Summer Research at Nemours

Nemours Summer Undergraduate Research Program

NSURP PROJECT #1

PROJECT TITLE

IDENTIFYING GENETIC AND PROTEOMIC DIFFERENCES BETWEEN THE SUBTYPES OF JUVENILE IDIOPATHIC ARTHRITIS

RESEARCH TEAM

Principal Investigator
Dr. Annamarie Brescia, MD
Division Chief of Rheumatology

Megan Simonds
Senior Clinical Research Assistant

PROJECT DESCRIPTION

BACKGROUND

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease of childhood and carries risk of permanent joint damage and disability. The focus of this research is the identification of informative synovial biomarkers to help predict the course and prognosis of subtypes of JIA. One subtype, persistent oligoarthritis affects no more than 4 joints throughout the disease course while extended oligoarthritis affects a cumulative total of 5 joints or more after the first 6 months of disease. Oligoarticular onset extending to the polyarticular course affects 21-50% of patients, and only 13-23% of them achieve remission. Because this evolution increases the risk for disability, early prediction of this course is desirable. Prognostic synovial biomarkers will lead to better risk stratification and will allow physicians to provide accurate information regarding prognoses and to initiate course-altering therapy earlier in children with higher risk for disease progression. Knowing the likely course a child's arthritis will take would allow us to make informed therapeutic decisions, weighing risks of medication side effects with likely severity of disease, for each individual patient. Patients likely to have an aggressive disease course with risk of permanent joint damage would be treated with more aggressive medication regimens, while patients likely to have a more benign course could be spared the toxicities of some of the medications used to treat arthritis.

HYPOTHESIS

Examining differences between persistent oligoarticular and extended JIA on gene and protein expression levels will lead to identifying potential biomarkers used to predict when a patient may extend.

SPECIFIC AIMS

1. Make prospective predictions of prognosis in newly diagnosed JIA using synovial fluid biomarkers
2. Define the role of the Fibroblast-like synoviocytes (FLS) in the growth disturbances seen in JIA.

METHODOLOGY

We will use microarray and scRNA-seq to examine differences in the transcriptomes of patients with different subtypes of JIA. We will confirm these findings using western blot and ELISA as a way to examine protein expression levels. Downstream signaling pathways will be studied for both intracellular and extracellular signaling in JIA FLS.

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NSURP PROJECT #2

PROJECT TITLE

THE FUNCTIONAL IMPACT OF ALTERNATIVE SPLICING OF CDKN1B IN CANCER

RESEARCH TEAM

Principal Investigator
Dr. Valerie Sampson, PhD
Assistant Research Scientist II

Arthur Currier, BS
Graduate Research Assistant

PROJECT DESCRIPTION

BACKGROUND

Osteosarcoma is the primary bone cancer in children and young adults. Tumors contain several genomic alterations including mutations, deletions and abnormal chromosome numbers. Alternative splicing changes are frequently observed in cancer and are starting to be recognized as important signatures for tumor progression and therapy. However, their functional impact and relevance to tumorigenesis remain mostly unknown. We will determine whether alternative splicing changes in the CDKN1B gene (encodes p27) represent independent oncogenic processes that may be relevant to explain the functional transformations in osteosarcoma.

HYPOTHESIS

We hypothesize that specific alterations in CDKN1B splicing induce functional changes in the p27 tumor suppressor and could represent targets of therapy.

SPECIFIC AIMS

1. Measure gene expression of differently spliced forms of CDKN1B in human osteosarcoma cells.
2. Compare expression levels to that of normal cells and determine whether abnormal CDKN1B expression promotes cancer cell growth.

METHODOLOGY

We will carry out a systematic analysis using PCR and immunoblot to characterize the potential functional consequences of alternative splicing changes in the CDKN1B gene.

