U and carrying two copies of risk alleles (DRB1*11 and 13) (OR 30, $p=0.0000007$). There was a decreased frequency of DRB1*01 in JIA-U compared to controls, although this was not statistically significant, reflecting the modest sample size. Conclusions. We have validated the reported associations between DRB1*13 and DRB1*11 in JIA-U. We also demonstrated the association between JIA-U and the presence of two risk alleles. These HLA risk genotypes should be further investigated in a large prospective group of children with JIA-U to determine the risk for uveitis severity and complications.

150: Inhibition of Eye Blinking Reveals Subjective Perceptions of Stimulus Salience in Children with Autism Spectrum Disorder

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

Background: Altered engagement with the social world is posited to be both cause and consequence of the social deficits characteristic of Autism Spectrum Disorders (ASD). While eye-tracking quantifies where individuals look when viewing social scenes, these measures fail to capture how engaged a viewer is with what he is attending to. Understanding what aspects of a scene are perceived by children with ASD as being particularly important or most relevant to process will shed light on cues that capture their attention. Objectives: (1) Are there differences in the type of stimuli that engage children with ASD and typically-developing (TD) children? And (2) what content is uniquely engaging to children with ASD? Methods: Viewer's engagement was quantified by measuring eye-blink inhibition while children with ASD ($n=57$) and TD children ($n=36$) viewed movies of social interaction. People spontaneously inhibit blinks when processing salient stimuli in order to minimize the loss of visual information that occurs when blinking. Exactly when inhibition occurs marks the viewers' subjective assessment of how engaging a stimulus is (Shultz, Klin, & Jones, 2012). Here, we used blink inhibition to measure between-group differences in engagement. Findings: Over the entire viewing session, children with ASD and TD children were engaged by the same content only 2% of the time, suggesting a marked between-group difference in the type of content perceived as being most important or relevant to process. TD children were more engaged when viewing the eyes and mouths of others (all p 's < .05) compared to children with ASD. By contrast, children with ASD were more engaged when viewing objects ($p < .001$). Ongoing analyses are aimed at examining the perceptual properties of stimuli that are uniquely engaging to children with ASD. Interpretation: This study furthers our understanding of altered social engagement in ASD by examining not only where a child is looking but how engaged a child is with what he is looking at. The results shed light on cues that capture the attention of individuals with ASD, and may identify (1) factors that adversely impact the efforts of individuals with ASD to make sense of complex social environments and (2) compensatory learning strategies that have adaptive value.

151: Hyperoxia Alters Barrier Integrity and Junctional Proteins in Neonatal Alveolar Epithelial Cells

Shilpa Vyas-Read, Jennifer C. Dodds, Satomi Kato, Nimita Fifadara, Theresa W. Gauthier, Michael Koval, and Lou Ann S. Brown

Rationale Hyperoxia exposure is nearly universal in extremely premature infants and contributes to pulmonary edema. Junctional proteins between alveolar epithelial cells (AEC), such as E-cadherin and claudins, are critical in mediating alveolar "leak." Oxidative stress increases the transcription factor SNAI1, which is an E-cadherin repressor that may affect claudins. We hypothesized that hyperoxia impairs permeability by enhancing SNAI1-mediated alterations in E-cadherin and AEC-specific claudins. Methods Transepithelial electrical resistance (TEER) and paracellular leak were assessed in primary rat AEC (P3) cultured in room air (RA) or hyperoxia (85%, H85) for 2 days. Taqman real-time PCR and immunoblots were performed on primary AEC for SNA1, E-cadherin, and claudins 3, 4, 5 and 18. Localization of E-cadherin, claudin 3 and claudin 18 was determined by total internal reflection fluorescence and confocal microscopy (TIRF). Results Two days of H85 disrupted AEC permeability as evidenced by a 50% reduction in TEER, a 3-fold increase in carboxyfluorescein, and ~6 -fold increase in dextran leak across the monolayer ($p<0.05$ for each). H85 also increased SNAI mRNA 1.5X and total SNAI1 protein 1.7X over RA ($p<0.05$, respectively), suppressed E-cadherin mRNA by 38% and inhibited E-cadherin expression at membranes using TIRF ($p<0.05$). Claudin 4 and 5 mRNA 40% and 30% were suppressed by hyperoxia, respectively, but claudins 3 and 18 were unaffected. ($p<0.05$). Although protein for claudins 3, 4, 5 and 18 did not differ between RA and H85-treated cells, claudin 3 and 18 membrane expression was diminished at cellular junctions in H85-treated cells when examined by TIRF. Conclusions Hyperoxia increased SNAI1, and reduced E-cadherin, claudin 4 and claudin 5 mRNA in neonatal AEC. E-cadherin, claudin 3, and claudin 18 were lost from the

membranes of hyperoxia-exposed cells, and this was accompanied by impaired barrier integrity and enhanced leak between AEC. Further studies are needed to determine a causal role for SNAI1 in the alterations of junctional proteins and the formation of pulmonary edema induced by hyperoxia.

152: Dissociating Content-influenced Changes from Maturational Changes in Oculomotor Function in Infants with Autism Spectrum Disorders

Tawny Tsang, BA; Warren Jones, PhD; Ami Klin, PhD

Background: Atypical gaze behaviors have been anecdotally and empirically observed in individuals with autism spectrum disorders (ASD). However, it remains unclear when differences in visual engagement emerge developmentally, and whether they stem from basic mechanisms of oculomotor function or motivational factors that guide attention. The current study longitudinally charts basic oculomotor responses of infants with and without genetic risk for ASD during natural viewing of social scenes and abstract stimuli to shed light on how physiological and attentional processes affect visual behaviors during the first two years of life. **Methods:** Study recruitment followed a standard “high-risk infant siblings design” in which risk was defined as having a relative with ASD. All participants received a confirmatory diagnosis at 36 months of age, assigning infants into ASD (n=19) and typically-developing (TD) groups (n=51). Fixation and saccades were identified from data collected at ten time points from 2-24 months of age while infants viewed videos of actresses engaging in child-directed caregiving behaviors and geometric animations. The following properties and content of eye movements were analyzed: the relationship between saccade amplitude and velocity, saccade latency, frequencies of saccades and fixations, and foci of fixations. **Results:** Preliminary analyses using linear mixed models suggest that basic properties of saccades and fixations undergo similar developmental change between infants with ASD and their TD peers. Moreover, there are clear indicators that saccadic properties for both groups are influenced by content, demonstrating the emergence of endogenous control of saccades in early infancy. Compared to TD infants, infants who develop ASD saccade less between eye and mouth regions and more between non-social aspects of the scene. **Conclusion:** Basic oculomotor circuitry appears to develop normally in individuals with ASD. This suggests that discrepancies in viewing patterns between infants with ASD and their TD peers are not the result of oculomotor impairments, but rather reflect differences in what aspects of a social scene are most salient to them. Our data provide converging evidence pointing to top-down rather than low-level visual factors driving differences in dynamic visual engagement in ASD. Furthermore, this speaks to the potential for eye-tracking methods to study endophenotypes of social deficits in ASD.

