



Poster Session Abstracts



**STANFORD
MATERNAL & CHILD HEALTH
RESEARCH INSTITUTE**

**SECOND ANNUAL RESEARCH SYMPOSIUM
FRIDAY, NOVEMBER 15, 2019**

LI KA SHING CENTER, BERG HALL

Session 1: 3:10pm – 3:55pm (Odd #'s)

Session 2: 4:00pm – 4:45pm (Even #'s)

Name: Yair Bannett, MD

Title: Instructor

Department: Pediatrics (Developmental Behavioral Pediatrics)

MCHRI Support: Clinical Trainee Award, Master's Tuition Program (MTP) Award

Category: Advocacy & Community Health

Poster #:

1

Primary Care Diagnosis and Management of Attention-Deficit/Hyperactivity Disorder in Children Aged 2 - 5 Years

This study assessed (1) rates of primary care provider (PCP) diagnosis of Attention-deficit/hyperactivity disorder (ADHD) in preschoolers, (2) PCP adherence to select clinical practice guidelines, and (3) patient factors influencing variation in diagnosis and management. We analyzed electronic health records from all 2015-2019 office visits of children (2-5 years) in Packard Children's Health Alliance.

Of 29,408 children, 195 (0.7%) carried an ADHD diagnosis. Of those, 105 (54%) had documented comorbidities (e.g., language delay). ADHD medications were prescribed only to children aged 4-5 years (40/195 (21%)); 34/40 received stimulants as initial medication, and 19/40 had follow-up visits within 2 months. Children with public or military insurance were more likely to have ADHD diagnoses (OR=1.64; CI: (1.17, 2.26); OR=2.22; CI: (1.32, 3.56)).

ADHD diagnosis rates were below estimated prevalence, with evidence of sociodemographic disparities. PCPs followed guidelines -- identifying comorbid conditions and choosing stimulants -- but had low rates of timely follow-up.

Name: Arielle Kempinsky
Title: Medical Student
Department: School of Medicine
MCHRI Support: Faculty Scholar Award
Category: Advocacy & Community Health

Poster #: 2

Engaging Young People as Agents of Change: A School-based Intervention to Reduce Arbovirus Transmission - 1 Year Follow-up Interviews

Sustainable behavior change is a necessary step in reducing the burden of mosquito-borne diseases in rural Kenya. Without the ability to cure these diseases, we must focus on source reduction, which is directly impacted by a household's perceptions. This study aims to better understand the impetus for or against container management focused behavior change following a school-based educational intervention. From a sample size of 500, 17 adopter households and 17 non-adopters were randomly selected for inclusion. Field assistants conducted structured interviews with each mother to synthesize why households did or did not change their behavior, along with the effect of these choices. For mosquito related priorities, we saw nine adopters rank container management in their top two, as compared with five non-adopters. The interviews revealed the most common extrinsic obstacle mothers faced was the behavior of other family members, while the most common intrinsic barrier was lack of time. Long-term behavior change requires empowering local community members to create structural changes from within.

Name: Annette Nasr, PhD
Title: Clinical Associate Professor
Department: Pediatrics (Gastroenterology)
MCHRI Support: Clinician Educator (CE) Award
Category: Advocacy & Community Health

Poster #:

3

A Qualitative Research Comparison of the Parental and Adolescent Perspectives on Live Liver Donation

Background: Live liver donation is one viable option that fills the current demand presented by children with end stage liver disease.

Methods: This research compares two perspectives on life after live liver donation one perspective taken from parental live liver donors and the other is taken from adolescent live liver recipients. A semi-structured interview guide was implemented in both cohorts.

Results: Thematic analysis was conducted on both data sets which provided categories and themes common to the participant group. Data from the parental donor reflected an overarching theme of “Transformation” while for the adolescent participants the theme that evolved was one of “Resiliency”.

Conclusion: Data suggests that both groups found that the transplant experience resulted in a personal growth to their lives whether it was feeling transformed or demonstrating resiliency.

Name: Destiny Phillips
Title: Medical Student
Department: Obstetrics & Gynecology
MCHRI Support:
Category: Advocacy & Community Health

Poster #:

4

State Policies on Sexual Education and their Effect on Teenage Birth Rates

Objective: Teen pregnancy and birth rates in the United States vary significantly by state. We sought to determine whether state policies on sex education had an effect on teen birth rates.

Methods: Data on teen birth rates from 2000-2017 from the National Vital Statistics Report by the CDC and on state policies from the Guttmacher Institute were used. Descriptive statistics, regression analyses, and difference in differences estimation were used to describe the impact of policies on birth rate over time by state and age group (15-17, 18-19).

Results and Conclusions: State policies alone were not predictors of teen birth rates with teen birth rates varying by age group and type of sex education policies. Difference in difference models demonstrated that states implementing comprehensive sex education policies had larger decreases in teenage birth rates for all age groups in subsequent years than those that had no change in policy.

Name: Krista Sigurdson, PhD
Title: Clinical Research Coordinator
Department: Pediatrics (Neonatology & Developmental Medicine)
MCHRI Support: Postdoctoral Support Award
Category: Advocacy & Community Health

Poster #:

5

Former NICU Families Reveal Gaps in Family-Centered Care

Care and outcomes of infants who require care in a neonatal intensive care unit setting vary significantly. Differences and gaps in family-centered care may contribute to this variation. The objective of this study was to understand families' experiences of neonatal care within a framework of family-centered care which situates parents as partners in the care of their infant and entitled to services and supports. We conducted focus groups and interviews with 18 family members whose infants were cared for in California NICUs to explore their experiences of care delivery using a grounded theory approach. Families identified the following counterforces to family-centered care: 1) conflict between families and social work or family lack of knowledge/ambivalence regarding social work, 2) staff judgment of, or unwillingness/inability to, address barriers to presence at bedside, 3) need for nurse continuity of care and a meaningful relationship with nurses and 4) inconsistent access to translation services.

Name: Elizabeth Wall-Wieler, PhD
Title: Postdoctoral Researcher
Department: Pediatrics (Neonatal & Developmental Medicine)
MCHRI Support: Postdoctoral Support Award
Category: Advocacy & Community Health

Poster #:
6

Benzodiazepine use around conception and risk of ectopic pregnancy

Objective: Compared the risk of ectopic pregnancy among women with and women without benzodiazepine prescriptions around conception.

Methods: We performed a cohort study of all pregnancies between November 1, 2008 and September 30, 2015 identified in the nationwide IBM® MarketScan® Databases (n = 1,890,810). Relative risks (RR) of ectopic pregnancy were obtained from unadjusted and inverse probability of treatment (IPT) weighted log-binomial models.

Results: Benzodiazepine prescriptions were identified around conception among 1.06% of pregnancies. Among women with a prescription, there was an excess of 135 ectopic pregnancies per 10,000 pregnancies, and their IPT-weighted risk of ectopic pregnancies was 1.52 (95% CI 1.40-1.65) times greater relative to women without benzodiazepine prescriptions around conception.

Conclusions and Relevance: An increased risk of ectopic pregnancy was identified among women who had benzodiazepine prescriptions around conception. Physicians should consider this when evaluating the risks and benefits of benzodiazepine use among women of reproductive age.

Name: Wei Jiang, PhD
Title: Instructor
Department: Pediatrics (Human Gene Therapy)
MCHRI Support: Postdoctoral Support Award
Category: Allergy / Asthma / Immunology

Poster #:
7

Hypocretin-specific CD4+ T cells in narcolepsy patients and controls: in vivo clonal expansion and phenotypes

Loss of neurons uniquely supplying hypocretin (HCRT) neurotransmitters causes narcolepsy. Previous studies found associations of narcolepsy with human leukocyte antigen (HLA)-DQ6 and T-cell receptor $\hat{I}\pm$ (TRA) J24 gene segment, and suggested that in vitro-stimulated T cells can target HCRT. However, evidence of in vivo expansion of HCRT-reactive cells expressing TRAJ24 has been lacking. Here, we isolate DQ6-HCRT tetramer+/CD4+ T cells directly ex vivo from DQ6+ individuals with/without narcolepsy. Within 74 informative TRAJ24+ TCR $\hat{I}\pm/\hat{I}^2$ from 8/12 patients and 11/12 controls, a conserved family of clonotypes from 2 patients and 2 controls use identical $\hat{I}\pm/\hat{I}^2$ genes. TRAJ24-G allele+ clonotypes only expand in the two patients, whereas a TRAJ24-C allele+ clonotype expand in a control. A representative tetramer+/G-allele+ TCR shows functional reactivity to the physiological form of the epitope HCRT87-97. Clonally expanded G-allele+ T cells exhibit an unconventional effector phenotype. Our analysis and findings open an avenue for further investigation of narcolepsy-relevant autoimmunity.