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NSURP PROJECT #3

PROJECT TITLE

EXERCISE STRESS TEST CAN IDENTIFY PRECLINICAL ANTHRACYCLINE-INDUCED CARDIOTOXICITY / CARDIOMYOPATHY

RESEARCH TEAM

Principal Investigator
Dr. Takeshi (Alan) Tsuda, MD
Physician - Cardiology

Gina DAlosisio, MS
Exercise Lab and Non-Invasive Testing Manager

PROJECT DESCRIPTION

BACKGROUND

Modern multidisciplinary cancer therapies have significantly improved cancer-free survival in children with malignant diseases. Anthracycline is a mainstay of cancer chemotherapy in both children and adults, but a major complication is cardiotoxicity and subsequent cardiomyopathy. There are three types of anthracyline-induced cardiotoxicity; acute onset (< 1 week after the treatment), early chronic onset (< 1 year after treatment), and late chronic onset (> 1 year after the treatment). Late chronic onset cardiotoxicity is the most common type of cardiotoxicity whose clinical presentation is insidious, progressive, and irreversible, causing exercise intolerance, dyspnea, refractory congestive heart failure, and even death. The underlying mechanism of anthracycline-induced myocardial impairment has not been fully understood. Early detection of preclinical cardiotoxicity is imperative, but the current recommended surveillance with echocardiogram is not efficient enough to identify this early stage of cardiomyopathy. Serum biomarkers are not proven to be helpful in recognizing this preclinical stage. New non-invasive screening modality needs to be introduced. From our recent experience, exercise stress test (EST) appears to be a useful method in identifying preclinical asymptomatic cardiomyopathy without left ventricular (LV) dysfunction in cancer survivors. However, clinical value of EST in detecting preclinical stage of cardiomyopathy is not well understood.

HYPOTHESIS

Exercise stress test is a sensitive and reliable surveillance method in identifying asymptomatic preclinical anthracycline-induced cardiotoxicity/cardiomyopathy.

SPECIFIC AIMS

1. Determine whether EST is a sensitive method to identify preclinical cardiotoxicity.
2. Examine maximum exercise performance and myocardial reserve in cancer survivors with normal echocardiographic profiles.
3. Investigate the patients' demographics (age, sex, ethnic background, BMI), age at initial chemotherapy and completion of the therapy, diagnosis, cumulated anthrocycline dosage, the use of therapeutic radiation and other cardiotoxic agents, echocardiographic findings, and current life style (physical active, athletic, or sedentary).

METHODOLOGY

In collaboration with Hematology/Oncology, we will recruited the patients to the study who are a) > 10 year-old and cooperative to have EST, b) completion of cancer treatment > 1 year, c) asymptomatic from a cardiac standpoint, and d) normal cardiac function by echocardiogram. We will study EST to assess maximum exercise performance and cardiac reserve on symptom-free cancer survivors who are off treatment for more than a year. In EST, we will specifically examine 1) peak oxygen consumption (peak VO2), 2) anaerobic threshold (AT), 3) maximum oxygen pulse, and 4) respiratory quotient (RQ).

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NSURP PROJECT #4

PROJECT TITLE

IMPACT OF FILM-ARRAY BLOOD CULTURE IDENTIFICATION (BCID) PANEL ON MANAGEMENT OF PATIENTS WITH CONTAMINATED BLOOD CULTURES IN A PEDIATRIC EMERGENCY DEPARTMENT (ED)

RESEARCH TEAM

Principal Investigator
Dr. Craig Shapiro, MD
Physician - Infectious Disease

Dr. Shannon Chan, PharmD
Clinical Pharmacy Specialist

Dr. Karen Ravin, MD
Division Chief of Infectious Disease

PROJECT DESCRIPTION

BACKGROUND

Blood culture contamination is a common occurrence in a busy pediatric ED which can lead to unnecessary interventions for patients including repeat lab draws, hospital admission, and antibiotic administration. Costs have also been estimated at up to several thousand dollars (USD) per single contaminated blood culture. Overall blood culture contamination rates are 1-3% but have been reported as high as 11% in busy pediatric emergency departments. In August 2014 the Alfred I. duPont Hospital for Children (AIDHC) clinical microbiology laboratory implemented the BCID PCR system which is able to detect and identify 24 common blood pathogens within 2 hours after growth is noted in standard blood culture bottles. Prior to the implementation of the BCID system blood culture results would take 48-72 hours for final identification and susceptibility. This project will evaluate whether a reduction in time to identification of positive blood cultures has impacted management of patients with contaminated blood cultures drawn in the ED at AIDHC.

HYPOTHESIS

There is a significant reduction in overall unnecessary interventions for patients with contaminated blood cultures drawn in the AIDHC ED following implementation of the BCID.

SPECIFIC AIM

1. Compare the unnecessary interventions including additional lab draws, hospital admissions, and antibiotic administrations pre and post implementation of the BCID system for patients with contaminated blood cultures drawn in the AIDHC ED.

METHODOLOGY

Retrospective observational cohort study to identify patients with contaminated blood cultures drawn in the AIDHC ED pre and post implementation of the BCID system. We plan to look at patients in the 4years pre and post implementation of BCID 2010-2014 and 2014-2018.