153: TALE Nuclease-Based Gene Correction for Cystic Fibrosis

Gang Bao, PhD; Nael McCarty, PhD; and TJ Cradick, PhD

Background: Cystic fibrosis (CF) is a common hereditary disease that begins in infancy and its care becomes the lifelong focus for CF patients and their families. The disease affects the entire body, causing progressive disability and often, early death. After sickle cell anemia, CF is the second most common inherited childhood disorder in the United States. CF is caused by a mutation in the CFTR (cystic fibrosis transmembrane conductance regulator) gene. The most common mutation, $\Delta F508$, is a deletion (Δ) of three nucleotides that results in a loss of the amino acid phenylalanine (F) at the 508th (508) position of the protein. This mutation accounts for two-thirds of CF cases worldwide and 90 percent of cases in the US. Only one functional copy of the gene is needed to prevent CF. Multiple approaches to replace the faulty CFTR gene have failed. In contrast, gene correction can be initiated by creating a specific DNA break near the mutation thus triggering the homologous recombination pathway, which repairs the DNA using a supplied donor DNA, thereby restoring the normal function of the gene. Specific DNA breaks can be generated using TAL Effector Nuclease pairs that can be engineered to cleave a genomic target site. **Methods:** The SAPTA TALEN design was used to engineer a TALEN pair targeting a well-conserved region upstream of the $\Delta 508$ site in CFTR. TALENs and donor DNAs are co-transfected into cells and the level of gene correction assayed to optimize methods and the donor DNA design in order to achieve correction rates capable of correcting CF. **Findings:** The TALEN pair had high activity in vitro, and in culture. Transfection of HEK293 cells with this TALEN pair results in bi-allelic cleavage and resulting NHEJ mutations in nearly every cell transfected. Activity levels are calculated using mutation detection assays. No published TALEN pairs have higher activity in this assay. Variants of this TALEN, which contained other di-nucleotide repeat variable domains to specify guanine, were constructed and also resulted in high NHEJ activity. The specificity of the TALEN pair and variants are being compared by assaying for off-target cleavage at similar sequences determined bioinformatically. High-throughput

sequencing is being used to quantitate cleavage and mis-repair down to very low levels, as verifying there is no or minimal off-target cleavage is essential for therapeutic applications.

154: TALE Nuclease-Based Gene Correction for Treating Spinal Muscular Atrophy

TJ Cradick, PhD; Wilfried Rossoll PhD; Han Phan MD and Gang Bao, PhD

Background: Spinal muscular atrophy (SMA) type I is a lethal childhood disease that is caused by low levels of the survival of motor neuron (SMN) protein. SMA is the leading genetic cause of death in infants, with an incidence of about 1 in every 6000 newborns. In the USA alone, more than 25,000 people are believed to suffer from SMA, and currently there is no cure for SMA or treatment to stop its progression. SMA is caused by homozygous deletions or mutations in the SMN1 gene, which leads to a very specific degeneration of motor neurons in the anterior horn of the spinal cord. Humans also possess a second copy of the gene, SMN2, which encodes the same protein, but harbors a splice site mutation that causes skipping of exon 7 in approximately 90% of the SMN2 transcripts, resulting in a truncated and unstable protein. The existence of the SMN2 gene in all SMA patients offers a unique therapeutic point of intervention. Results from SMA mouse models carrying a human SMN2 transgene show that postnatal delivery of oligonucleotides that restore SMN2 splicing can rescue the spinal muscular atrophy disease phenotype. The aim of this project is to develop and optimize engineered TAL Effector Nucleases (TALENs) and efficient delivery methods to correct the splice site mutation in the SMN2 locus as a novel approach for treating SMA. **Methods:** The TALENs will be expressed in cultured cells to measure the rate of cleavage and repair at the specific target sequence. Stable cell lines that have a single copy of a modified human SMN2 transgene that produces an SMN-luciferase fusion protein when exon 7 is included are being used to test the activity of the TALEN pair on an endogenous target. Successful genome editing of the SMN2 gene will increase splicing of exon 7 and luciferase activity. TALENs and donor DNAs will be co-transfected into cells and the level of gene correction will be assayed to optimize methods and the donor DNA design. The PROGNOS program and high-throughput sequencing will be used to assay for non-specific, off-target cleavage. New TALEN designs will be used if significant off-target cleavage occurs, as this will be detrimental to use as a therapeutic. **Findings:** The SAPTA program was used to engineer a pair of TALENs targeting SMN. The activity of the TALEN pair was measured in vitro, and in culture on episomal targets. In vitro testing and single-strand annealing assays in cultured cells validated this highly active TALEN pair.

155: Lack of Associations Between Autoimmunity Associated Variants in PDCD1 And Juvenile Idiopathic Arthritis

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Variants in the gene encoding Programmed Cell Death 1 (PDCD1) have been associated with susceptibility to SLE and other autoimmune diseases. Given that clinically distinct autoimmune phenotypes share common genetic susceptibility factors, we sought to determine whether the PDCD1 variants were associated with Juvenile Idiopathic Arthritis (JIA). We genotyped over 650 cases and 750 controls for 4 single nucleotide polymorphisms (SNPs) in the PDCD1 gene. Subjects had been recruited from the Pediatric Rheumatology Clinics at the University of Utah and Emory University/Children's Healthcare of Atlanta. Four SNPs (rs10204525, rs7568402, rs7421861 and rs11568821) in the PDCD1 gene were genotyped using TAQMan allelic discrimination assay. Variants were investigated for allelic association with JIA. PDCD1 variants showed no association with JIA in our cohort overall. Specifically no association between JIA and SNP rs10204525 (OR 1.19, $p < 0.1318$), rs7568402 (OR 0.93, $p < 0.3373$), rs7421861 (OR 1.00, $p < 0.9889$) and rs11568821 (OR 0.85, $p < 0.2102$) were observed. Stratification by gender did not alter the results. Additional 500 cases have been genotyped and analysis will be repeated including additional subjects as well as after stratification by subtype. Using a combined cohort of more than 1300 subjects, we found no association between the PDCD1 variant and JIA as a whole. Given that the phenotype of JIA is heterogeneous, stratified analysis will be critical. Unlike other autoimmunity associated genes like PTPN22 and TNFA, PDCD1 does not appear to be associated with JIA, despite showing strong associations with other autoimmune phenotypes like SLE.