Name: Hesam Movassagh, PhD
Title: Postdoctoral Researcher
Department: Medicine (Pulmonary, Allergy & Critical Care Medicine)
MCHRI Support:
Category: Allergy / Asthma / Immunology

Poster #:
8

Dysregulation of Circulating Monocytes is Associated with Exposure to Air Pollution and Asthma Onset in Children

Exposure to particulate matters may be associated with dysregulation of monocytes and asthma onset in children. We recruited children from an area with elevated air pollution (Fresno-CA). Using cytometry time-of-flight (CyTOF), we characterized immune cells including monocytes in PBMC. Furthermore, we measured markers of inflammation using Luminex 63-plex assay. Increased exposure to PM_{2.5} was associated with elevation of monocytes in children. Monocytes from high PM_{2.5} exposed children upregulated expression of aryl hydrocarbon receptor, AhR. Decline in FEV₁/FVC was associated with accumulation of monocytes. A significant negative correlation between FEV₁/FVC and frequency of monocytes was observed. Increase in circulating IL-1 β was associated with elevation of both CD14 and AhR in children. Elevation of monocytes and upregulation of IL-1 β and AhR upon AP suggest an inflammasome-mediated mechanism of immune dysregulation. Increased accumulation of monocytes may represent a novel immune signature as a prognostic biomarker for children living in highly polluted areas.

Name: Chris Severyn, MD, PhD
Title: Postdoctoral Researcher
Department: Pediatrics (Hematology/Oncology)
MCHRI Support: Clinical Trainee Award
Category: Allergy / Asthma / Immunology

Poster #:
9

Impact of Gut Decontamination on Intestinal Microbiome Composition in Pediatric Allogeneic Hematopoietic Stem Cell Transplant Patients

Clinical studies demonstrate that suppressing bacterial growth in the intestine with broad spectrum oral antibiotics (called "gut decontamination" (GD)) can decrease the risk of acute graft-versus-host disease (aGVHD) following allogeneic hematopoietic stem cell transplantation (HSCT). In contrast, recent adult HSCT studies show that GVHD-related mortality is associated with decreased bacterial diversity, suggesting that some bacterial species may protect against GVHD and that the practice of gut decontamination may not improve patient outcomes. Here we present the preliminary findings for two pediatric patients undergoing HSCT using shotgun metagenomic sequencing (ClinicalTrials.gov NCT02641236) for a total of 20 randomized patients.

Name: M. Peter Marinkovich, MD
Title: Associate Professor
Department: Dermatology
MCHRI Support: SPARK Award
Category: Biodesign / Biotechnology / SPARK

Poster #: 10

Results from a Phase I/II study of topical gene therapy (bercolagene telsepavec, B-VEC) in pediatric and adult recessive dystrophic epidermolysis bullosa (RDEB) patients

Recessive dystrophic epidermolysis bullosa (RDEB) is a severe blistering skin disorder, without approved corrective therapies, caused by type VII collagen (C7) gene (COL7A1) mutations. We report results of a novel gene therapy employing a replication defective herpes simplex virus-1 vector encoding COL7A1, bercolagene telsepavec (B-VEC), which is applied directly to RDEB skin. Eight wounds in six pediatric and adult RDEB patients were repeatedly treated with topical B-VEC, and compared with placebo controls. All eight B-VEC treated wounds healed without inflammation, remaining healed for up to 6.6 months. In addition, robust C7 basement membrane expression in anchoring fibrils were demonstrated in B-VEC treated skin. Two additional pediatric patients are currently undergoing treatment of chronic wounds up to 70 cm² and the Phase 2 study is ongoing in these two additional patients. Overall, results from the Phase I/II studies demonstrate a novel, safe, effective and easily administered approach to RDEB molecular correction.

Name: Nicole Neiman, MPH
Title: Research Assistant
Department: Anesthesiology, Perioperative, and Pain Medicine
MCHRI Support:
Category: Biodesign / Biotechnology / SPARK

Poster #:
11

Feasibility of Virtual Reality (VR) Mindfulness for Anxiety and Pain Management in Pediatric Inflammatory Bowel Disease (IBD) Patients

Mindfulness based exercises have grown in practice to help manage chronic pain and anxiety, common symptoms of children with inflammatory bowel disease (IBD). Virtual reality (VR) has been found to be an effective and feasible tool for alleviating pain and anxiety. This study explored the feasibility and efficacy of a six minute immersive mindfulness experience within a VR headset for 39 pediatric IBD patients at Stanford Children's IBD Center. Patients completed pre- and post- pain and anxiety numerical rating scales (NRS) and visual analogue scales (VAS), along with a satisfaction survey. VR mindfulness significantly improved patient reported pain (NRS: $t_{38}=2.553$, $p=0.015$; VAS: $t_{38}=2.818$, $p=0.008$) and anxiety (NRS: $t_{38}=3.918$, $p<0.001$; VAS: $t_{38}=3.762$, $p=0.001$) on both scales. 51.3% and 48.7% of patients rated 5/5 for feelings of enjoyment and relaxation, respectively, during the VR experience. Preliminary results demonstrate that VR mindfulness is effective in improving pain and anxiety in pediatric IBD patients.

Name: Anoop Rao, MD, MS
Title: Instructor
Department: Pediatrics (Neonatal & Developmental Medicine)
MCHRI Support:
Category: Biodesign / Biotechnology / SPARK

Poster #: 12

Continuous Non-Invasive Blood Pressure Monitoring in Neonates Using a Wearable Capacitive Sensor

Objectives: Evaluate the feasibility of a wearable continuous non-invasive blood pressure (cNIBP) monitoring device in critically ill neonates. Eleven critically ill but normotensive neonates with umbilical catheters (gestational age ranged from 26-6/7 to 40-1/7 weeks, weight ranged from 0.9 kg to 3.6 kg) novel capacitive sensors placed on wrist and foot to obtain pulse waveform measurements for up to 10 hours per infant. Changes in capacitance captured by cNIBP sensor were wirelessly transmitted to an Android application which used proprietary and highly efficient artificial neural network (ANN) algorithms to derive SBP, DBP, and MAP values. These BP data were then compared with gold-standard umbilical arterial line data to determine the accuracy.

Results: Approximately 100 hours of cNIBP data from eleven patients was correlated with corresponding arterial line data. Bland-Altman plots for systolic (SBP), diastolic (DBP), and mean arterial blood pressure (MAP) show mean average errors (MAE) $< \hat{A} \pm 5$ mmHg with standard deviations (SD) < 8 mmHg.

Conclusions: The cNIBP sensor can non-invasively monitor the blood pressure of neonates who are less than a week old with an accuracy within FDA specifications. Our study is limited to critically ill but normotensive neonates.

Name: Tulio Valdez, MD, MSc
Title: Associate Professor
Department: Otolaryngology
MCHRI Support: Biodesign Faculty Fellowship Award
Category: Biodesign / Biotechnology / SPARK

Poster #: 13

SWIR Fluorescence Imaging for Otitis media diagnosis

Otitis media is one of the most common reasons for pediatrician visits, antibiotic prescription, and surgery in the pediatric population. The difficulty in identifying middle ear conditions is mainly responsible for both the over-diagnosis of cases of AOM and the frequent under-diagnosis of cases of OME. With these challenges in mind, we have recently developed a probe fluorescent in the shortwave infrared (SWIR, 1-2 micrometer) wavelengths of light to improve middle ear disease diagnoses. Fluorescence SWIR otoscopy provides two fundamental advantages over conventional visible light-based pneumatic otoscopy. The first one is the augmented contrast in the presence of middle ear fluid due to increased water absorption, and second, the ability to detect fluorescence in the presence of inflammation.

Name: Mingxia Gu, MD, PhD

Title: Instructor

Department: Pediatrics (Cardiology)

MCHRI Support: Cardiovascular Institute (CVI) Award, Instructor K Award Support Award

Category: Cardiovascular Medicine

Poster #:

14

Single-Cell RNA-Seq and Patient-Specific iPSCs Reveal Endocardial Abnormalities in Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) is one of the most devastating forms of congenital heart defects. Previous studies have only focused on intrinsic defects in the myocardium. However, this does not sufficiently explain the abnormal development of cardiac valve, septum, and vasculature, which are known to originate from the endocardium. Here, using single-cell RNA profiling, induced pluripotent stem cells, and fetal heart tissue with underdeveloped left ventricle, we identified a developmentally impaired endocardial population in HLHS. The intrinsic endocardial deficits contributed to abnormal endothelial to mesenchymal transition, NOTCH signaling, and extracellular matrix organization, all of which are key factors in valve formation. Consequentially, endocardial abnormalities conferred reduced proliferation and maturation of cardiomyocytes through a disrupted fibronectin-integrin interaction. Several known HLHS de novo mutations all contributed to the abnormal endocardial gene expression through the alteration of promoter activities. These mechanistic discoveries provide an alternative angle for early intervention and heart regeneration in HLHS.

Name: Vivian Saper, MD
Title: Clinical Professor
Department: Pediatrics (Human Gene Therapy)
MCHRI Support:
Category: Cardiovascular Medicine

Poster #:
15

An emergent high fatality lung disease in systemic juvenile arthritis

Background: Systemic onset juvenile idiopathic arthritis (SJIA) is a chronic inflammatory disease. IL-1 and IL-6 inhibitors have shown striking efficacy in SJIA, but coincident with their use, a novel and high-fatality lung disease (LD) has emerged.

Methods: A multi-center international retrospective study of 61 cases of SJIA-LD collected clinical information, with centralized analyses of radiologic, pathologic and genetic data.