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NSURP PROJECT #5

PROJECT TITLE

NORMAL AND ABNORMAL APPEARANCE OF THE OVARIES ON RAPID MRI OF THE ABDOMEN FOR ACUTE LOWER QUADRANT PAIN

RESEARCH TEAM

Principal Investigator
Dr. Sharon Gould, MD
Radiologist

Dr. Arabinda Choudhary, MD
Department Chair - Medical Imaging

PROJECT DESCRIPTION

BACKGROUND

Acute lower abdominal pain has many possible causes. Rapid MRI of the abdomen is often obtained to assess for acute appendicitis, but other etiologies of the patient's symptoms can sometimes be found. Ovarian torsion is associated with high morbidity if not diagnosed in a timely fashion, but other diseases can mimic the findings of ovarian torsion. Rapid abdominal MRI has the potential to provide additional information to differentiate torsed ovaries from other causes of lower abdominal pain.

HYPOTHESIS

Rapid MRI of the abdomen can detect ovarian torsion as an etiology for the patient's pain providing a reliable method for identifying ovarian torsion in the setting of unclear clinical or ultrasound findings and leading to timely tissue salvage.

SPECIFIC AIMS

1. Describe imaging characteristics of ovaries utilizing rapid MRI.
2. Assess the imaging quality of the rapid MRI for ovaries.
3. Examine clinical correlates of normal and abnormal ovarian findings.

METHODOLOGY

A retrospective review of MRI examinations performed in girls will be performed with sizes, volumes and signal characteristics of the ovaries tabulated. Analysis of the data will be performed and correlated with clinical information to differentiate normal from abnormal findings in the ovaries.

Summer Research at Nemours

Nemours Summer Undergraduate Research Program

NSURP PROJECT #6

PROJECT TITLE

A POPULATION-BASED STUDY OF READMISSION AFTER SURGERY FOR HYDROCEPHALUS

RESEARCH TEAM

Principal Investigator
Dr. Joseph Piatt, MD, MAS
Division Chief of Neurosurgery

PROJECT DESCRIPTION

BACKGROUND

Hydrocephalus is characterized by failure to recycle cerebrospinal fluid. It has many causes, and it is common, with a prevalence in childhood of about 5 per 1000. Most children require treatment with an implanted drain, called a "shunt," and because such devices do not work forever, children with hydrocephalus require life-long surgical maintenance. There is ample documentation of treatment of hydrocephalus at major research children's hospitals, but there has been no longitudinal population-based study in the United States.

HYPOTHESIS

Readmission and reoperation rates vary by age groups and by underlying diagnoses.

SPECIFIC AIMS

1. Describe readmission and reoperation in the first year after surgery for hydrocephalus using Kaplan-Meier plots
2. Compare times-to-event among various classes of patients.

METHODOLOGY

De-identified data from the Nationwide Readmissions Database for 2012 will be extracted, organized, and analyzed using statistical software.

PROJECT NOTE

This project will require heavy utilization of statistical programs (i.e. SPSS). While experience with statistical programs and / or knowledge of statistics would be helpful, it is not prerequisite. A sincere interest and desire to learn these methodologies is required.

Summer Research at Nemours

Nemours Summer Undergraduate Research Program

NSURP PROJECT #7

PROJECT TITLE

ELBOW FLEXION ROBOT DEVELOPMENT

RESEARCH TEAM

Principal Investigator
Dr. Tariq Rahman, PhD
Principal Research Scientist

PROJECT DESCRIPTION

BACKGROUND

This will help children with upper extremity neuromuscular conditions that affect their ability to perform activities of daily living such as self-feeding. This includes kids with muscular dystrophy, spinal muscular atrophy and arthrogryposis. The project will be an adjunct to the WREX device. The WREX (Wilmington Robotic Exoskeleton) is an upper extremity wheelchair-mounted orthosis that attaches to the arm and helps children with arm weakness to move their arms. Currently, bending the elbow to eat is performed by passive elements (springs). This has not shown to be adequate in achieving the task. External energy in the form of a motor is needed, while under the control of the subject.

HYPOTHESIS / GOAL

The student will design and fabricate a powered elbow flexion device that can be mounted to the WREX and be operated by an external sensor such as force, displacement, and electromyograph (EMG).

SPECIFIC AIMS

1. Study literature on robotic upper extremity devices
2. Explore what type of motor to use
3. Explore what type of sensor to use (force, displacement, EMG)
4. Design the joint and incorporate into the existing WREX
5. Test it with an able bodied subject

METHODOLOGY

After reviewing the literature the student will develop a plan for selection and control of the actuators and sensors. Fabrication of a prototype will follow with programming in Matlab or related software. This will be followed with testing of the prototype while mounted to the WREX. This project will assist in the overall improvement of the WREX functionality.