156: The Juvenile Idiopathic Arthritis Microbiome

Mina Rohani Pichavant; Kelly Ann Shaw; Lori A. Ponder; Judith L. Fridovich-Keil; Gabriel Wang; Michael E. Zwick; Subra Kugathasan; Jennifer G. Mulle; and Sampath Prahalad

An individual's microbiome is relatively distinct in composition and adapts to environmental changes and host genetics. Previous studies in adults with RA have shown a link between the intestinal microbiome and disease risk. So far there have been no investigations into the role of the microbiome in children with JIA. The goal of this project was to determine whether the gut bacterial species distribution is different in children with JIA compared to control children. Subjects included 5 children with JIA (2 with rheumatoid factor negative JIA and 3 with RF positive JIA) from the Emory Pediatric Rheumatology clinic and 7 controls with galactosemia. Fecal samples were collected from all subjects, DNA was extracted using the MoBio isolation kit as done in the Human Microbiome Project protocols, and 16S DNA sequencing was performed. The distribution of bacterial phyla was compared between children with JIA and controls, as well as children with RF-negative JIA and those with RF-positive JIA. Due to the small sample sizes, this is a descriptive study. All samples were successfully sequenced. Bacteroides and Firmicutes were the two most abundant phyla in all samples, followed by Actinobacteria and Proteobacteria. Children with RF-positive JIA had higher ratios of Bacteroidetes to Firmicutes compared to children with RF-negative JIA. In comparison to the children with galactosemia, samples from children with JIA seemed to have less gut microbiome diversity. It appears that children with RF-positive JIA potentially have a different gut bacterial distribution compared to children with RF-negative JIA. Children with JIA also appear to demonstrate less bacterial diversity compared to children with galactosemia. Studies will be repeated with more, newly enrolled cases with RF-positive JIA, as well as their unaffected siblings and healthy controls. Demonstration that the microbial diversity is different in children with JIA would allow us to explore ways to alter the microbial balance to influence disease severity of JIA.

157: Replication of Putative Candidate-Gene Associations in Juvenile Idiopathic Arthritis

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Although more than 100 non-HLA variants have been tested for associations with juvenile idiopathic arthritis (JIA), only a few have been replicated. Most studies have been in small cohorts and have been underpowered. We sought to replicate reported associations of single nucleotide polymorphisms (SNPs) in genes encoding PTPN22, TNFA and MIF genes in a large JIA cohort, and to perform meta-analyses to improve the statistical power to detect associations. We genotyped 4 SNPs in three genes: PTPN22 C1858T (rs2476601), TNFA G-308A, G-238A (rs1800629, rs361525) and MIF G-173C (rs755622) in 647 JIA cases and 751 healthy controls. Variants were tested for association with JIA. Allele frequency data derived from published JIA association studies were used for meta-analyses under a fixed-effects model. While the PTPN22 variant showed modest association with JIA (OR=1.29, p=0.0309), it demonstrated a stronger association with rheumatoid-factor positive polyarticular JIA (OR=2.12, p=0.0041). The MIF variant was not significantly associated with the JIA cohort as a whole or with any subtype. The TNFA-238A variant was nominally associated with JIA (OR 0.66, p=0.0309), but demonstrated a stronger association with the oligoarticular JIA subtype (OR 0.33, p=0.0006) that was statistically significant after correction for multiple testing. Although TNFA-308A was not associated with JIA in our overall cohort, it was nominally associated with systemic JIA (OR=0.33, p=0.0089) and ERA JIA (OR=0.40, p=0.0144). Meta-analyses confirmed significant associations between JIA and PTPN22 (OR 1.39, p <0.0001) and TNFA-238 (OR 0.69, p <0.0086) variants. Using our cohort of nearly 1400 subjects, we found a statistically-significant association between the TNFA-238A variant and oligoarticular JIA and discovered other nominal associations that merit follow up study. Our meta-analyses confirm the associations between JIA and variants in the PTPN22 and TNFA-238A variants. The modest magnitude of association of these variants suggests that large cohorts and/or meta-analyses are necessary to detect and replicate genetic associations. These findings confirm the association between variants in PTPN22 and TNFA with JIA. These variants have been implicated in susceptibility to other autoimmune diseases. Our findings support the hypothesis that clinically distinct phenotypes can share genetic susceptibility factors.

158: Sexually Dimorphic Genome-wide Binding of RXR α Determines Male-Female Differences in the Expression of Hepatic Lipid Processing Genes

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Many hepatic functions are regulated in a gender specific manner, influencing hepatic pathways including lipid metabolism, drug metabolism, inflammatory responses and cancer. Many of these sex-dependent differences are due to distinct patterns of hepatic gene expression in males (M) and females (F), the majority under the control of Class II Nuclear Receptors (NRs). Retinoid X Receptor alpha (RXR α) is an obligate heterodimerization partner for over a dozen NRs and therefore a master regulator of hepatic gene expression, yet the full extent of RXR α chromatin binding in M and F livers is unknown. To identify a role for RXR α in sex-specific liver functions, Chromatin ImmunoPrecipitation Sequencing (ChIP-Seq) analysis of RXR α and of RNA Polymerase 2 (Pol2) binding was performed on adult M and F mouse livers. Mice were gavaged fed with RXR ligand LG268 for 5 days (30 mg/kg/day) and RXR α binding determined by ChIP-qPCR and RNA levels were determined by qPCR. Using ChIP-Seq revealed a large number (47,845-M; 46,877-F) of RXR α binding sites (BS) in liver chromatin. This binding was associated with ~12700 unique genes for M and a similar amount in F livers, indicating an average of 3-4 RXR α BS per gene. Of these genes, there was a 91% overlap between sexes, whereas for 2227 unique genes RXR α binding was significantly enriched in M and for 1498 unique genes RXR α binding was significantly enriched in F liver. Correlating strength of RXR α BS with Pol2-binding revealed 44 genes highly enriched in M, 43 in F, many previously unknown to be sexually-dimorphic. Of these genes, a surprising enrichment in genes fundamental to lipid metabolism was noted in F mice, including PNPLA3, implicated in Fatty Liver Disease pathogenesis, as well as Scd1, Fasn, and Elovl6. Activation of RXR α by treating mice with the rexinoid LG268 confirmed RXR α binding was 2-3 fold higher in F mice at multiple binding sites upstream of the transcription start sites including for Pnpla3 and Elovl6 by ChIP-qPCR, as well as a ~10-fold and ~2-fold increase in Pnpla3 and Elovl6 RNA respectively in F livers, supporting a role for RXR α regulation of sexually-dimorphic responses for these genes. In sum, RXR α appears to be one of the most widely distributed transcriptional regulators in mouse liver and is engaged in determining sexually-dimorphic expression of key lipid processing genes, suggesting novel gender- and gene-specific responses to NR-based treatments for lipid-related liver diseases.