Results: LD was marked by features atypical for SJIA and, in some cases, drug-related anaphylaxis or delayed drug hypersensitivity. In 23/36 biopsies, pathology was pulmonary alveolar proteinosis/endogenous lipoid pneumonia (PAP/ELP). Chest CT patterns were unusual for PAP/ELP. 5-year survival was 42%. Whole-exome sequencing (20/61) did not identify novel defects or other likely causal genetic variants. Trisomy 21 and young SJIA onset increased risk. Exposure to inhibitors (46/61) was associated with multiple LD features.

Conclusions: A rare, life-threatening LD in SJIA is defined by a constellation of unusual clinical characteristics. Exposure to inhibitors may promote lung disease.

Name: Alison Schroer, PhD
Title: Postdoctoral Researcher
Department: Pediatrics (Cardiology)
MCHRI Support: Transdisciplinary Initiatives Program (TIP)
Category: Cardiovascular Medicine

Poster #: 16

Hypertrophic cardiomyopathy mutations with opposite effects on β -myosin biomechanics show similar structural and biomechanical phenotypes in human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs)

Hypertrophic cardiomyopathy (HCM) is the most prevalent heritable cardiovascular disease, commonly caused by mutations in beta cardiac myosin heavy chain (β MYH). We found intriguing heterogeneity in velocity and force of isolated myosin with HCM mutations, but it is not well understood how these alterations converge to the HCM phenotype. We have used CRISPR/Cas-9 gene editing to create hiPSCs with two different β MYH mutations that result in opposite effects on the molecular scale. Cell morphology was quantified by both fluorescence and transmission electron microscopy (EM) and force generation measured by traction force microscopy on engineered micropatterned platforms. Both HCM lines showed increased contractile force and cellular hypertrophy compared to isogenic controls and both had altered Akt signaling. Immunostaining for β MYH and EM revealed microstructural changes including myofibrillar disarray, and thickened z-discs in cells containing these mutations. Ongoing work will clarify distinct mechanisms that contribute to cellular hypercontractility and hypertrophy.

Name: Alisha Tolani, MD
Title: Resident
Department: Obstetrics & Gynecology
MCHRI Support:
Category: Cardiovascular Medicine

Poster #:
17

Care of the pregnant cardiac patient – the importance of a multidisciplinary approach

Objective: The objective was to assess outcomes among pregnant women with cardiac disease managed by a multidisciplinary team.

Study Design: This retrospective cohort study was conducted in a single-center between 2012-2018. At our center, all pregnant patients with cardiac disease are cared for by a multidisciplinary team. Monthly meetings are held to coordinate care and develop detailed delivery and postpartum plans including intrapartum monitoring, labor analgesia, and postpartum location.

Results: Among 136 pregnancies in 117 women, 7% developed pre-eclampsia, 7% had PPROM, and 26% had preterm birth. Thirty nine percent were induced, 26% of whom had worsening cardiac function. Fourteen percent experienced an intrapartum cardiac or thrombotic event. Fifty seven percent delivered vaginally. Of the cesarean sections, 45% were scheduled, and the remainder were for obstetric or neonatal indications. Fifteen percent developed a postpartum cardiac event, and 12% experienced severe maternal morbidity (SMM) at the time of delivery.

Conclusion: Peripartum SMM and obstetric complications among cardiac patients are higher than the rate described in the general population. Given the increased morbidity, such pregnancies mandate multidisciplinary comprehensive pregnancy care and planning.

Name: Xuan Yu, MD, PhD
Title: Postdoctoral Researcher
Department: Anesthesiology, Perioperative, and Pain Medicine
MCHRI Support:
Category: Cardiovascular Medicine

Poster #:
18

E-cigarette vapor elevates cardiovascular oxidative stress in ALDH2*2 variant young adult male mice

20.8% of high school students in the US are current e-cigarette users. E-cigarette aerosol contains reactive aldehydes, which induce cellular oxidative stress. Reactive aldehydes are metabolized by a mitochondrial enzyme aldehyde dehydrogenase 2 (ALDH2); a genetic variant known as ALDH2*2 limits the ability to metabolize reactive aldehydes. Little is known how e-cigarettes, coupled with genetic differences in aldehyde metabolism, affect cardiovascular oxidative stress in young adults. E-cigarette Juul aerosol was collected and quantified to measure nicotine and reactive aldehydes levels. Paired age-matched male wild type ALDH2 and homozygous ALDH2*2 mice (8 weeks old) were implanted with EKG telemeters to monitor heart rate daily, and were exposed to Juul or air for 10 days. Hearts were then subjected to oxidative stress assays. We found Juul aerosol contains reactive aldehydes (acetaldehyde, formaldehyde and acrolein) and nicotine. Heart rate was significantly increased in ALDH2*2 mice unlike ALDH2 wild type mice (32.5 ± 32.6 bpm versus -88.2 ± 23.1 bpm, relative to baseline heart rate, $*p < 0.01$, $n=8$), when rodents were exposed to Juul aerosol. Hearts from ALDH2*2 mice also had higher levels of HNE adducts, protein carbonyls and lipid peroxides relative to wild type ALDH2 hearts. A deficiency in aldehyde metabolism by having an ALDH2*2 variant contributes to increases in heart rate and cardiovascular oxidative stress within young adult male mice while smoking e-cigarette Juul.

Name: Kathleen Dantzler, PhD
Title: Postdoctoral Researcher
Department: Medicine (Infectious Diseases)
MCHRI Support: Postdoctoral Support Award
Category: Global Health / Infectious Disease

Poster #: 19

Mechanisms driving V δ 2+ γ δ T cell function during recurrent malaria infection

Natural immunity to the most deadly human malaria parasite provides some protection against symptomatic disease but is unable to eliminate parasite replication—likely due to chronic inflammation caused by innate cell activation. Repeated malaria exposure leads to attenuation of the pro-inflammatory response from V δ 2+ γ δ T cells, which associates with a reduced likelihood of symptoms upon subsequent infection. Leveraging clinical samples from a longitudinal cohort in Uganda, we are utilizing several epigenetic and transcriptional approaches to identify putative mechanisms underlying this altered V δ 2+ T cell function. Preliminary results indicate significant differences in chromatin accessibility between V δ 2+ T cells from children with high vs. low malaria exposure. We are further establishing in vitro assays to quantify changes in V δ 2+ T cell functions. By deepening our understanding of the molecular mechanisms driving inefficient acquisition of antimalarial immunity, this work could enable novel therapeutic approaches that enhance parasite clearance and/or reduce disease severity.

Name: Prasanna Jagannathan, MD
Title: Assistant Professor
Department: Medicine (Infectious Diseases & Geographic Medicine)
MCHRI Support: Pilot (Early Career) Award
Category: Global Health / Infectious Disease

Poster #:
20

Cellular correlates of protective immunity to malaria in pregnancy

Malaria during pregnancy remains a significant cause of morbidity and mortality for both pregnant women and their infants, though with successive pregnancies, women eventually develop immunity against these adverse outcomes. To identify cellular correlates of protection from malaria in pregnancy, we obtained cryopreserved PBMCs during the 2nd trimester and at delivery among primi- and multigravid pregnant women living in a high malaria transmission setting in Uganda. Malaria parasite-induced intracellular cytokine production was assessed by flow cytometry. We found that primigravid women have a malaria-specific CD4+ T cell response characterized by high IL-10, with significantly higher effector memory responses co-producing IL-10, IFN γ , and IL-21, than multigravida women. In contrast, multigravid women had significantly higher frequencies of malaria-specific CD4+ T cell responses that produced TNF in the absence of these other cytokines. Higher malaria-specific CD4+ IL10 production was associated with a higher risk of placental malaria, and TNF responses were associated with protection against placental malaria. Identification of cellular correlates and mechanisms of protection against malaria in pregnancy will inform the rational design of preventive interventions in pregnancy, including vaccines.

Name: Amy Krystosik, PhD, MPH
Title: Postdoctoral Researcher
Department: Pediatrics (Infectious Diseases)
MCHRI Support: Postdoctoral Support Award
Category: Global Health / Infectious Disease

Poster #:
21

The use of spatial video geonarratives to describe localized environmental risk patterns for arboviral transmission in urban Kenya

Urban arboviral disease mitigation depends on costly vector control targeted to high-risk areas which are difficult to identify. Disease ecology and epidemiology vary over space and time, requiring fine scale data on environmental factors to evaluate disease risk. We interviewed local vector control technicians, community health workers, and leaders in urban areas of Kwale, County, Kenya to describe fine scale risks. Environmental risks hotspots will be compared with previously identified dengue and chikungunya exposure and *Aedes* spp. vector abundance hotspots. Micro-scale risk pattern identification will allow forecasting of high-risk exposure areas and provide policy recommendations to maximize vector control in resource limited settings.