Summer Research at Nemours

Nemours Summer Undergraduate Research Program

NSURP PROJECT #8

PROJECT TITLE

THE IMPACT OF THERAPY DOSAGE ON FUNCTIONAL OUTCOMES AFTER SINGLE EVENT MULTI-LEVEL SURGERY (SEMLS) FOR CHILDREN WITH CEREBRAL PALSY

RESEARCH TEAM

Principal Investigator
Dr. Laura Owens, MD
Physician - Rehabilitation & Acute Care

Jason Beman, PT
Senior Physical Therapist

Nancy Lennon, PT
Cerebral Palsy Program Manager

Nicole Mamula, OT
Occupational Therapist

Abigail Gilmore, OT
Occupational Therapist

Dr. Timothy Niiler, PhD
Volunteer

PROJECT DESCRIPTION

BACKGROUND

Cerebral Palsy is the most common cause of physical disability in pediatrics. Children with a diagnosis of cerebral palsy often present with significant limitations in their motor function and mobility, which affects their ability to participate in age-appropriate activities at home, school, and in their communities. The function and participation of children with CP typically decreases for 1-2 years after major orthopedic surgery to correct alignment abnormalities. Physical and occupational therapy are frequently prescribed to help these children regain their function quickly. There is little evidence regarding an optimal "dosage" for therapy after surgeries. A better understanding of the relationship between therapy duration and improvement in function after surgery will help clinicians determine optimal therapy dose during recovery.

HYPOTHESIS

There will be a direct relationship between therapy dosage and participation/functional improvement after SEMLS for children with cerebral palsy.

SPECIFIC AIMS

1. Evaluate clinical course of post-surgical patients with CP who received OT and / or PT.
2. Assess therapy (type, duration, dose) provided during post-op observation period.
3. Utilize standardized tools to assess effectiveness of therapy.
4. Examine relationship of therapy dosage and outcomes measures.

METHODOLOGY

The student will compare length of stay with change in functional outcome measures administered at admission and discharge. The student will categorize and analyze based on type of surgery, classification scores (GMFCS/MACS), baseline function (ambulator vs non-ambulator). Categories of therapy dosage will be used as a metric of analysis (QD PT vs BID PT, sessions per week of PT/OT, duration of intervention).

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NSURP PROJECT #9

PROJECT TITLE

MUSCLE SATELLITE CELL DYSFUNCTION IN SPASTIC CEREBRAL PALSY

RESEARCH TEAM

Principal Investigator
Dr. Rob Akins, Ph.D.
Center Director & Precision Research Scientist

Stephanie Yeager, MS
Prospect Research Coordinator

Karyn Robinson, MS
Research Lab Manager

PROJECT DESCRIPTION

BACKGROUND

Cerebral palsy is a group of disorders attributed to disruption of the developing brain and affecting movement, posture, and activity. Spastic CP involves high muscle tone, muscle contractures, musculoskeletal deformation, and movement disorder, causing debilitation and requiring surgical correction. An improved understanding of muscle involvement in spastic CP is needed to (i) help reduce progressive impairment, (ii) decrease the need for invasive surgery, and (iii) improve motor function and functional outcomes. The mechanisms of muscle involvement in progressive debilitation in spastic CP are only partially understood, but muscle resident stem cells (satellite cells) have been implicated. Muscle satellite cells contribute to muscle fiber growth and repair and have significant roles in extracellular matrix production and the maintenance of neuromotor synapses. In this set of studies, we use muscle tissue biopsies and isolated primary satellite cells to improve our understanding of satellite cell involvement in spastic CP and to test the hypothesis that phenotypic differences between CP and control satellite cells are associated with altered DNA methylation. Successful completion of the proposed studies will advance our understanding of skeletal muscle tissue and satellite cells in spastic CP and will identify potential molecular mechanisms associated with dysfunction.

HYPOTHESES

Hypothesis 1: The self-renewal potential of muscle satellite cells from individuals with spastic CP is reduced relative to controls.
Hypothesis 2: The myogenic potential of muscle satellite cells from individuals with spastic CP is reduced relative to controls

SPECIFIC AIMS

1. Validate an epigenetic signature for spastic CP in muscle tissue.
2. Determine DNA methylation pattern differences in cultured satellite cells.
3. Assess the phenotypic potential of satellite cells from individuals with spastic CP.

METHODOLOGY

We will use cultures of satellite cells using established culture protocols, immunodetection of stem cell and muscle cell biomarkers using established staining protocols, fluorescence microscopy and image analysis to acquire quantitative data, as well as non-parametric statistical analysis.

