Title: Delineating Pulmonary Cellular Responses to Prenatal Chorioamnionitis and Postnatal Hyperoxia

Mentors: Deepthi Alapati, MD; Yan Zhu, PhD

Project Description:

Background:
Bronchopulmonary dysplasia (BPD) is the most common cause of death, severe neurodevelopmental impairment, and hospital readmissions in preterm infants. BPD, a chronic lung disease affecting 50-55% of extremely-low-birth-weight, preterm infants, is often complicated by pulmonary hypertension (PH). Chorioamnionitis, an infection of the placenta, is the most common identifiable cause of preterm labor, and affected preterm infants often require postnatal treatment with supplemental oxygen (O2). As such, the severity of BPD and PH is significantly higher in preterm infants with a combined history of infection and a need for O2. There is a critical need for advanced therapies for BPD and PH in preterm infants, but the cellular and molecular mechanisms underpinning the onset and progression of disease are not well understood.

Hypothesis:
Intrauterine exposure to inflammation amplifies postnatal O2-induced impairment of alveolar and vascular development by modulating distinct pulmonary cell-specific differential gene expression.

Specific Aim:
Determine the transcriptomic differences in individual pulmonary cell types induced by combined exposure to LPS and O2 in neonatal rats.

Methodology:
RNA will be extracted from the sorted cells and a non-biased global transcriptomic analysis will be performed. Differential gene expression between the four groups will be analyzed. Significantly differentiated top genes will be validated by RT-PCR and Western blot.
Title: AAV8 Gene Therapy in Mucopolysaccharidosis IVA Murine Model

Mentors: Shunji Tomatsu, MD, PhD; Shaukat Khan, PhD

Project Description:
Background:
Morquio A disease is a rare disorder caused by a deficiency of the enzyme N-acetylgalactosamine-6-sulfate-sulfatase, leading to accumulation of two glycosaminoglycans: keratan sulfate (KS) and chondroitin-6-sulfate (C6S) mainly in bone, and showing systemic skeletal dysplasia with short stature, hypoplasia of the odontoid process, prominent chest, kyphoscoliosis, knock-knee, and loose joints. We speculate 1,200-1,500 MPS IVA patients live in developed countries (incidence: approximately 1 out of 200,000 births). There is no effective therapy available. We will develop novel, innovative therapies by using gene therapy with bone-targeting strategy, leading to the benefit to the community.

Hypothesis:
Our central hypothesis is that the proposed therapeutic approach will improve bone lesions in MPS IVA based on our preliminary data.

Specific Aim:
Assess the efficacy of bone-targeting gene therapy by using multiple copies of AAA oligopeptide on the viral capsid.

Methodology:
We will examine the following effects of bone-targeting AAV8 gene therapy in murine model: 1) levels of expression of target enzyme in bone, 2) therapeutic effects of gene therapy, and 3) adverse effects or toxicity of each therapy. These are critical points that need to be assessed in pre-clinical trials before moving forward to clinical trials in patients. We will use two types of MPS IVA mice and conduct minimum effective dose (MED) studies to determine the optimal dosage regimen of AAV gene vector. Blood and urine samples will be taken every other week. After 8 weeks of treatment, tissues will be collected for further analysis.
Title: Lymphocytic Expansion of Hematopoietic Stem Progenitor Cells (HSPCs) Derived by Induced Pluripotent Stem Cell Differentiation.

Mentors: Anilkumar Gopalakrishnapillai, PhD; Ishnoor Sidhu, MS

Project Description:

Background:
Down syndrome, characterized by trisomy 21, is the most common genetic disorder. The role of an extra copy of chromosome 21 in the hematopoietic differentiation is poorly understood, especially with respect to the lymphocytic arm. This study will potentially shed light on the role of key genes located on chromosome 21 that modulate the development of lymphocytes and thereby regulate inflammation and immune response to diseases including cancer.

Hypothesis:
Trisomy 21 modulates lymphocytic differentiation.

Specific Aim:
Compare the lymphocytic differentiation of disomic and trisomic hematopoietic stem progenitor cells (HSPCs) generated from disomic and trisomic induced pluripotent stem cells (iPSCs).