Name: A. Desiree LaBeaud, MD, MS

Title: Professor

Department: Pediatrics (Infectious Diseases)

MCHRI Support: Bridge Support Award, Faculty Scholar Award, Institute for Immunity, Transplantation, & Infection (ITI) Award, Pilot (New Ideas) Award

Category: Global Health / Infectious Disease

Poster #:

22

No evidence for adverse Zika virus-associated birth and one-year outcomes in a prospective Grenadian cohort

The impact of Zika virus (ZIKV) on neurocognitive outcomes remains unknown. We followed women in Grenada exposed to ZIKV during pregnancy and their offspring at prenatal, postpartum and one-year post-partum to assess maternal and child ZIKV exposure and child delivery outcomes by nurse assessment, child growth, and child neurodevelopment outcomes by Oxford Neurodevelopment Assessment (OX-NDA). We enrolled 384 women and their 388 children. ZIKV infection during pregnancy was classified in 376 women by plasmonic-gold IgG (PGOLD) and PCR testing as probable (113), possible (144), and none (119). We observed no differences in demographics across maternal exposure groups. Of the 388 infants, only 1.6% (2/122) were positive for ZIKV IgG. Amongst 92 children completing the 12 month OX-NDA assessment, overall, motor, and cognitive domain scores increased with age by 2-3 points per month after controlling for age and parish. We observed no differences in child delivery, anthropometrics, or OX-NDA outcomes across maternal exposure strata. At 12 months of age, children exposed to ZIKV in utero appear to be growing and neurodeveloping on par with their peers.

Name: Melisa Shah, MD, MPH
Title: Postdoctoral Researcher
Department: Medicine (Infectious Diseases & Geographic Medicine)
MCHRI Support: Clinical Trainee Award
Category: Global Health / Infectious Disease

Poster #: 23

Dengue virus circulation in western and coastal Kenya: clinical presentation, epidemiology, and phylogenetics (2014-2017)

Dengue virus is an emerging worldwide threat. In Africa, little is known about the burden and circulation of dengue virus. This study identified contemporary dengue strains and their phylogenetic associations in Kenyan children with undifferentiated fever. We used multiplexed rRT-PCR including serotype specific assays to test 1078 febrile children for dengue. We conducted whole genome and Sanger sequencing on select samples. There were 364 cases of dengue viremia during the 2014-2017 study period. Over 50% of dengue viremic patients were positive for malaria by microscopy. Dengue 2 was the most common serotype (72.6%). Dengue 1 strains matched to genotype II, dengue 2 strains matched to genotypes I and II, dengue 3 strains matched to genotype V, and dengue 4 strains matched to genotype II. This study shows the presence and circulation of multiple serotypes of dengue virus in Kenya and adds valuable field strains to public databases.

Name: Xin She, MD, MPH
Title: Clinical Assistant Professor
Department: Pediatrics (Hospital Medicine)
MCHRI Support:
Category: Global Health / Infectious Disease

Poster #: 24

Mental health in underserved rural Chinese children compared to urban children: A gender-focused analysis

Mental health disorders lead to 23% of all years lost worldwide. Half of these conditions start before 14 years-old. Although 90% of young people live in developing countries, only 10% of studies come from these. China has the world's second largest pediatric population. Historically, girls had significantly poorer health.

A combination of urban-rural samples included 1729 students ages 12-14 surveyed using the 2003 WHO GSHS. Multivariate regression analysis was used to compare girls to boys in terms of depressive symptoms, suicidal ideation/ attempt, bullying, substance use and injuries, absenteeism, perceived school support and parental supervision. Rural vs. urban findings were analyzed.

Girls are significant more likely to feel lonely. Boys are significantly more likely to be bullied, engage in fighting, suffer injuries, use tobacco, get drunk, and miss school. Compared to urban children, rural children had much higher prevalence of most mental health problems. The relative gender differences remained similar.

Name: Maureen Ty, PhD
Title: Postdoctoral Researcher
Department: School of Medicine (Infectious Diseases & Geographic Medicine)
MCHRI Support:
Category: Global Health / Infectious Disease

Poster #:
25

Immunologic profiles defining clinical states in malaria

Malaria due to *Plasmodium falciparum* remains a compelling global health problem. The knowledge gap regarding mechanisms of protective immunity and pathogenesis is a major challenge in vaccine development. To better understand the development of clinical immunity, longitudinal samples from children in Uganda were used to investigate the molecular networks underlying various clinical states of infection. PBMCs from 37 Ugandan children ages 1-11 years at three clinically-diverse timepoints were phenotyped by CyTOF, and malaria-specific responses assessed by intracellular cytokine staining. Clustering analysis indicates B-cells are enriched in symptomatic infection, and myeloid cells are abundant in asymptomatic infections. We also observed that malaria-specific responses were reduced at symptomatic timepoints, suggesting that there are marked differences among the immune profiles of children in different clinical states. Elucidating the dynamics of these different immune responses will be crucial to understanding clinical immunity and may have implications for future vaccine development and better malarial interventions.

Name: David Vu, MD, MS

Title: Instructor

Department: Pediatrics (Infectious Diseases)

MCHRI Support: Instructor K Award Support Award, Pilot (Early Career) Award

Category: Global Health / Infectious Disease

Poster #:

26

Dengue virus and malaria co-infections among febrile Kenyan children challenge the paradigm of diagnostic parsimony

Identification of concurrent dengue virus (DENV) and malaria infections in a cohort of febrile Kenyan children challenges the paradigm of diagnostic parsimony (Occam's Razor). Of the 5,429 febrile Kenyan children enrolled between 2014-2018 who had test results for both DENV and malaria, 5.4% were DENV/malaria co-infected, 3.9% were DENV solo-infected, and 51.4% were malaria-solo infected. Classic symptoms for DENV infection, such as retro-orbital headache and bruising, were rare. Surprisingly, DENV/malaria co-infected children were less likely to have joint pain than DENV solo-infected children, and less likely to report dizziness and abdominal pain than malaria solo-infected. However, co-infected children were more likely to have joint tenderness on exam than malaria solo-infected children. Stratification of malaria-infected children by concurrent DENV infection revealed effect modification on some malaria-associated signs and symptoms. In malaria-endemic areas, practicing diagnostic parsimony risks missing DENV/malaria co-infection, perpetuating under-recognition of the interactions between concurrent pathogeneses of the two infections.

Name: Hee-Don Chae, PhD
Title: Research Scientist
Department: Pediatrics (Hematology/Oncology)
MCHRI Support:
Category: Hematology / Oncology

Poster #: 27

RSK Inhibition Induces Metaphase Arrest and Apoptosis in Acute Myeloid Leukemia Cells

The 90 kDa Ribosomal S6 Kinase (RSK) drives cell proliferation and survival in several cancers, although its oncogenic mechanism has not been well characterized. Treatment of BI-D1870, a potent inhibitor of RSK, increased the G2/M population and induced apoptosis in AML cell lines. Further characterization of mitotic phases showed that the metaphase/anaphase transition was significantly stalled by RSK inhibition following release from mitotic arrest. BI-D1870 induced apoptosis and metaphase arrest in primary patient AML cells. BI-D1870 treatment impeded the association of activator CDC20 with APC/C, but increased binding of inhibitor MAD2 to CDC20, preventing metaphase/anaphase progression. The inactivation of spindle assembly checkpoint (SAC) released cells from BI-D1870-induced metaphase arrest. MAD2 knockdown also reduced the BI-D1870-induced metaphase arrest. Furthermore, the combination treatment of BI-D1870 with vincristine in HL-60 cells showed a synergistic effect. These data show that RSK inhibition impairs metaphase/anaphase progression by inactivating APC/C, resulting in apoptosis of AML cells.

Name: Lauren Heathcote, PhD

Title: Postdoctoral Researcher

Department: Anesthesiology, Perioperative, and Pain Medicine (Pediatric Anesthesia)

MCHRI Support: Postdoctoral Support Award

Category: Hematology / Oncology

Poster #:

28

Living with uncertainty: a mixed-methods study of symptom perception after pediatric cancer

When a child lives beyond cancer, they face a lifetime of uncertainty about new or changing physical symptoms. Symptoms such as pain could indicate a normal health event (e.g. muscle ache), a consequence of toxic treatment, or cancer recurrence. The challenge for every survivor is knowing how to monitor, attend to, and interpret everyday experiences of pain. We conducted semi-structured interviews with 40 Adolescent and Young Adult (AYA) cancer survivors (15-25 years old; 45% female, 45% male, 10% non-binary) and their parents. AYA cancer survivors and their parents reported struggling with pain-related fear after cancer, including knowing how to interpret and respond to pain within the context of potential disease recurrence and late effects. Pain is a complex and often threatening experience after cancer. Assessment and intervention for post-cancer pain must be considered within a biopsychosocial framework, including fears and anxieties that patients hold about post-cancer symptoms such as pain.

Name: Mark Wilkes, PhD
Title: Postdoctoral Researcher
Department: Pediatrics (Hematology/Oncology)
MCHRI Support: Postdoctoral Support Award
Category: Hematology / Oncology

Poster #:
29

Pharmacological inhibition of Nemo-like Kinase rescues erythroid expansion in pre-clinical models of Diamond Blackfan Anemia

Diamond Blackfan Anemia (DBA) is associated with anemia, congenital abnormalities, and cancer. The disease typically presents within the first year of life. Approximately 70% of DBA patients possess a mutations in one of at least 12 ribosomal proteins, with RPS19 and RPL11 accounting for over 25% and 5% of cases respectively. Standard of care includes steroids, transfusion and stem cell transplantation, each with limitations. New therapies are needed.