159: Lost in Translation: Complex Interactions in Sickle Cell Disease May Interfere with Targeted Therapeutics

Beatrice Gee, MD

BACKGROUND: Sickle cell disease (SCD) is caused by a single mutation in beta-globin, but triggers several pathophysiologic pathways and results in a highly complex and variable disease. The role of each pathway is likely to be situation-dependent, e.g. during acute infection, hypoxia, hyper-hemolysis, cold exposure, or stress. This complexity is likely to be a major barrier to the success of targeted treatments. The failure of promising clinical trials may be the result of a reductionist approach, correcting a single mechanistic pathway without having demonstrated its relative contribution to SCD complications. **OBJECTIVES:** A visual model was developed to help better understand complex interactions of pathophysiologic mechanisms in SCD, and was then applied to the analysis of selected clinical trials. **METHODS:** Applying concepts of systems theory and network biology, a model was developed describing relationships between the primary defect of sickle hemoglobin (Hb S) polymerization, known pathophysiologic mediators, and the clinical outcome of acute pain. The primary process of Hb S polymerization is followed by secondary pathways of hemolysis and vaso-occlusion. Inflammation and oxidative stress are downstream by-products of hemolysis and/or vaso-occlusion. Pain is itself a complex process and may be influenced by additional circumstances, such as the nervous system, environment and psycho-social factors. **RESULTS:** When viewed from this perspective, it becomes apparent that treatments targeting a single pathway, e.g. erythrocyte adhesion to endothelium or nitric oxide deficiency, may not be effective in halting acute vaso-occlusive pain if other processes continue to actively contribute. Red cell replacement with either transfusions or stem cell transplantation is currently one of the most effective therapies because it corrects the underlying defect of Hb S polymerization and consequently the downstream effectors. **CONCLUSIONS:** Research approaches that better address biologic complexity are needed to advance the field of SCD science and help identify new therapeutic targets. It would be helpful to demonstrate the relevance of individual pathways on important sickle cell outcomes prior to investing in clinical trials. There is also opportunity for applying systems biology methods to understanding the effects of the sickle cell internal milieu on the body and to help identify "master regulators" that may be involved in multiple mediator pathways.

160: Anti-inflammatory and anti-atherogenic role of BMP Receptor II in endothelial cells

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Atherosclerosis is a multifactorial disease that arises from a combination of endothelial dysfunction and inflammation, occurring preferentially in arterial regions exposed to disturbed flow. Bone morphogenetic protein-4 (BMP4) produced by disturbed flow induces inflammation, endothelial dysfunction and hypertension, suggesting the importance of BMPs in vascular biology and disease. BMPs bind to two different types of BMP receptors (BMPRI and II) to instigate intracellular signaling. Increasing evidences suggest a correlative role of BMP4 and atherosclerosis, but the role of BMP receptors especially BMPRII in atherosclerosis is still unclear and whether knockdown of BMPRII is the cause or the consequence of atherosclerosis is still not known. It is therefore, imperative to investigate the mechanisms by which BMPRII expression is modulated and its ramifications in atherosclerosis. Initially, we expected that knockdown of BMPRII will result in loss of pro-atherogenic BMP4 signaling and will thereby prevent atherosclerosis. Contrarily, we found that loss of BMPRII expression causes endothelial inflammation and atherosclerosis. Using BMPRII siRNA and BMPRII^{+/-} mice, we found that BMPRII knockdown induces endothelial inflammation in a BMP-independent manner via mechanisms involving reactive oxygen species (ROS), NF κ B, and NADPH oxidases. Further, BMPRII^{+/-}ApoE^{-/-} mice develop accelerated atherosclerosis compared to BMPRII^{+/+}ApoE^{-/-} mice, suggesting loss of BMPRII may induce atherosclerosis. Interestingly, we found that multiple pro-atherogenic stimuli such as hypercholesterolemia, disturbed flow, pro-hypertensive angiotensin II, and pro-inflammatory cytokine, TNF α , downregulate BMPRII expression in endothelium, while anti-atherogenic stimuli such as stable flow and statin treatment upregulate its expression, both in vivo and in vitro. Moreover, we found that BMPRII expression is significantly diminished in human coronary advanced atherosclerotic lesions. These results suggest that BMPRII is a critical, anti-inflammatory and anti-atherogenic protein that is commonly targeted by multiple pro- and anti-atherogenic factors. BMPRII could be used as a novel diagnostic and therapeutic target in atherosclerosis.

161: Time-Resolved Imaging of Endosome Acidification and Single Retrovirus Fusion with Endosomes

Sergi Padilla-Parra, PhD; Pedro M. Matos, PhD; Naoyuki Kondo, PhD; Mariana Marin, PhD; Nuno C. Santos, PhD, and Gregory B. Melikiana, PhD

Avian Sarcoma and Leukosis Virus (ASLV) enters cells by receptor-mediated endocytosis followed by low pH-dependent fusion with endosomes. We examined the pH dynamics in virus-carrying endosomes and the relationship between endosome acidification and ASLV fusion in cells expressing alternative receptor isoforms. The pH drop in endosomal lumen was measured by incorporating a genetically encoded pH sensor into the viral membrane. The subsequent single virus fusion was visualized as the release of a fluorescent viral content marker into the cytosol. To our knowledge, this is the first implementation of real-time measurements of endosomal pH dynamics and single virus fusion in the same experiment. We found that the pH in early acidic compartments harboring the virus was broadly distributed, ranging from 5.6 to 6.5. Surprisingly, after initial acidification, the endosomal pH did not decrease further for as long as we could track the viral particles (up to 20 min). Analysis of the relationship between the endosome motility and luminal pH showed that cells expressing the transmembrane isoform of the receptor (TVA950) preferentially sorted ASLV to slowly moving, less acidic endosomes. In contrast, ASLV showed no preference for fast vs. slow vesicles in cells expressing the GPI-anchored isoform (TVA800). The rate of fusion (distribution of time intervals between acidification and fusion) was significantly shorter and fusion pores were larger in mobile endosomes compared to more stationary compartments. In addition, TVA950 supported faster fusion than TVA800 in spite of the same average pH values in mobile compartments of these cells. Taken together, our results revealed that the ASLV can be selectively sorted to distinct endosomal pools and that the virus fuses with different kinetics and efficiency with these intracellular compartments. This work was partially supported by NIH AI053668 grant to G.B.M.

162: An Ethogram of Behaviors Guiding Dynamic Visual Scanning in 12-24 Month-Olds with Autism Spectrum Disorder

Grace A. Marrinan, BA; Ami Klin, PhD; and Warren Jones, PhD

Background: Previous research has demonstrated that two-year-olds with autism spectrum disorder (ASD) look more to mouths, bodies and objects when viewing video scenes of caregivers, while typically-developing (TD) toddlers look more to their eyes. Related research has shown that two-year-olds with ASD preferentially attend to physical contingencies, regardless of their social context. These past analyses of visual fixation on discrete regions of interest suggest that toddlers with ASD attend more to physically salient aspects of a scene while TD toddlers preferentially attend to elements with social adaptive value. Rather than summarizing fixations in relation to regions of interest, the current study aims to characterize functional social actions that drive the attention of TD children but fail to capture the attention of children with ASD. Methods: Eye-tracking data were collected as 12-24 month-old TD children (N = 28) and children with ASD (N = 48) viewed naturalistic videos of peer interactions. We matched children on chronological age and non-verbal function. We quantified dynamic visual scanning using kernel density analysis, and the resulting measures of fixation density, at each moment in time, allowed us to model the allocation of attention for both groups throughout all video scenes. Using these measures, we tested for between-group differences in dynamic visual scanning. In parallel, we categorized functionally distinct categories of social behavior occurring in the videos using an ethographic analysis. We then analyzed the catalog of behaviors during frames of the videos when the visual scanning of children with ASD and TD children differed significantly. Results: Preliminary analyses suggest that socially functional elements of the video scenes, including gaze cues and intense facial expressions drive the visual scanning of TD 12-24 month-olds more strongly than that of 12-24 month-olds with ASD. In contrast, preliminary results suggest that physical motions and vocalizations drive the scanning behavior of both children with ASD and TD children in a more similar fashion. Conclusions: Socially relevant behaviors appear to serve as salient social signals to TD toddler and to drive attention more strongly among TD toddlers than among toddlers with ASD. The social and communicative outcomes of children with ASD may thus result from a divergent foundation of knowledge gained from atypical allocation of attention from an early age.