Methodology:
Step-wise differentiation of iPSCs first into HSPCs and then into lymphocytes will be performed. Lymphocytic differentiation in free culture will be compared with that in support cultures.
Title: Molecular Mechanisms in Cerebellar Granule Cell Differentiation

Mentors: Sigrid Langhans, PhD; Zhiquin Lee, PhD

Project Description:

Background:
Cerebellar granule cells are the most common neurons in the brain. Aberrant function of cerebellar granule cells has been associated with diverse diseases ranging from neurological and neuropsychiatric disorders to the most common malignant pediatric brain tumor, medulloblastoma. Despite the need for new therapeutic approaches, our understanding of cerebellar granule cell proliferation and differentiation in health and disease remains limited.

Hypothesis:
Na,K-ATPase is an ion pump intimately involved in neuronal differentiation and function. While modifications of the Na,K-ATPase catalytic α subunit are responsible for numerous disorders in the cerebellum, the roles of the auxiliary β1 and β2 subunits in the cerebellum remain unclear. By characterizing the unique differences between these subunits, we can identify new subunit-specific therapeutic targets for disorders of the cerebellum.

Specific Aim:
Characterize isoform-specific molecular interactions of Na,K-ATPase β-subunits that mediate cerebellar granule cell precursor differentiation during postnatal maturation of the cerebellum.

Methodology:
Standard cell and molecular biology techniques in cultured cells and primary neuronal cultures will be employed.
Title: Impact of a Child Physical Abuse Clinical Pathway on Abuse Diagnosis and Identification

Mentors: Stephanie Deutsch MD, Allan DeJong MD, Andrea Repine NP, Jennifer Macaulay MSW

Project Description:

Background:
Exorbitant costs have shifted the healthcare industry’s attention towards promotion of value-based care (VBC), a concept of better, higher quality care for less cost by enhancing emphasis on preventive services that positively improve long-term patient outcomes. Loosely meaning "getting more for less", VBC's definitive goal to improve health across the life-span de-emphasizes focus on any single hospitalization and prioritizes cost-effectiveness and quality, typically through elimination of unnecessary, repetitive care and creation of standardized, best practices using clinical decision support, guidelines, and pathways. While frequently developed for high volume conditions (often as cost-saving measures), these best practice algorithms can (perhaps more importantly) also eliminate "shotgun" approaches for uncommon clinical scenarios with less robust evidence bases. Posing an interesting conundrum, the question becomes - "how much will doing the "right thing" actually cost us?"

Child physical abuse assessments may uniquely represent one such clinical scenario, whereby increased associated costs (financial, time/resource) may result from "doing more", including recommended laboratory and diagnostic imaging tests for occult injury screening. How consequential these costs are, especially when potentially predictive of future, high quality outcomes, likely depends on how one defines cost and value - whether these principles are viewed through a short versus long term lens. In October 2019, Nemours/AIDHC implemented an emergency department based child physical abuse pathway to standardize the laboratory and imaging evaluation of suspected abuse victims and their siblings/household contacts, in accordance with national clinical practice guidelines. This study will examine how implementation of this clinical pathway has impacted our practice, clinical outcome, and costs.

Hypothesis:
We hypothesize that the child physical abuse clinical pathway impacted clinical care at Nemours/AIDHC by increasing assessment and diagnostic testing rates, diagnosis of abuse, and emergency department discharges, as well as shortening hospital length of stay, in total positively impacting care for children who have sustained abuse.

Specific Aim:
We aim to analyze the impact of the Nemours/AIDHC ED-based child physical abuse clinical pathway implemented in October 2019, using pre and post-pathway data.

Methodology:
Retrospective examination of the clinical course of patients who were cared for using the child physical abuse clinical pathway (as detailed above), through data access from the electronic medical record and metrics from the Nemours Continuous Improvement and Utilization Review Offices.
**NSURP Project #6**

**Title:** Impact of Early Insulin Administration on Critically Ill Patients in Diabetic Ketoacidosis

**Mentors:** Andrew Depiero MD, Amy Thompson MD, & Kelvin Fong MD

**Project Description:**

**Background:**
Diabetes is one of the common diseases among the pediatric population. Diabetic ketoacidosis (DKA) is a leading cause of morbidity and mortality in diabetic patients. Management of DKA consists of prompt identification, insulin administration, and fluid and electrolyte resuscitation. Currently the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends timely insulin administration one hour after starting fluid resuscitation. New animal models have shown early administration of insulin in DKA is associated with faster resolution of DKA without an increase in adverse events. However, there have been few recent human studies to evaluate the potential effect of early insulin administration in DKA.