Nemo-like Kinase (NLK) is chronically hyper-activated in RPS19- and RPL11-haploinsufficient murine and human models of DBA, as well as erythroid progenitors from DBA patients. Knockdown of NLK by siRNA increases erythroid expansion in DBA models. Through inhibitor screens we have identified compounds that increase progenitor expansion through NLK inhibition. We continue to develop these compounds pre-clinically towards clinical applications and have begun to elucidate the upstream and downstream signaling molecules that link NLK activation to the pathogenesis of DBA.

Name: Isabel Beshar, MPhil
Title: Medical Student
Department: School of Medicine
MCHRI Support:
Category: Maternal & Fetal Health

Poster #:
30

Sociodemographic Trends in LARC vs. Sterilization, 2006-2017

Introduction:

Historically, female sterilization (FS) has been disproportionately concentrated among racial minorities and women with lower education and income. Given increasing LARC popularity, we sought to examine changing sociodemographic patterns of FS and LARC usage.

Methods:

We used data files from the National Survey of Family Growth 2006-2010 and 2015-2017 survey waves, and analyzed all women of reproductive age not seeking pregnancy, with a sub-analysis of FS and LARC.

Results:

We included 11,073 respondents. From the earlier to later cohort, the prevalence of LARC increased 3-fold (7% to 20%), while FS dropped (25% to 22%). Overall, the most significant predictors of LARC use in the later cohort remained younger age (<34yo), higher income (>\$75,000), and more education (OR 3.6 [1.9, 6.6], 5.3[1.8, 15.9], and 4.5[2.1, 9.7]).

Conclusion:

Although LARC use has increased and FS decreased, predictors of LARC over FS include higher income and education, suggesting inequities in access.

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MCHRI Support:
Category: Maternal & Fetal Health

Poster #:
31

Maternal outcomes in planned and unplanned pregnancies in women with cardiac disease

Introduction: Pregnancy places women with cardiac disease at increased risk. Effective contraception allows patients and providers to plan pregnancy to optimize outcomes.

Methods: This was a retrospective cohort study of 136 pregnancies in women with maternal cardiac disease delivered at a single institution between 2012 and 2018. We investigated differences in outcomes between those with planned vs. unplanned pregnancy.

Results: Of 136 pregnancies in 117 women, 31 (22.8%) were unplanned vs. 36 (26.5%) planned. Rates of antepartum hospitalization, preterm delivery, cesarean section, cardiac complications, ICU admissions, and postpartum hospitalizations were similar. 37.5% of all pregnancies received contraception prior to discharge: 41.2% long-acting reversible contraception, 23.5% bilateral tubal ligation, and 33.3% contraceptive pills or condoms. Women with unplanned pregnancies were significantly more likely to be discharged with contraception (48.4% vs 19.4%, $p=0.02$).

Conclusion: We did not identify increased obstetric or cardiac risk with unplanned pregnancies when compared with planned pregnancies.

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MCHRI Support:
Category: Maternal & Fetal Health

Poster #:
32

Preterm birth occurrence among Asian women relative to their place of birth

Objective: To investigate preterm birth (PTB) rates between United States (US-born) vs. foreign-born Asian women.

Study Design: Linked birth certificate and maternal discharge data were used to identify nulliparous women with singleton livebirth and Asian race in California between 2007-2011. PTB was defined as delivery at <37 weeks gestation and further divided into spontaneous and medically indicated PTB. The rate of PTB was examined by self-reported race and place of birth among ten Asian subgroups.

Results: We observed lower overall and spontaneous PTB rates among foreign-born compared to US-born Asian women in nine out of ten subgroups. There were marked differences in PTB rates between individual Asian subgroups: Korean women had a very low PTB rate whereas both foreign-born and US-born Filipino women had twice as high PTB rates.

Conclusion: Among Asian subgroups examined, women who were foreign-born had lower overall and spontaneous PTB rate compared to US-born Asian women.

Name: Stephanie Leonard, PhD
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MCHRI Support: Postdoctoral Support Award
Category: Maternal & Fetal Health

Poster #:
33

Weight Gain during Pregnancy & Severe Maternal Morbidity

High and low prepregnancy body mass index (BMI) are risk factors for severe maternal morbidity (SMM), but the contribution of gestational weight gain (GWG) is not yet understood. We used linked birth certificate and hospitalization discharge records from 2,483,684 Californian births during 2007-2012 to evaluate the relationship between GWG and SMM. We used established z-score charts to standardize GWG for gestational duration. We found modest U-shaped relationships between GWG z-score and SMM in all BMI groups except class 3 obesity, for which risk was lowest with weight loss. The prevalence of SMM was highest in women with class 3 obesity and excessive GWG (147 per 10,000 births) and underweight women with inadequate GWG (128 per 10,000 births). However, confidence intervals for these differences included the null and current recommended GWG ranges did not include the GWG amounts at which the risk of SMM was lowest, except in women with underweight.

Name: Nurlybek Mursaliyev, PhD Candidate
Title: Graduate Student
Department: Biology and Obstetrics & Gynecology
MCHRI Support:
Category: Maternal & Fetal Health

Poster #: 34

Obesity induced alteration in energy homeostasis and lipid metabolism in preimplantation embryos can be reflected by non-invasive single embryo density measurements.

Assisted reproductive technology (ART) is a term that broadly refers to technologies used to treat or aid patients with infertility to achieve successful pregnancies. In humans, obesity has been linked to low fertility and low embryo viabilities. In our study we use high fat high fructose induced females and leptin mutant mouse models to address the effects of obesity on embryo qualities. We also use novel non-invasive magnetic levitation based approach to investigate the roles of density in preimplantation embryo development potentially to score embryo viability. Using this device, we for the first time characterized density properties of mammalian preimplantation embryos. Lipid droplet content in embryos correlated with densities during normal development. Female obesity increased embryonic lipid content and lowered density measurements compared with control embryos. We confirmed low qualities of embryos from obese mice, which are reflected by slow developmental rate and high apoptotic cells. RNAseq analysis revealed metabolic/energy homeostasis genes being significantly down regulated, such as AMPK and SIRT1. This indicates maternal obesity alters embryonic metabolic homeostasis that could explain high lipid content, low embryo qualities and low-density measurements under obese conditions. Ultimately, we want to use the density properties to predict the most viable embryos and potentially induce AMPK pathway to enhance preimplantation embryo development for ART purposes.

Name: Kate Shaw, MD, MS
Title: Clinical Associate Professor
Department: Obstetrics & Gynecology (Family Planning)
MCHRI Support:
Category: Maternal & Fetal Health

Poster #: 35

Effect of early postpartum contraceptive implant insertion timing on breastfeeding: A non-inferiority randomized controlled trial

Background: Initiation of postpartum contraception prior to hospital discharge has been limited by concerns around the impact of progestins on breastfeeding.

Objective: To determine if time to lactogenesis stage II (LTII, initiation of copious milk secretion) differs by timing of contraceptive implant insertion.

Methods: We randomly assigned 95 parturients desiring an implant for postpartum contraception to implant insertion 0-2-hours (delivery room) or 24-48-hours (delayed) post-delivery. We collected self-reported information on LTII using a validated tool.

Results: As-treated analysis included 71 participants (n=35 delivery room, n=36 delayed). Mean time to LTII did not differ significantly (delivery room: 65-hours, SD 25 vs. delayed: 74-hours, SD 51; p=0.37). Delivery room insertion was non-inferior with regard to onset of LTII, when compared to delayed insertion, using an a priori non-inferiority margin of 12 hours (mean difference -8.64, 95% CI -27.69 – 10.42).

Conclusion: Delivery room insertion of the contraceptive implant does not delay onset of lactogenesis and should be offered.

Stanford IRB e-protocol # 38505
ClinicalTrials.gov Identifier: NCT02866643

Name: Amy Braun, PhD
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Category: Neonatal & Developmental Medicine

Poster #: 36

“Females are not just ‘protected’ males”: Sex-specific vulnerabilities in placenta and brain after prenatal immune disruption

Current perceptions of fetal vulnerability are focused on male outcomes. Here we examine this assumption in the context of a maternal immune disruption of fetal development and its postnatal outcomes in female and male mice. Pregnant mice were treated with low dose lipopolysaccharide (LPS) at embryonic day 12.5. Acute changes in placenta and fetal brain, were compared between male and female offspring, along with long-term changes in adult cortex cytoarchitecture and behavior. Males experience more pronounced placental pathology, fetal brain hypoxia, depleted Parvalbumin+ (PV) and Satb2+ densities, and social and learning-related behavioral abnormalities typically associated with autism. In contrast, females exhibit acute inflammatory signaling in fetal brain, opposite alterations in cortical PV densities, postnatal growth delay, changes in juvenile behavior, and elevated anxiety-related behavior as adults. Our results highlight disparate sex-specific features of prenatal vulnerability to maternal inflammation and warn against the casual extrapolation of male disease mechanisms to females.

Name: Mariia Burdyniuk, PhD
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MCHRI Support:
Category: Neonatal & Developmental Medicine

Poster #: 37

Altered GABAergic Interneuron Development in a Human 3D Cellular Model of Hypoxic Brain Injury of Prematurity

Extremely premature birth predisposes to brain injury and neuropsychiatric disorders. Hypoxia following preterm birth is thought to disrupt GABAergic interneuron development and increase the risk for neurodevelopmental impairments including epilepsy and autism.