163: The Kinetics of 2D Binding of CD4 to HIV Envelope Glycoprotein gp120

Ke Bai, PhD; Samadhan Jadhao, PhD; Gregory Melikian, PhD; Cheng Zhu, PhD

The human immunodeficiency virus (HIV) is one of the most serious and deadly diseases in human history. Until 2010, 34 million people live with HIV/AIDS and 3 millions of them are children. T cells are the main target of HIV in the blood, especially the helper T cells that express CD4. The first step of HIV infecting T cell is the binding of the viral envelope glycoprotein gp120 subunit and its primary receptor CD4. This leads to the conformational change of gp120 to expose the binding site for its co-receptor CCR5 or CXCR4 on the T cell, which eventually mediates fusion between the viral and cellular membrane. Although the specific interaction between CD4 and co-receptors with gp120 has been broadly studied, the direct physical binding kinetics between them remains unclear. The present study aims to fill this gap by measuring the on-rates and off-rates of the bimolecular interactions between HIV gp120 and CD4 or co-receptors, and characterizing the kinetics of the trimolecular interaction among gp120, CD4, and CCR5 or CXCR4. We measured adhesion between gp120 and CD4 using micropipette adhesion frequency assay. This method quantifies the dependence of adhesion probability on contact duration and densities of gp120-CD4 bond, which allows us to evaluate the kinetic on- and off-rates. Binding specificity of the CD4 vs. HIV virus-like particles (VLPs) expressing gp120 (gp120+) group was controlled using 1) BSA vs. VLPs gp120+, 2) CD4 vs. VLPs gp120-, 3) BSA vs. VLPs gp120-, and 4) CD4 vs. VLPs-gp120+ in the presence of blocking antibody. The adhesion frequency of the CD4 vs. VLP gp120+ group (13.7% at 1 s contact duration) was significantly lowered under the control conditions, demonstrating the binding specificity between CD4 and gp120. In addition, dependence of adhesion frequencies on contact time was measured. As the contact time prolonged, the adhesion frequency mediated by gp120-CD4 binding increased from <10% at 0.25 s to >40% at 5 s, then reached a plateau from 5 to 10 s. The site densities of CD4 and gp120 affect the adhesion frequencies as well, where the increase of CD4/gp120 ratio leads to higher adhesion frequency. The micropipette adhesion frequency assay has provided specific 2D binding kinetics between CD4 and gp120 at zero force. We will use biomembrane force probe assays to further measure the force-dependent lifetimes of bonds between CD4 and gp120, which will complete the 2D kinetic analysis of the CD4-gp120 interaction.

164: Teaching a Child with Developmental Disabilities to Tolerate a Two-Day Ambulatory Electroencephalogram

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Medical procedures are often invasive and sometimes frightening for young children, which can lead to a variety of problematic behaviors. These behaviors can lead to inaccurate or incomplete data or the use of less effective medical interventions. Children who engage in high intensity aggressive and destructive behavior, or self-injurious behavior pose a challenge to completing medical procedures. Thus, it is important to develop strategies to aid in the completion of medical procedures that may be aversive for children, such as electroencephalograms (EEGs). Further complicating this issue is the fact that up to 30% of children diagnosed with a developmental disability also experience seizures by the time they are adolescents (Slifer, Avis, & Frutchey, 2008), making children with developmental disabilities more likely than typically developing children to require medical procedures such as an (EEG). The purpose of the current investigation was to teach a child with developmental disabilities and severe problem behavior to complete a 2-day ambulatory EEG by increasing his tolerance of the medical equipment and decreasing problem behavior related to the procedure. Prior to the implementation of the ambulatory EEG, an intervention was developed and implemented to teach Albert to wear the EEG device without problem behavior and to increase compliance with the application of the EEG equipment using stimulus fading, verbal instructions, and an overcorrection procedure. Specifically, Albert was taught to wear an apparatus similar to that of an ambulatory EEG so that he could complete the procedure at a later time. The result was that Albert was able to complete the 48-hour EEG successfully for the first time. This allowed his neurologist to provide more accurate treatment of his seizures.

165: Streamlining Clinical Testing for Type 2 Diabetes in At-Risk Obese Adolescents

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Dysglycemia including type 2 diabetes (T2D) and impaired glucose tolerance (IGT) in 12-19 year old children increased in NHANES from 9 to 23 percent between 1999-2008. The consequences of diabetes are well known; but, less appreciated are reports of high risk cardiovascular disease profiles among children with IGT. Yet, screening protocols for dysglycemia are not established. Fasting blood glucose is a simple, but insensitive measure whereas fasting 2 hour oral glucose tolerance tests (OGTT) are definitive, but complex and expensive. This study investigated whether a non-fasting, 1-hour oral glucose challenge test (GCT), similar to that used to detect gestational diabetes is feasible as a screening instrument in asymptomatic children who are at high risk for dysglycemia. Children aged 12-18 years, with body mass index >95th percentile, a family history of T2D, and no personal history of dysglycemia underwent both a GCT (50 g oral glucose load) and an OGTT (75 g) at least 2 weeks apart. In the GCT, 1 blood sample was obtained 60 minutes after glucose ingestion whereas samples were obtained at -10, 60, and 120 minutes in relation to glucose ingestion in the OGTT. All blood glucose and lipids were measured with a Cholestek benchtop analyzer.

166: Virulence Factors Associated with MRSA USA300 Carriage Among Children with Skin and Soft Tissue Infections (SSTIs)