**Hypothesis:**
The early administration of insulin in pediatric patients presenting to the emergency department with DKA leads to safer and faster resolution of disease.

**Specific Aim:**
The primary outcome of this project will be the time to clearance of urinary ketones. Secondary analysis will include resolution of acidosis as measured by achieving a serum bicarbonate level of > 13 and hospital length of stay.

**Methodology:**
This is a retrospective cohort study. A data collection form will be utilized. An internal quality improvement database and the electronic medical record will be used as source data. Data will be analyzed using SPSS statistical software. Statistical analysis including chi square and t-tests will be performed.
Title: An Examination of Instrument-Based Vision Screen for Preschool-Aged Children

Mentors: Jing Jin MD, Amanda Friess OD, Julia Reid MD

Project Description:
Background:
Amblyopia is the most common cause of monocular vision loss in children in the United States. Its prevalence is between 1 and 5% of preschool-aged children. The identification, prevention and treatment of amblyopia not only enhances individual health and wellness but also decreases the societal burden of blindness. Amblyopia develops during an early sensitive period in childhood. When recognized during this critical period, many cases are treatable. However, treatment success decreases with age and amblyopia is unlikely to resolve spontaneously without treatment. Therefore, screening for amblyopia and its risk factors in the youngest children affords the best opportunity for treatment to be effective.

Direct measurement of visual acuity using eye charts is the preferred method of screening for amblyopia in childhood. However, eye chart testing can be problematic in young children and/or nonverbal and developmentally delayed older children. Instrument-based vision screening is quick and requires minimal cooperation of a child. Multiple studies have reported instrument-based vision screening improved the ability to complete screening among preschool aged children, better family satisfaction and decreased referral rates. The instrument-based screen has traditionally been performed by eye care providers, trained nurses and volunteers in selected environments. In recent years, many pediatric practices including Nemours pediatric primary care clinics have adopted instrument-based screening. Many young children who failed the screening were referred to our Ophthalmology clinic for evaluation. This study will evaluate the effectiveness of instrument-based screening in pediatric primary care settings. In addition, its longer-term effect on referrals and the prevalence of amblyopia will be examined.

Hypothesis:
The positive predictive value of instrument-based screening for children referred to Nemours pediatric Ophthalmology service is compatible to that reported in the literature, and the referral rate to Ophthalmology has decreased since implementation of instrument-based screening

Specific Aim:
1. To examine common abnormal findings detected through an instrument-based screening.
2. To identify factors that affect the accuracy of instrument-based screening.

Methodology:
Retrospective study of convenience sample of children referred to Ophthalmology over the past 5 years. Variable examined will include vision screen results, vision testing results, referring offices, instrument used, patient demographics, etc. Microsoft Excel and SPSS will be used for analysis/statistics.
NSURP Project #8

Title: The Impact of Dose on Surgical Recovery in Children and Youth with Cerebral Palsy

Mentors: Jason Howard MD, Chris Church MPT, Nancy Lennon MS PT, Tim Niiler PhD

Project Description:
Background:
Cerebral Palsy (CP) is the most common cause of physical disability in pediatrics, often characterized by limitations in mobility and motor function. Helping children with CP reach optimal levels of mobility and motor function requires knowledge of how various doses of corrective surgery impact daily physical activities. The Gait Analysis Lab collects both laboratory-based and field-based measures of walking that provide surgeons and rehabilitation professionals with details revealing the underlying causes and functional consequences of gait disorders. A portable accelerometer is used to measure baseline and post-surgical walking activity, including step totals, intensity, and duration. The post-op data gauges the child's functional recovery from surgery. Differences in recovery trends are expected based on both surgical dosing and child specific factors. Knowledge of these trends would allow better customized post-surgical rehabilitation programs directed at reaching optimal mobility function.

Hypothesis:
1. Recovery of walking activity post orthopedic surgery will be related to the surgical dose. Youth with a high surgical dose will recover more slowly compared to youth with a low dose as measured by accelerometry every 3 to 6 months up to 2 years post-surgery
2. Factors including pain, amount of post-operative physical therapy, and level of involvement will influence the speed of post-operative recovery

Specific Aim:
The primary aim of this project is to determine how the dose of orthopaedic surgery affects the recovery of daily walking frequency, duration, and intensity in children with CP. A secondary aim of this study is to examine additional factors that affect surgical recovery in children with CP.