To study the migration of GABAergic interneurons into the developing excitatory cortex, we used pluripotent stem cells to generate 3D human brain organoids and assembloids, which recapitulate key cortical development processes.

Exposure of assembloids to hypoxia at the developmental stage relevant for prematurity identified a significant migration defect of GABAergic interneurons under hypoxic conditions. Furthermore, transcriptional profiling indicated changes in molecular pathways related to metabolic processes important for neurons under hypoxic stress.

In summary, we developed the first human 3D cellular model for hypoxic brain injury of prematurity and identified specific interneuron developmental alterations. Overall, this approach could serve as an important tool for identification of hypoxia-induced corticogenesis defects and pharmacological interventions with high translational potential.

Name: Gregory Goldstein, MD

Title: Clinical Fellow

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MCHRI Support: Clinical Trainee Award, Master's Tuition Program (MTP) Award

Category: Neonatal & Developmental Medicine

Poster #:

38

Trends in Racial/Ethnic Disparities in Necrotizing Enterocolitis

Background: Whether vulnerable racial/ethnic groups have benefited equally from a recent decline in necrotizing enterocolitis (NEC) incidence is unclear.

Methods: Trends in NEC incidence and breast milk use were evaluated by race/ethnicity among 47,336 very low birth weight infants born in California from 2008-2017. We interrogated the association between race/ethnicity and NEC using multilevel regression analysis, and evaluated the mediating effect of breast milk in this relationship.

Results: Annual NEC incidence declined across all racial/ethnic groups from an aggregate average of 4.8% in 2008 to 2.6% in 2017. Breast milk use increased over the time-period across all racial groups. Non-Hispanic (NH) black infants received the least breast milk each year. Hispanic ethnicity (OR 1.27, 95% CI 1.02-1.57) and Asian or Pacific Islander race (OR 1.35, 95% CI 1.01-1.80) were each associated with higher odds of NEC. NH black race was initially associated with NEC, but was no longer statistically significant (OR 1.13, 95% CI 0.86-1.50) after adding breast milk use to the model. Mediation analysis revealed that breast milk use accounted for 21% of the total risk of NEC for non-white vs. white infants.

Conclusion: Though NEC incidence has declined substantially over the past decade, a sizable racial/ethnic disparity persists. Quality improvement initiatives augmenting breast milk use may further reduce the incidence of NEC in vulnerable populations.

Name: Samantha Piekos
Title: Graduate Student
Department: Dermatology
MCHRI Support:
Category: Neonatal & Developmental Medicine

Poster #:
39

Evaluating the contributions of genetic variants in polymorphic craniofacial disorders

Craniofacial disorders are among the most common birth defects occurring in 1:400 live births. They are polygenetic diseases with the cause unknown in over half of cases. Using the Oro Lab's chemically defined in vitro differentiation system I studied craniofacial disorders in the developmental context of the surface ectoderm for the first time. I developed a pipeline that integrates multi-dimensional -omics and chromatin conformation data to identify craniofacial disorder-associated genetic variants within known surface ectoderm regulatory elements and connected to distal target genes by chromatin looping. Representation learning and graph theory analyses, such as centrality, were performed to predict polymorphic gene regulation in a single locus. These bioinformatic inferences were biologically validated by knocking out the regulatory elements containing craniofacial disorder-associated genetic variants and measuring the effect on gene expression of their distal target genes. Here, I have pioneered an approach to study polygenetic disease within a developmental context.

Name: Elizabeth Sherwin
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MCHRI Support:
Category: Neonatal & Developmental Medicine

Poster #:
40

Individualized Growth Assessment in pregnancies complicated by fetal gastroschisis

Individualized Growth Assessment (IGA) evaluates growth based on serial US measurements, unlike conventional methods using population-based curves. We assessed the potential of IGA for separating normal and pathological growth in gastroschisis cases. Twenty-one pregnancies with fetal gastroschisis were classified into four groups by IUGR and SGA. Fetal and neonatal measurements were entered into iGAP software, which calculates fetal and neonatal growth pathology scores. Agreement between conventional US methods and IGA was assessed. In the no IUGR/no SGA group, there was 75% prenatal agreement (9/12), and 100% neonatal agreement. In the yes IUGR/yes SGA group, there was 100% prenatal agreement but 40% (2/5) neonatal agreement. In the yes IUGR/no SGA group, there was 67% (2/3) prenatal agreement and 100% neonatal agreement. In the one no IUGR/yes SGA case, IGA did not identify pathology. While we found general agreement, IGA was able to identify normal and pathological growth missed by conventional methods.

Name: Lisa Bruckert, PhD
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Department: Pediatrics (Developmental Behavioral Pediatrics)
MCHRI Support: Clinician Educator (CE) Award
Category: Neurobiology & Behavioral Medicine

Poster #:
41

White matter differences in children with NF1 compared to neurotypical peers.

Neurofibromatosis type 1 (NF1) is a common genetic condition that affects children. Approximately 50% of children with NF1 experience neurocognitive deficits. White matter abnormalities are a common feature of NF1. White matter pathways are also relevant for cognitive functioning. Here, we employed diffusion MRI tractography to examine the microstructural characteristics of multiple cerebral white matter pathways in children with NF1. Participants were 20 children with NF1 and 20 age- and sex-matched controls (9.5 years, 24 male) who underwent diffusion MRI at 3T (25 directions, $b=1000$ s/mm²). We used an automated approach to segment and extract fractional anisotropy (FA) and mean diffusivity (MD) of 10 major white matter pathways bilaterally. Compared to controls, children with NF1 had significantly reduced FA and increased MD in multiple tracts, including the forceps minor, anterior thalamic radiation, and inferior fronto-occipital fasciculus. These findings have implications for understanding neurocognitive deficits observed in children with NF1.

Name: Lori Dershowitz, MSc
Title: Graduate Student
Department: Neurosurgery
MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #:
42

Effects of Breastmilk on Ganglia Development in the Enteric Nervous System

The enteric nervous system (ENS) is the largest portion of the peripheral nervous system and controls the secretory and motor functions of the gut. In many vertebrae, the ENS is a nerve net with neurons sparsely scattered. However, in the mammalian ENS, neurons are condensed into discrete structures called ganglia. The functional significance of ENS ganglia are not known, and a better understanding of how ganglia arise may elucidate their role in health and disease.

Breastmilk is the first external force encountered by the developing ENS. Breastmilk contains many neurotrophic factors, yet the effects of breastmilk on ENS development have never been studied. Additionally, formula-fed infants have an increased risk of developing obesity and diabetes as compared to breast-fed infants, a clinical observation that may be rooted in differences in ENS development. Here I present a timeline of gangliogenesis in embryonic and neonatal mice and propose a model to compare the structure and function of ENS ganglia in breast-milk fed and formula-fed rodents.

Name: Jessica Diaz, DVM, MS
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MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #: 43

microRNA controls over cortical projection neuron development

Disruptions in early cerebral cortex development can lead to neurodevelopmental disorders impacting motor function, such as cerebral palsy, or cognition, such as autism. In the cerebral cortex, cortical projection neurons comprise classes of neurons that send long axons to distant regions of the central nervous system. Our recent work suggests that gene regulation by microRNAs controls cortical neuron identity. We have identified a microRNA cluster in mice that is selectively expressed by corticospinal vs. callosal projection neurons during their development. Here we present our preliminary ATAC-Seq analysis designed to elucidate how differential expression of this microRNA cluster is regulated in cortical projection neurons. We have previously shown that one microRNA from the cluster, miR-CSMN-1, promotes corticospinal fate in primary culture. Here we show that overexpression of miR-CSMN-1 in embryonic cortical neurons *in vivo* results in a shift from callosal to corticospinal projections.

Name: Sarah Dubner, MD
Title: Clinical Fellow
Department: Pediatrics (Developmental Behavioral Pediatrics)
MCHRI Support: Clinical Trainee Award
Category: Neurobiology & Behavioral Medicine

Poster #:
44

Reading abilities in relation to quantitative T1 MRI metrics for assessing myelin content in 8-year old children born preterm

We aimed to determine if individual reading differences in children born preterm (PT) could be explained by variations in myelin content. We examined associations among a summary diffusion MRI (dMRI) white matter measure (fractional anisotropy, FA) and a quantitative MRI (qT1) measure directly related to myelin ($1/T_1$, R1) in relation to reading abilities (Gray Oral Reading Test-5). We obtained dMRI (30-directions, $b=1,000$ s/mm) and qT1 (spoiled gradient echo sequence, 4 flip angles and an inversion-recovery sequence, 4 inversion times) in 8-year old PT children (N=29). Whole brain deterministic tractography identified white matter pathways. We quantified FA and R1 values along the trajectory of three dorsal and six ventral reading-associated tracts. Pearson correlations revealed no significant associations between reading scores and FA. Reading abilities were significantly positively correlated with R1 from one dorsal- and four ventral tracts. qT1 may aid in understanding the neural bases of reading in PT children.