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Background: In the US, SSTIs have been largely attributed to MRSA USA300. Little is known about which virulence factors may be linked to MRSA USA300 carriage and developing a SSTI or recurrent SSTI. Objective: To better understand which major virulent determinants are associated with Staphylococcus aureus carriage and SSTI infection, and to observe the short and long term clinical outcomes due to MRSA USA300 SSTIs. Design/Methods: Two phases: (1) Case control study of children who presented to ED with/ without SSTIs. Specimens from nares/ axilla were collected to determine Staphylococcus aureus carriage and isolates were tested for 18 virulence genes using PCR based assays (sea, seb, sec, sed, see, seg, seh, sei, tst, eta, etb, bsaB, lukS/F-PV(PVL), arcA, agr-I, agr-II, agr-III, agr-IV). (2) Surveillance for recurrent SSTI or Staphylococcus aureus infection up to 5 years after initial SSTI. Outcomes of initial SSTI were observed and assessment of risk factors were determined for 336, who were initially Staphylococcus aureus carriers (246) or not Staphylococcus aureus carriers but had Staphylococcus

aureus SSTI (90). Results: In phase 1, *Staphylococcus aureus* carriage was higher with SSTI (31.9%, 79/247) compared to those without SSTI (22.6%, 167/739, $p=0.003$). MRSA carriage rates were also higher for SSTI (17%, 42/247) versus those without SSTI (2.4%, 18/739); MSSA carriage rates were similar ($p=0.086$). MRSA USA300 carriage was higher among SSTI (OR 9.48, 95%CI: 5.03-17.88). To date, virulence genes have been determined for 102 *Staphylococcus aureus* isolates (59 MRSA, 43 MSSA). 40/41 (98%) MRSA isolates were USA300 with 98% (39/40) testing positively for PVL, agr I, bsaB genes, and 95% (38/40) for arcA. These were not seen in the MRSA USA800. Long term follow-up occurred in 23% (78/336); 15% (12/78) were MRSA carriers, 51% (40/78) MSSA carriers, and 34% (26/78) lacked carriage but had previous *Staphylococcus aureus* SSTI. Recurrent SSTI was reported in 18% (14/78), and 12% (9/78) had household member with SSTI. Conclusions: Children with SSTI are more likely to be colonized with MRSA USA300. The PVL, agr-I and bsaB genes may play a role in MRSA USA300 carriers developing SSTIs. Risk for recurrence is higher among MRSA USA300 SSTIs.

167: Optimization of an Eye-Tracking-Based Categorical Screener For Autism Spectrum Disorders in 18- to 42-Month-Old Children

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Background: The overarching goal of this project is to develop performance-based measures that can be used as quantitative diagnostic screeners for autism spectrum disorders (ASD). Past work in eye-tracking measured spontaneous visual fixations during viewing of naturalistic social situations. While watching scenes of social interaction, toddlers with autism spent—relative to age- and verbal IQ-matched typically-developing (TD) controls—markedly increased time fixated on mouth, body, and object regions and markedly less time fixated on the eyes. Subsequent research identified measures of dynamic visual scanning (moment-by-moment variation in looking patterns) that distinguished the ASD from TD groups with still larger effect sizes. These results, however, looked at group comparisons, and not at classification of individual children. Concurrent to this study, we are assessing the validity of visual scanning measures as a categorical screener for ASD in children between 18 and 42 months of age. The current study aims to optimize the sensitivity and specificity of that screener by constraining the heterogeneity of the training set. **Methods:** Eye-tracking data were collected while 50 toddlers, aged 18 to 42 months, viewed dynamic scenes of other children at play. Standardized clinical assessment measures (ADOS, ADI, cognitive, and language testing) confirmed diagnostic status for ASD and TD children. The ASD training sample (ASD-1, N=50) focused on children with lower autism severity scores. Relative to TD children (N=50), these children provided a training set with which to develop a model of expected differences between ASD and TD visual scanning. We then tested the remaining ASD children (ASD-2, N=50) as an external validation sample. Receiver operating characteristic (ROC) curves were created to analyze sensitivity and specificity. **Results:** Preliminary results indicate that use of the constrained training sample decreased sensitivity but increased specificity of classification. Children in the validation sample were classified with sensitivity of 80% and specificity of 84%, above recommended benchmarks for Level 1 developmental screeners. In ongoing analyses, we are measuring the extent to which additional approaches to optimization (time- and event-based, as well as cohort-based) will improve the classification, testing the viability of using differences in visual scanning as a categorical screener for autism spectrum disorders.

168: Changing the Status Quo: Combining Magnetic Resonance Imaging with Computational Fluid Dynamics to Evolve Fontan Palliations for Children with Single Ventricles

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Background: Children born with single ventricle anatomy undergo a series of surgical palliations, ultimately resulting in a Fontan completion. Here the inferior vena cava is connected to the pulmonary arteries via either a straight tube graft or lateral tunnel created within the right atrium, forming a total cavopulmonary connection (TCPC). Though this procedure has improved patient survival, many morbidities and early mortality still remain for many of these children and young adults; some of these have been related to the suboptimal hemodynamic environment created by the TCPC. Our research team from Children's Healthcare of Atlanta and Georgia Institute of Technology utilize a synergistic "bench to bedside" approach, melding cardiac magnetic resonance imaging (CMR), advanced segmentation, modeling techniques, and computational fluid dynamics (CFD). The current project represents our refinement of Fontan geometries, with utilization of a novel bifurcated Fontan baffle (Y-graft), which seeks to provide superior hemodynamics and consequently improved patient outcomes. **Methods:** CMR images were

acquired in patients after Fontan completion utilizing the Y-graft technique. Patient-specific anatomies were reconstructed using previously developed segmentation tools. CFD simulations were carried out using patient-specific flows to assess the hemodynamic performance of the connection. Relevant energetic and functional parameters were extracted to assess the connection's efficiency (i.e., power loss and hepatic flow distribution). Results: The Y-graft has been utilized in 20 patients to date at Children's Healthcare of Atlanta. Hemodynamic results show similar energetic efficiency when compared to traditional lateral tunnel and extracardiac TCPC connections. The hepatic flow distribution, whose absence has been linked to development of pulmonary arterio-venous malformations, showed improved symmetry. Conclusions: Our study demonstrates ongoing successful collaboration between medical clinicians and biomedical engineers, assessing and refining the performance of novel surgical techniques. The Y-graft Fontan baffle has showed acceptable energetic characteristics and symmetric hepatic flow distribution between the right and left lungs, which position this technique as a novel improvement in single ventricle palliation.

169: Analysis of Molecular Pathways in the Regulation of Human Pluripotent Stem Cells to Cardiomyocyte Differentiation

Rajneesh Jha, PhD; Qingling Wu, MS; Brian Wile, MS; Xuemin Chen, PhD; Paul Spearman, PhD; Gang Bao, PhD; Chunhui Xu, PhD

Human pluripotent stem cells can give rise to spontaneously beating cardiomyocytes in vitro. The in vitro cardiomyocyte differentiation is a very dynamic process which is tightly regulated by signaling proteins and transcription factors and recapitulates in vivo cardiogenesis. Understanding molecular mechanisms controlling differentiation to cardiomyocytes could shed light on the cardiogenesis during development and help to guide optimization of in vitro cardiomyocyte differentiation for potential cell therapy to treat heart failure. From a microarray analysis, we have identified several genes that may modulate cardiomyocyte differentiation, including a G-protein coupled receptor, a homeobox protein, and a non-coding RNA during growth-factor (activin A and bone morphogenic protein-4) induced cardiomyocyte differentiation. Temporal gene expression and molecular regulation of these genes are being examined. We have also designed short hairpin RNA (shRNA) to target these genes and are currently optimizing silencing assays via lentiviral vector delivery method to further elucidate whether these genes indeed play functional roles in cardiomyocyte differentiation.