Methodology:
In this retrospective, cross-sectional study community based physical activity levels in youth with cerebral palsy will be reviewed from before and after orthopedic surgery (3, 6, 9, 12, 18, 24 months) using the StepWatch (SW). The SW is calibrated using a standard protocol, worn for 8-14 days, and returned by pre-paid mail. Surgical episodes will be defined according to burden as low (soft tissue surgery with or without a single unilateral osteotomy) or high (bilateral or multiple unilateral osteotomies). The mean total daily strides, the % change in strides from baseline, and the stride count as a percentage of expected strides according to GMFCS level will be analyzed.
Title: Exploring Moderators and Mediators of the Association between Postpartum Depression Symptoms and Infant Development

Mentors: J. J. Cutuli PhD, Danielle Hatchimonji PhD

Project Description:
Background: Maternal PPD (depression in the infant's first year of life) affects roughly 13-17% of mothers and is associated with risk for poor cognitive, behavioral, and health outcomes for children. This project examines factors that influence the relationship between maternal postpartum depression (PPD) symptoms and developmental outcomes for infants. Our ultimate goal is to develop more effective interventions to promote resilience for new mothers and their babies.

Specific Aims and Hypotheses:
1: Investigate the mediating role of parenting practices in the association between postpartum depression symptoms and infant development in the first year of life. We expect that PPD symptoms will be negatively associated with infant development and that negative parenting practices will explain this relationship. These relationships would suggest that a mother’s PPD symptoms may lead to poorer parenting, which may then lead to poorer development for the infant.
2: Identify factors that buffer against or exacerbate the negative association of postpartum depression symptoms with parenting practices. We expect that for mothers who have PPD symptoms, if they also have social support and/or a purpose in life (a meaningful life goal), they may demonstrate less negative parenting practices than mothers without these protective factors. We also expect women with both PPD symptoms and a history of adverse life experiences may demonstrate more negative parenting practices than mothers without a history of adverse life experiences.
3: Assess purpose and its development for new mothers over course of the first year after their child's birth. Because purpose in new mothers has been largely unexplored, we will assess the longitudinal development of purpose over the three study time points. We hypothesize that purpose among new mothers will increase over the first year of their child's life.

Methodology: We will recruit first-time mothers and their infants (birth through two months old) at their pediatrician's office to complete assessments at three time points (0 months, 6 months, 12 months). Research staff will interview patients using a structured assessment using standardized measures of depression, parenting, and child development.

Please note: This position will require weekly transportation to/from primary care sites that may be located in Philadelphia, Wilmington, or elsewhere in Delaware. Students will be expected to provide their own transportation.
Title: Impact of a Guideline on Antibiotic Selection for Children Hospitalized with Pneumonia

Mentors: Craig Shapiro MD, Karen Ravin MD, Shannon Chan PharmD, Neil Rellosa MD, Salwa Sulieman MD, Jobayer Hossain PhD

Project Description:

Background:
In the United States community acquired pneumonia (CAP) is among the most common causes for hospitalization in children with approximately 124,000 pediatric hospitalizations annually. It also accounts for more antibiotic use than any other condition in US Children’s hospitals. In June of 2019 the antibiotic stewardship program at Nemours AI duPont Hospital for Children updated the antibiotic recommendations for management of CAP to be more in line with national guidelines. The goal was to further reduce broad spectrum antibiotic use which is a known driver of adverse drug events and resistance of bacteria to antibiotics.

Hypothesis:
There is a reduction in broad spectrum antibiotic use following implementation of the updated antibiotic management guidelines without increases in hospital length of stay, readmission or need for escalation of care.

Specific Aim:
This study will compare the prescribing of broad spectrum antibiotics for children hospitalized with pneumonia at A.I. duPont Hospital for Children pre and post-implementation of a revised antibiotic guideline.

Methodology:
Retrospective cohort study of children greater than 6 months hospitalized for pneumonia (based on ICD-10) from June 2018-June 2019. Study will examine guideline concordance with antibiotic prescribing based on multiple factors including age, location where antibiotics prescribed, and previous administration of antibiotics prior to admission, along with severity of illness. We will also looking at secondary outcome measures such as hospital length of stay, readmission, and need for escalation of care.