Name: Mustafa Fattah
Title: Graduate Student
Department: Psychiatry and Behavioral Sciences
MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #: 45

Assessing the impact of PTPN11 Noonan syndrome on the white matter microstructure of the developing human brain

ADHD is the most prevalent neurodevelopmental disorders, affecting up to 10% of children in the U.S. ADHD can have deleterious effects on the affected child's academic, social, and emotional development. Mutations in the Ras/mitogen-activated protein kinase (RMK) pathway known as "RASopathies" that include Noonan syndrome manifest a variety of neurodevelopmental disorders but most notably, ADHD. Children with Noonan syndrome often exhibit attentional deficits, learning disabilities, and anxiety, but maintain a cognitive profile within the normal range. To date, there have been no studies analyzing the white matter tract connectivity within the brains of individuals with Noonan syndrome. In this study, diffusion tensor imaging (DTI) was used to evaluate the white matter microstructure of a group of individuals with Noonan syndrome in comparison to age- and sex-matched neurotypical controls. The results of the scans and several statistical analyses indicate strong and widespread effects of decreased fractional anisotropy and increased radial diffusivity in the group with Noonan syndrome relative to the control group. These measures both indicate a loss of structural integrity in the white matter tracts of individuals with Noonan syndrome, offering insight into the neurophysiological underpinnings of the disease. Moreover, given the significant comorbidity of Noonan syndrome and attentional deficits, these results may offer a new path for studying disorders such as ADHD.

Name: Grace Gengoux, PhD
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Department: Psychiatry and Behavioral Sciences (Child & Adolescent Psychiatry)
MCHRI Support: Clinician Educator (CE) Award
Category: Neurobiology & Behavioral Medicine

Poster #: 46

The AMOR Method: Resilience Training for Parents of Children with Autism Spectrum Disorder

Introduction: The AMOR Method (Acceptance, Mindfulness, Optimism, Resilience) is a novel resilience training for parents of children with Autism Spectrum Disorder (ASD) that aims to improve resilience and other domains of well-being.

Methods: Twenty-four parents of children (4-10:11 years) with ASD participated in a randomized controlled trial (AMOR = 12, Control = 12). Parents completed questionnaires about resilience, optimism, acceptance, mindfulness, and stress before and after treatment.

Results: Preliminary analyses revealed significant improvements in the AMOR group in resilience ($t = 4.55, p < 0.01$), optimism ($t = 2.39, p = 0.03$), and parenting stress ($t = -2.86, p = 0.01$). No group differences emerged for acceptance ($t = 1.71, p = 0.10$) or mindfulness ($t = 1.58, p = 0.12$).

Discussion: The AMOR Method may be an effective, brief intervention for parents of children with ASD in improving resilience, optimism, and stress management. Continued investigation with larger samples is warranted.

Name: Tamar Green, MD

Title: Assistant Professor

Department: Psychiatry and Behavioral Sciences (DIBS)

MCHRI Support: Eureka Institute for Translational Medicine Award, Pilot (Early Career) Award

Category: Neurobiology & Behavioral Medicine

Poster #:

47

Bridging the gaps in our knowledge: brain development of children with Noonan syndrome.

This talk/poster will cover the essential neuroscience and cognitive-behavioral aspects of Noonan syndrome, particularly as related to neuropsychiatric issues. Recent findings from the careful study of genotype-phenotype associations in Noonan syndrome will be covered. Specifically, as related to brain structure and connectivity. These data will be used to propose and examine new approaches for diagnosis and treatment of human neuropsychiatric disorders such as ADHD and autism.

Name: Michael Khoury, BS
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MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #: 48

Using Virtual Reality to Promote Cooperation and Reduce Anxiety during Minor Procedures in the Pediatric ENT Outpatient Clinic

This study examines if interactive virtual reality (VR) during pediatric ENT outpatient procedures will reduce anxiety and promote cooperation, resulting in increased patient and parental satisfaction. The primary aim was to determine differences in child fear, pain, and anxiety between those utilizing VR compared to the control group. Children aged 7-17 were randomized into a control or VR group. The control group received standard of care, while the VR group played an immersive game. Children were excluded if they had developmental delay or were non-English speaking. Patients reported having significant reduction in fear, pain, and anxiety during their procedure when using virtual reality. Parents reported feeling more comfortable when their child used VR. Our results support the effectiveness of VR as a distraction tool for reducing anxiety and promoting cooperation in patients receiving ENT minor procedures. The formal statistical comparison will be completed once the sample size is met.

Name: Madison Kist
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MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #: 49

Reducing Anxiety and Pain with Virtual Reality during Minor Surgical Procedures in Pediatric Outpatient Orthopedic Clinic

Minor orthopedic outpatient procedures can cause anxiety in pediatric patients. Virtual reality (VR) has been shown to be an effective non-pharmacological alternative for anxiolysis in various clinical settings. Our primary aim was to determine the effect of VR utilization during minor procedures on fear, anxiety, pain, and satisfaction. 150 patients aged 7-17 undergoing cast and/or pin removals were enrolled and randomized into three treatment groups: control/standard of care, passive VR, and active VR. The VR groups were fitted with Samsung Gear VR headsets displaying either a passive or active experience during procedures. There was a significant reduction in fear between the control group and both VR groups and in anxiety between the control group and passive VR group. Patients and parents reported increased satisfaction with VR. These results suggest that VR may be an effective anxiolytic during minor orthopedic outpatient procedures.

Name: John Leikauf, MD
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MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #: 50

Apple Watch Pilot for Youth with Attention-Deficit/Hyperactivity Disorder

Objectives: Wearable devices including the Apple Watch measure movement (actigraphy) and provide users with feedback. Actigraphy has shown increases in movement for youth with Attention-Deficit/Hyperactivity Disorder (ADHD) but has not been used for treatment. We sought to establish the feasibility of developing and piloting an Apple Watch app that measures movement and provides visual feedback.

Methods: Open label pilot , with actigraphy, clinical rating scales, and computerized cognition data (WebNeuro), and conducted semi-structured exit interviews.

Results: Thirty-two participants ages 8-17. Better visualization of movement and the ability to customize the movement threshold were the 2 most common suggestions. On the ADHD-Rating Scale, symptoms of both Inattention ($p = .003$) and Hyperactivity/Impulsivity ($p = .004$) improved. Movement data transferred successfully in all but 6 cases.

Conclusions: It is feasible to collect actigraphy data from youth using an Apple Watch application. Users reported improved symptoms over the course of the study and the results inform future directions.

Name: Kelley Paskov, PhD, MS
Title: Graduate Student
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MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #:
51

Microdeletions Contribute to Inherited Autism Susceptibility in Multiplex Families

Autism spectrum disorder is a neurodevelopmental condition affecting 1 in 53 children, resulting in restricted, repetitive behaviors as well as impaired social interaction and communication skills. Both inherited and de novo deletions have been shown to play a role in autism susceptibility. We use whole-genome sequencing data from 781 families with two or more autistic children to study the impact of inherited autosomal deletions on autism risk. Using a hidden Markov model, we identify inherited deletions ranging from 0.1Kbp-20Mbp in size. Family structure allows us to resolve even small deletions of 0.1-10Kbp with high fidelity. We show that autistic children inherit a larger deletion burden from their parents than their neurotypical siblings. We further identify 17 deletions that are significantly over-transmitted to autistic children. Using data from multiplex families, we show that inherited deletions play an important role in autism risk.

Name: Shamma Rahman, PhD
Title: Postdoctoral Researcher
Department: Pediatrics (Human Gene Therapy)
MCHRI Support:
Category: Neurobiology & Behavioral Medicine

Poster #:
52

A novel circulating monocyte subset in pediatric acute-onset neuropsychiatric syndrome (PANS)

PANS is characterized by a sudden development of severe psychiatric symptoms. ~65% of patients undergo repeated episodes of flare and remission; 20% develop a chronic-static illness. Monocytosis is reported in PANS (Frankovich, 2015), but a detailed characterization of monocytes is missing. We found that elevations in the “classical”, CD14+ monocyte subset account for the monocyte increase at PANS flare. Using a novel antibody panel focused on markers likely associated with brain-homing, we found reduced frequency of CD14+CCR2+CX3CR1+VLA-4+CD166+ cells at flare versus remission. CSF from new acute-onset PANS contained these monocytes, confirming brain-homing. Increases in these cells at remission suggest possible immunosuppressive function; their reduced frequency and absence in CSF of chronic-static patients suggest reduced production in this PANS subgroup. Incubation of healthy PBMC with active PANS plasma increased CCR2, CX3CR1, VLA-4, Iba1, HLA-DR. Together, these results implicate a novel subset of monocytes, capable of crossing the BBB, in PANS.