170: Assessing the Effectiveness and Public Health Impact of One Dose of Rotavirus Vaccine in Developing Countries like Pakistan

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BACKGROUND: Introduction of the rotavirus vaccine has resulted in a decrease in prevalence of rotavirus in the United States. In developing countries, like Pakistan, diarrhea remains a major cause of infant mortality and morbidity. Based on US studies' data, even one dose of vaccine is better than not receiving any doses of vaccine. Giving a single dose of vaccine to children in a developing country can reduce rotavirus cases significantly. **METHODS:** This study involved: (1) Case control study of children with rotavirus tests (Dec-June 2006, 2007, and 2008) from 2 pediatric hospitals (2) active surveillance of children with acute gastroenteritis symptoms during Dec-June 2010 and 2011 from 3 pediatric hospitals. Vaccinations records were collected from state immunization registry. We examined the association between vaccine status (receiving only 1 dose of Rotarix® or RotaTeq® vs. no vaccine) and contracting rotavirus for each season. **RESULTS:** We detected a significant association between vaccine group (1 dose vs. none) and contracting rotavirus for seasons 1, 3, and 5. Overall, for children receiving only 1 dose of either vaccine, the odds of contracting rotavirus was significantly less when compared to children who received no vaccine (OR = 0.22, 95% CI [0.11 – 0.44], p-value < 0.001). We also noticed a change in the proportion of children vaccinated each season (received at least 1 vaccine) (20%, 42%, 37%, 65%, 64%, p < 0.001). **CONCLUSION:** Receiving only one dose of the Rotarix® or RotaTeq® vaccine reduces a child's risk of contracting rotavirus. Furthermore, there appears to be an increasing trend in rotavirus vaccine use in the US.

171: Inhibition of Mechanosensitive MicroRNA, mir-712, Atypical MicroRNA Derived From Pre-Ribosomal RNA, Decreases Endothelial Dysfunction And Atherosclerosis

Dong Ju Son, Sandeep Kumar, Wakako Takabe, Chih-Wen Ni, Chan Woo Kim, Noah Alberts-Grill, Sang Ok Kim, Wan Kyu Kim, Jai Woong Seo, Katherine W. Ferrara and Hanjoong Jo

Atherosclerosis is the underlying cause of cardiovascular events, such as heart attack and stroke, and preferentially occurs in arterial regions exposed to disturbed flow (d-flow) by mechanisms involving broad changes in gene expression. While microRNAs (miRNAs) are known to regulate various aspects of cardiovascular biology and disease, their role in atherosclerosis has not been directly demonstrated. Here, we identified mechanosensitive miRNAs using a mouse partial carotid ligation model and endothelial miRNA array. Of those mechanosensitive miRNAs identified, miR-712 was the most shear-sensitive miRNA upregulated by d-flow both in vivo and in vitro. We found that miR-712 is derived from the internal transcribed spacer 2 (ITS2) region of pre-ribosomal RNA (RN45S gene) in a XRN1 exonuclease-dependent, but DGCR8-independent manner, suggesting that it is an atypical miRNA derived from an unexpected source. Studies including gain-of-function (pre-miR-712) and loss-of-function (anti-miR-712) approaches and target-binding assays showed that miR-712 directly downregulated the tissue inhibitor of metalloproteinase 3 (TIMP3) expression. This in turn activated downstream metalloproteinases (MMPs and ADAM family) and stimulated pro-atherogenic responses, endothelial tubule formation and sprouting, in a flow-dependent manner. Further, treatment with anti-miR-712 prevented atherosclerosis in two different models of murine atherosclerosis using ApoE^{-/-} mice: a chronic conventional western-diet or an acute carotid partial ligation model on a high-fat diet. Our results suggest that targeting mechanosensitive "athero-miRs" with anti-miR-based approaches may provide a new treatment paradigm in atherosclerosis.

172: Dynamic Visual Search Strategies During Natural Viewing in 12-24 Month-Olds with Autism

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Background: The natural environment of toddlers contains a wide array of competing attentional demands: from other people in motion—talking, gesturing, and interacting—to objects in the surrounding world. By measuring how individuals direct limited attentional resources in pursuit of a goal, we may gain insights into how goals that guide behavior may differ in young children with autism. In a natural viewing task using scenes of social interaction, this case was operationalized by measuring the first fixations immediately following the presentation of new visual information (following a movie scene cut). Past research with older children in a similar paradigm demonstrated that individuals with autism spectrum disorders (ASD) were more likely to direct their fixations to body and object areas than to the face, while their typically-developing (TD) peers were significantly more likely to shift their first fixations to the eyes of onscreen actors. Our aim was to understand differences between toddlers with and without ASD in the rapid deployment of initial fixations when presented with new visual information. Methods: 37 children with ASD (mean age, 22.1 months) and 19 age-matched TD controls (mean age, 20.3 months) watched dynamic social scenes of young children at play. Scene cuts provided instances where new visual information required viewers to shift attention from an old location (in the previous frame) to a new target location (in the current frame). Eye-tracking technology was used to collect visual scanning data. Dependent measures included reaction times to shift gaze following a movie scene cut; location of initial fixations within the scene following a cut; and overall fixation time spent looking at different regions. Results: The ASD group spent significantly less time fixating on eyes ($p < 0.001$), mouths ($p = 0.029$) and faces as a whole ($p < 0.001$). Reaction times to shift visual attention were not significantly different between-groups, but TD children were more likely than their peers with ASD to direct first fixations towards the eyes ($p = 0.01$) and faces ($p = 0.02$) of on-screen actors and when analyzing the temporal onset of these differences, we found that between-group comparisons became significantly different ($p < 0.05$) within 700 ms after the presentation of new visual information. This study explores how the analysis of initial fixations may serve as a proxy for 'social intuition' (the first reactions that guide behavior in novel situations).

173: Developmental Profiling of Voice Quality in Infants at Risk of Autism

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Introduction: Autism is a developmental disorder that may be present at birth, and is defined by core deficits in social communication and restricted repetitive behaviors that are often comorbid with other conditions, including basic motor deficits. Atypical prosody is one of the characteristic traits of the communication deficit in autism, which

may be related both to the derailment of social engagement in early infancy, bootstrapped by intonational exchanges between infant and caregiver, and to other oral-motor control problems. The aim of this study is to analyze developmental patterns of voice quality (VQ) in the first year of life in infants at risk of autism in order to test the hypothesis that prosodic differences in ASD may reflect specific impairments in socially-relevant patterns of intonation, as opposed to general comorbid deficits in phonatory control. Methods: Day-long home recordings of 4 low-risk infants and 4 high-risk infants were made with a digital audio recorder at monthly intervals between 2 and 24 months of age. Non-cry vocalizations for each child were extracted from each recording using speech recognition technology. Standard measures of VQ including fundamental frequency, open quotient, return quotient and speed quotient were estimated for all segmented speech files. Using Functional Data Analysis, developmental profiles for VQ were derived by aligning the resulting longitudinal profiles of all these measures across individuals. Clinical assessments were carried out at 24 months to determine outcome. Results: Two high-risk infants were diagnosed with broader autism phenotype (BAP) and two with non-autistic language delays (LD). All low-risk infants were found to be typically developing (TD). VQ profiles showed that fundamental frequency was elevated and more variable across BAP and LD infants, diverging from TD infants at around 9 months. No significant differences are currently observed in other measures in our present sample. Conclusions: Our results indicate that atypical vocal behavior in infants at risk of autism begins to develop towards the end of the first year of life, and may present as specific differences in intonational prosody rather than properties reflecting more general problems in phonatory control. Impact: This study demonstrates quantification of prosodic differences in the first year of life using acoustic measures that may help to identify biomarkers for early detection of the prosodic deficit in autism.