Summer Research at Nemours

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NSURP PROJECT #10

PROJECT TITLE

ROLE OF THE GUT-BRAIN GUANYLIN-UROGUANYLIN-GUANYLYL CYCLASE 2C RECEPTOR AXIS IN AUTISM SPECTRUM DISORDER

RESEARCH TEAM

Principal Investigator
Dr. Matthew D. DiGuglielmo, MD, PhD
Physician - Gastroenterology

Heather Hardy, BSAH, HT
Director of Histology Core Lab

Bobbie Boyce
Histology Specialist III

Jennifer Holbrook, BS
Assistant Director of Biomolecular Core Lab

Deborah Stabley, BS
Research Associate

Dr. Katie Robbins, PhD
Director of Biomolecular Core Lab

PROJECT DESCRIPTION

BACKGROUND

Many children with Autism Spectrum Disorder (ASD) experience gastrointestinal (GI) problems. The gut-brain guanylin-uroguanylin-guanylate cyclase 2C (GUCY2C) receptor axis has been shown to regulate food intake, intestinal permeability, and function; it is altered in diet-induced obesity (Valentino 2011; Kim 2016; DiGuglielmo 2017; 2018). Recent studies showed evidence of altered intestinal and blood-brain barrier in children with ASD (Fiorentino 2016, Esnafoglu 2017). In both brain and intestine, there were changes in proteins called claudins involved in the formation of tight junctions that form these barriers; the guanylin-uroguanylin-GUCY2C receptor axis regulates claudins. Another study showed that chronic enteroviral infections were associated with the alteration of zonulin, a tight junction regulator in the intestine and the brain (Vorobjova 2017). We propose to study the GUCY2C gut-brain axis in children with GI diagnoses and ASD.

HYPOTHESIS

The GUCY2C gut-brain axis will be disrupted (decreased expression) in children with ASD and GI problems in the setting of chronic enteroviral infection.

SPECIFIC AIMS

1. Measure guanylin-uroguanylin-guanylate cyclase 2C receptor in children with ASD and GI problems.
2. Assess whether the guanylin-uroguanylin-guanylate cyclase 2C receptor axis is altered.
3. Evaluate evidence of chronic enteroviral infection in the intestine, in children with ASD with GI problems.

METHODOLOGY

A preliminary search of the Nemours electronic medical record showed that there were approximately 300 unique patients with ASD who underwent a GI procedure for biopsy. We propose to review the medical records of these children and to study up to 50 available banked tissue samples from these patients. We will assess the expression of mRNA and protein for uroguanylin, guanylin, and GUCY2C, and we will stain the tissue with an antibody for enteroviruses.

Summer Research at Nemours

SUMMER RESEARCH AT NEMOURS PROGRAM

MENTOR-FUNDED PROJECT

PROJECT TITLE

A MIXED-METHODS EXPLORATION OF SLEEP AMONG CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS (CF)

RESEARCH TEAM

Principal Investigator
Dr. Kimberly Canter, PhD
Clinical Psychologist

Dr. Abigail Strang, MD
Pulmonologist

Dr. Aaron Chidekel, MD
Division Chief of Pulmonology

Dana Geiser, BS
Clinical Research Coordinator

PROJECT DESCRIPTION

BACKGROUND

As the average life expectancy continues to increase for individuals with Cystic Fibrosis (CF), attention has begun to shift from an exclusive focus on survival towards improving outcomes in a range of important physical and psychosocial domains. Despite the recognized and multidimensional impact of sleep on physical and mental health, sleep health and hygiene have not been widely studied in the CF community.

HYPOTHESES

Hypothesis 1: Using standardized, validated self- and parent-report questionnaires will allow for a multidimensional examination of sleep habits and hygiene among youth with CF.

Hypotheses 2: Analyzing actigraph data from a subset of participants will provide objective data to corroborate self-report and parent-report data regarding sleep habits.

Hypothesis 3: Utilizing the Electronic Medical Record (EMR) will allow for the exploration of relationships between health variables and sleep habits and hygiene.

Hypothesis 4: Conducting interviews with youth with CF and their families will lead to the identification of clear intervention targets and inform the development of a behavioral sleep intervention.

SPECIFIC AIMS

1. Explore sleep health and hygiene among youth with CF through the use of mixed quantitative methods.
2. Identify sleep intervention targets and goals through qualitative interviews with youth with CF and their families.

METHODOLOGY

The proposed study includes a cross-sectional quantitative aim, which utilizes self-report and parent-report data to explore sleep habits and hygiene for youth with CF, and a qualitative aim, which utilizes semi-structured interviews to identify potential targets and goals for a CF-specific behavioral sleep intervention.