Name: Inge Timmers, PhD
Title: Postdoctoral Researcher
Department: Anesthesiology, Perioperative, and Pain Medicine
MCHRI Support: Postdoctoral Support Award
Category: Neurobiology & Behavioral Medicine

Poster #:
53

Scanning Circles of Pain Engagement (SCOPE): Investigating Parent's Empathic Distress Responses in the Context of their Child's Chronic Pain

Chronic pain in childhood is a significant public health concern. Growing evidence indicates that parents' responses and behaviors to their child's pain may modulate (i.e., mitigate or magnify) their child's functioning. These parent behaviors toward their child in pain may be largely motivated by empathy. In this study, we aim to define the physiological and neural correlates of empathic distress in parents of youth with chronic pain using an experimental empathy paradigm with high ecological validity - parents hear their child talk about their painful experiences and see their child's painful facial expressions. Pilot data from the paradigm will be presented. In addition, we will present preliminary survey data on parent empathic distress in the context of pediatric chronic pain. These data will increase understanding of mechanisms driving parental affective responses and behaviors to their child's pain and will determine to what extent empathic distress contributes to individual differences in child functioning.

Name: Brandon Cieniewicz, PhD
Title: Postdoctoral Researcher
Department: Pediatrics (Stem Cell Transplantation and Regenerative Medicine)
MCHRI Support: Postdoctoral Support Award
Category: Stem Cell / Regenerative Medicine

Poster #:
54

Engineered Tr1 cells designed for clinical use can eliminate primary pediatric AML blasts

Acute myeloid leukemia (AML) is the deadliest pediatric leukemia. Treatment of AML with hematopoietic stem cell transplantation (allo-HSCT) replaces the diseased marrow but can result in life-threatening graft-vs-host disease (GvHD). Current treatment for GvHD has numerous side effects, including general immunosuppression. T regulatory type 1 cells (Tr1) can both induce antigen-specific tolerance and lyse myeloid cell lines, making them suitable for treatment of GvHD in AML patients. However, it is unclear if pediatric AML are sensitive to Tr1-mediated killing.

We measured the killing of 23 AML blasts by Tr1 cells. Blasts were either efficiently killed, or displayed several levels of resistance. We sequenced these AML and discovered that sensitive and resistant blasts had significantly different gene expression. We discovered a putative resistance factor that can protect AML against Tr1-mediated killing. Altogether, Tr1 cells can eliminate many pediatric AMLs, and AML resistance to killing is governed by their underlying molecular signature.

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Category: Stem Cell / Regenerative Medicine

Poster #: 55

Modeling RUNX1 deficiencies in human HSPCs reveal cytokine dependencies and RUNX1mut AML signatures

Germline mutations in RUNX1 cause an autosomal dominant disorder characterized by lifelong thrombocytopenia and increased risk of progression to acute myeloid leukemia (AML). Indeed, unlike sporadic AML, which commonly presents in the elderly, the average age of onset for RUNX1 familial AML cases is 35, with over one-third of patients developing leukemia as a child. The mechanisms by which germline RUNX1 mutations progress to leukemia remains unclear and the prognosis for patients is very poor. This project models and characterizes the effect of different familial mutations on hematopoietic stem cell function to pinpoint possible therapeutics. To determine the cell-autonomous effects of RUNX1 deficiency, we knocked out RUNX1 or introduced familial mutations into the endogenous RUNX1 locus in cord blood HSPCs. RUNX1 disruption caused defects in erythroid and megakaryocytic maturation, as well as a skew toward CD14+ monocytes cells. ATAC-seq and RNA-seq profiling indicate these changes in differentiation are caused by both changes in hematopoietic transcription factor activity and cytokine signaling, including changes in EPO, TPO, IFN, NFKB, and JAK/STAT signaling. Notably, RUNX1 disrupted cells may be dependent on IL-3 and GM-CSF for proliferation. Further molecular profiling of RUNX1 disrupted cells show that the gene expression and chromatin profile correlate with known RUNX1-mutant signatures or cellular hierarchies.

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Poster #:

56

CRISPR Activation (CRISPRa) Enhanced Thymic Reprogramming of Human Induced Pluripotent Stem Cells (hiPSCs) as A Platform Technology for T Cell Reconstitution

The thymus is the central immune organ instructing T cell development. Recapitulating the complex thymic development in vitro has proven challenging because of the largely unknown regulatory signaling network for thymic ontogeny. FOXP1 is the master regulator of thymic development. Forced expression of ectopic FOXP1 from cDNA has provided proof of principle that FOXP1 alone is sufficient to reprogram mouse fibroblasts into thymic epithelial cells, suggesting FOXP1 an excellent candidate for trans-differentiation into thymic fate. The application of this approach for clinical purposes is limited due to safety concerns. In addition, lack of dynamic FOXP1 expression results in incomplete thymic reprogramming in human cells. Combining a stepwise cytokine-mediated hiPSC differentiation protocol with CRISPRa-enhanced expression of FOXP1, we developed a unique approach to bypass the hurdles of unknown regulatory networks during thymic development. This could serve as a platform technology to generate clinically relevant regenerative thymic tissues in vitro.

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Poster #:
57

Engineered Type-1 Regulatory T Cells for Treatment of Graft-versus-Host Disease in Allogeneic Hematopoietic Stem Cell Transplant Recipients

Type 1 regulatory cells (Tr1) are a promising therapy for the prevention of graft-versus-host-disease (GvHD) in allogeneic hematopoietic stem cell transplantation (aHSCT). Since Tr1 cells are difficult to isolate and expand ex vivo, our groups has developed a protocol to produce Tr1 cells by lentiviral transduction of the human IL-10 gene (LV-10) into human CD4+ T cells. In vitro, LV-10 cells kill myeloid cells through a perforin/granzyme B-mediated mechanism and suppress the proliferation of responder CD4+ T cells through secretion of IL-10 and TGF- β 1. In vivo, LV-10 cells suppress xeno-GvHD in NSG mice and synergize with PBMCs to retain a GvL effect against myeloid-derived tumors while not inducing xeno-GvHD on their own. We are working on finding novel biomarkers that correlate with the acquired Tr1 phenotype that will help us identify cell lines suitable for use in the clinic as well as uncovering potential mechanisms for Tr1 polarization.

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Poster #:
58

Engineered (LV) FOXP3 Treg-like cells protect from lymphoproliferation while preserving immune responses in humanized-mice models.

FOXP3 is an essential transcription factor for the regulatory T cell (Treg) function and a key regulator of immune tolerance. CD4⁺ T cells from healthy donor and IPEX patient were successfully converted into functional Treg-like cells using lentiviral-mediated FOXP3 gene transfer (CD4LVFOXP3), thus supporting this approach as a therapeutic for IPEX syndrome, a unique model of genetic autoimmunity due to FOXP3 mutations.

Delivery of either allogeneic or autologous CD4LVFOXP3 to xeno-GvHD mice can extend their survival. Mice rescued from xeno-GVHD by the CD4LVFOXP3 remain refractory to a secondary xeno-GVHD challenge. Furthermore, CD4LVFOXP3 administration to immunodeficient mice reconstituted with human HSC knocked-out for FOXP3, can rescue the lymphoproliferation in this IPEX-like hu-mice model without impairing immune reconstitution.

Thus, CD4LVFOXP3 exert potent suppressive activity in healthy and pathological conditions while sparing host immune system. These data support preclinical development of CD4LVFOXP3 as a treatment for IPEX syndrome and autoimmunity of different origin.

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Poster #: 59

CRISPR-Blastocyst Complementation: a novel technique to study congenital eye disease pathogenesis

A number of orphan diseases such as anophthalmia, microphthalmia and congenital retinal degeneration lead to malformation of eyes at birth and almost invariably lead to blindness. These diseases can be caused by both heritable and environmental factors and can occur in 3 infants in a population of 100,000. Unfortunately, there is limited understanding of how to treat them. We propose to combine two novel techniques, CRISPR-cas9 gene-editing (CRISPR) and blastocyst complementation (BC), to efficiently knockout different candidate genes that have been implicated in congenital blindness. We propose to create knockout mice for Rax, Mitf and Lhx2, which are known to cause anophthalmia, microphthalmia and retinal degeneration in humans. We have created a streamlined pipeline to rapidly and simultaneously validate these knockouts in vivo. Gene deletion will create an empty niche in the embryos that can be complemented with wild-type mESCs, which have normal gene expression. This method could lead to path breaking discoveries and help infants and children suffering from debilitating eye diseases.

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Poster #: 60

Adenylate Kinase 2 Links Energy Metabolism and Cell Fate in Hematopoietic Stem and Progenitor Cells

Biallelic mutations in mitochondrial Adenylate Kinase 2 (AK2) cause Reticular Dysgenesis (RD), one of the most serious forms of SCID, characterized by severe neutropenia in addition to lymphopenia. AK2 catalyzes the phosphoryl exchange between adenine nucleotides and scavenges AMP for ADP required during oxidative phosphorylation. We engineered a biallelic AK2 knock-out model in human hematopoietic stem and progenitor cells (HSPCs) using CRISPR/Cas9. AK2^{-/-} HSPCs recapitulate the RD neutrophil maturation defect in vitro. Global metabolomics showed specific metabolite depletion in AK2^{-/-} neutrophils that point to defects in electron transport chain, glutathione metabolism, phospholipid metabolism and urea cycle, disrupting specific biological processes that lead to dysregulated HSPC differentiation. Currently, we are examining the impact of AK2 depletion on mitochondrial functions, oxidative stress and epigenetic modifications. Understanding how metabolism governs HSPC fate will advance our understanding of many immune disorders, and will help improve stem cell products and transplantation outcomes.