174: Avian Retrovirus Entry Occurs in Distinct Intracellular Compartments in Different Target Cells

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Enveloped viruses infect cells by fusing their envelope with the host cell membranes. Our laboratory combines time-resolved and high-resolution imaging techniques with recombinant and chemical viral fluorescent labeling approaches, to probe viral entry, fusion and restriction in cells through biochemical assays both in vitro and in vivo. One of the current areas of focus in our laboratory is to understand the mechanism of endocytosis and pH-mediated fusion of the avian sarcoma-leukosis virus (ASLV). Previous studies on the mechanism of ASLV entry and fusion in CV1 (African green monkey kidney) cells indicate rapid receptor-mediated endocytosis of ASLV, followed by low-pH triggered fusion in early endosomes. Furthermore, the rates of endocytosis and fusion of ASLV in CV1 cells are receptor-isoform dependent. These observations stand in contrast to our preliminary findings on another cell type – adenocarcinomic human alveolar basal epithelial (A549) cells. These results were arrived at by a combination of imaging of single particle ASLV entry and fusion, and the kinetics of escape from several inhibitors of viral fusion using a β -lactamase based fluorimetric viral fusion (BlaM) assay. In A549 cells, as in CV-1 cells, ASLV endocytosis and trafficking into early endosomes with low pH (~6.0) is rapid and proceeds with a $t_{1/2}$ in the order of a ~2-5 mins. Single particle fusion kinetics based on cytosolic dilution of a viral content marker mCherry that is released upon fusion, also indicate a $t_{1/2}$ of ~5 minutes underscoring the rapid formation of fusion pores once the viral envelope senses low pH. However, the BlaM assay shows a significant lag of ~15-20 mins between progression of fusion beyond low pH-dependent steps, and the appearance of significant BlaM activity in the cytosol. This difference in the kinetics of core release between the two assays may point to the possibility that, while viral envelope glycoprotein-receptor interactions can lead to the formation of small pores following the low pH trigger, the enlargement of these pores could depend on cell type-specific factors, such as lipid bilayer properties and endosomal proteins. Our goals, therefore, include delineating the key differences in the endocytic trafficking of ASLV between CV1 and A549 cells, and extending these studies to other viral envelope glycoproteins.

175: Novel Anti-Inflammatory Nanocarriers for Spinal Cord Injury

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Introduction Spinal cord injury (SCI) is a devastating event leading to lifelong paralysis. Children and young adults make up a significant proportion of patients afflicted with SCI. The goal of any medical intervention is to minimize the secondary injury, which is primarily characterized by heightened inflammation, and causes prolonged cell death and a pervasive loss of motor function. The current clinical gold standard for SCI is systemic administration of methylprednisolone (MP). This has deleterious side effects and the gains are modest. Further, there is a narrow time window for MP administration; 8-12 hours. Site specific delivery to the spinal cord is also hampered by the blood-spinal cord barrier (BSB). The BSB is open transiently post-SCI, providing us with an opportunity to deliver

therapeutic agents to the site of injury. A critical objective is to ascertain, what is the maximum sized particle that can cross the BSB, and how this size selectivity varies with time, allowing us to deliver the maximal therapeutic dose. The second objective of the study is to determine alternatives to MP. We propose to evaluate the use of immunomodulatory cytokines, which instruct immune cells to become anti-inflammatory. Materials and Methods: A severe contusion injury at the thoracic 9 vertebral level in rats was induced using a force controlled impactor. Fluorescent nanoparticles of various sizes (100 nm, 200 nm, and 1000 nm) were intravenously injected at 24, 48, and 96 hours post-SCI. 4-6 hours post-injection, spinal cords were evaluated for particle presence under a fluorescent microscope. Liposomal formulations of cytokines (interleukin-4 [IL-4]) and MP were intravenously administered to animals and the animals were assessed for motor and histological improvements. Results and Discussion We have determined that the BSB is open for a period of at least 7 days, as evaluated by extravasation of fluorescently labeled albumin. Ongoing experiments are evaluating the size permeability of the BSB and liposomal drug delivery. The study should be complete by the end of summer 2013. We are further evaluating the efficacy of liposomal methylprednisolone, and comparing it with liposomal formulations of immunomodulatory compounds. The results of this study have a direct impact on the management of SCI as they inform us of the time window available for maximal site specific drug delivery to the spinal cord and evaluate alternatives to MP.

176: Breastfeeding and Severe Food Selectivity: A Retrospective Chart Review Comparing Rates of Breastfeeding among Children with and without Autism Spectrum Disorders

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Introduction: Autism spectrum disorders (ASD) and chronic feeding concerns are frequently linked, with some estimates approaching 90% of children with ASD. Food selectivity (i.e., only eating a narrow range of foods) represents the most frequent and widely documented feeding concern in the ASD population. Much remains unknown, however, regarding the etiology of atypical patterns of intake in ASD, including the timeframe during which chronic feeding problems emerge and/or are evident in a child's feeding history. Emerging evidence suggests children with autism spectrum disorders may be at increased risk for early feeding issues, including increased likelihood of early termination or absence of breastfeeding. The current retrospective chart review sought to add to this line of research by assessing the early feeding practices among children with and without ASD who present at a multidisciplinary feeding clinic. Methods: We reviewed 160 charts over a 2 year timeframe, identifying 69 children who presented for assessment and treatment of severe food selectivity at a multidisciplinary feeding clinic. Data collected from charts included age (months), gender, referral reason, developmental concerns, medical concerns, and early feeding practices (i.e., breastfeeding, bottle feeding, feeding tube usage). We summarized these data using descriptive statistics, as well as compared rates of breast feeding and bottle feeding with expressed breast milk between groups of children with and without ASD using independent samples t tests. Results: A total of 45 children with ASD (39 male and 6 females) were compared to 24 children without ASD (18 male and 6 females). The average age of participants was 5 years, 6.57 months (ASD: 5 years, 7.16 months; non-ASD: 5 years, 5.46 months). Findings indicated similar rates of breastfeeding for children with and without ASD (41.07% vs. 45.03%, respectively). In addition, the percentage of children fed expressed breast milk by bottle did not significantly differ between the two groups (7.14% vs. 4.17%). Conclusion: Results indicate children with ASD do not differ from non-ASD peers with food selectivity in occupancy of breastfeeding. Future research in this area should include a more detailed assessment of breastfeeding among children who develop chronic feeding concerns, including the duration, quality, and possible use of formula supplementation.

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