



Nemours Summer Undergraduate Research Program
2018 Project Descriptions

NSURP Project 1

Title: Chimeric antigen receptor design for T cell-based immunotherapy against allergic diseases

Research Team: Zhengyu (Mark) Ma, PhD (PI), Brittany Fay

Project Description:

Background:

The prevalence of allergic diseases has dramatically increased among children in developed countries. Severe diseases such as allergic asthma and food allergy significantly impact quality of life and create heavy social and economic burdens for families.

Hypothesis:

IgE antibody is the key mediator of allergic diseases. Current medications target IgE and its downstream effector molecules but not B cells that produce IgE. To achieve long-term suppression of IgE, we propose to develop an immunotherapy approach that uses the patient's own cytotoxic T lymphocytes to kill IgE-producing B cells. To this end, we have designed two types of chimeric antigen receptors (CARs) that recognize membrane IgE, which is expressed on the surfaces of all IgE-producing B cells. We hypothesize that the CARs can mediate specific recognition and killing of IgE-expressing B cells in vitro and in SCID-human PBMC mouse models.

Specific Aim:

We will express CARs on cytotoxic T cells and determine their cytotoxicity towards IgE-producing human B cells in vitro and in SCID-human PBMC mouse models.

Methodology:

Human B cells will be differentiated to produce IgE with IL4 and IL10. The killing of B cells by CAR T cells in vitro will be determined by ELISPOT. For in vivo testing, human PBMCs containing IgE producing B cells will be injected into SCID mice. CAR T cells will be administered and their effect will be determined by measuring the level of serum IgE.



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NSURP Project 2

Title: Effect of CDK4/6 inhibition in pediatric preclinical models of sarcoma

Research Team: Valerie Sampson, PhD (PI), Christopher Mills

Project Description:

Background:

Osteosarcoma and Ewing sarcoma are the most common malignancies of bone in children and adolescents (1). Patients diagnosed with local disease are treated with surgical resection and adjuvant chemotherapy. New therapies are being studied for patients with metastatic and recurrent disease which are generally refractory to standard chemotherapy. Several new inhibitors that target cyclin-dependent kinases (CDKs) are undergoing clinical testing. CDK4/6 inhibitors have emerged as promising therapeutics. In this study, we will test the efficacy of CDK4/6 inhibitors against human sarcoma cell lines, as single agents and in combination with chemotherapeutic agents.

Hypothesis:

Cyclin dependent kinases are key components in the proliferation and survival of cancer cells and inhibition of CDK4/6 activity is an effective therapeutic strategy for pediatric sarcomas.

Specific Aim:

Determine the viability of human osteosarcoma and Ewing sarcoma cells treated with palbociclib and combinations of palbociclib with standard chemotherapy. In addition, characterize the effect of targeting CDK 4/6 on cell cycle and apoptotic pathways.

Methodology:

Drug efficacy will be measured using cell viability assays. mRNA and protein levels of cell cycle and apoptotic markers will be determined using quantitative pcr (qpcr) and western blot, respectively.

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NSURP Project 3

Title: Study the role of fusion genes in the development of pediatric non-downsyndrome acute megakaryoblastic leukemia.

Research Team: Anilkumar Gopalakrishnapillai, PhD (PI)

Project Description:

Background:

Acute megakaryoblastic leukemia (AMKL) is characterized by the dysregulation of megakaryopoiesis and represents around 15% childhood acute myeloid leukemia. AMKL in non-Down syndrome children has very poor prognosis. Use of exome sequencing and RNA-seq on a large number of non-DS AMKL patients has aided in the stratification of this disease based on the expression of certain fusion genes. It has been shown that the presence of fusion genes such as NUP98-KDM5A and CBFA2T3-GLIS2 predicts the poorest survival. However, the role of these fusion genes in the dysregulation of megakaryopoiesis is largely unknown. Delineating the function of such fusion genes helps us identify novel targets for diagnostic/therapeutic purpose.

Hypothesis:

Expression of NUP98-KDM5A or CBFA2T3-GLIS2 fusion genes plays a role in the disruption of megakaryopoiesis leading to initiation of non-DS AMKL.

Specific Aim:

Determine if expression of NUP98-KDM5A or CBFA2T3-GLIS2 fusion genes disrupts megakaryopoiesis leading to initiation of non-DS AMKL.

Methodology:

Standard recombinant DNA techniques will be used for the construction of chimeric fusion genes under hematopoietic stem cell promoter. This construct will be transfected into induced pluripotent stem cells using nucleo-transfection method. The recombinant iPSCs will be hematopoietically differentiated using method already standardised in the lab.



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NSURP Project 4

Title: Does treating vitamin D deficiency in children and adolescents with chronic pain improve their functioning?

Research Team: Catherine Soprano, MD (PI), Katherine Salamon, PhD, Dara Devinney, RN

Project Description:

Background:

Chronic pain in all people, but especially in children and adolescents, has become a hot topic in the news recently. There is much to explore in order to more deeply understand the co-morbidities and confounders that contribute to this chronic pain epidemic. There is emerging evidence that adult patients who have both chronic pain and Vitamin D deficiency report lower pain scores if they supplement their diet with Vitamin D. To date, there are only a few reports that studied Vitamin D deficiency in youth. In one study, Vitamin D supplementation helped to increase pain free days in children and adolescents with sickle cell disease and chronic pain. In another study, improved Vitamin D levels were correlated with improved mobility and functioning in patients with musculoskeletal and orthopedic problems.

Hypothesis:

A correlation between pain scores and Vitamin D levels as well as a link between Vitamin D deficiency and functional impact of chronic pain in children and adolescents.

Specific Aim:

Understand how prevalent Vitamin D Deficiency is in a population of children and adolescents who have a variety of chronic pain diagnoses, compare this to the prevalence of Vitamin D deficiency in all youth, and determine whether patients who receive Vitamin D supplements while undergoing treatment have a better outcome as assessed by subjective pain reports and PROMIS Pain Interference Questionnaire.

Methodology:

In order to study this, we plan to do a retrospective chart review of all patients who were evaluated in our Integrated Pain and Wellness Program since August 2014 looking for youth who had Vitamin D levels measured before or during their treatment in our program. We will determine if supplementation occurred and whether there was an improvement in vitamin D status. We will also link this data set with a data set that has already been collected as a quality improvement instrument through psychology and physical therapy to determine how successful the patients were in improving functional status through our program. Once this data is linked, we will do statistical analyses to understand if there are any correlations between those patients with Vitamin D deficiency, whether the deficiency was effectively treated, and the success.



Biomedical Research



Summer Research
at Nemours

Nemours Summer Undergraduate Research Program **2018 Project Descriptions**

NSURP Project 5

Title: Retrospective assessment of juvenile onset recurrent respiratory papillomatosis

Mentor: Jenna Briddell, MD (PI)

Project Description:

Background:

Juvenile onset recurrent respiratory papillomatosis (JORRP) is caused by the human papilloma virus (HPV). This pediatric disease can have a significant impact on a child's life resulting in multiple surgeries per year, and in rare cases progressing to death. The CDC is looking to track the incidence and prevalence of the disease as well as assess the impact of the HPV vaccine.

Hypothesis:

The incidence and prevalence of JORRP has decreased after the introduction of the HPV vaccine in 2006.

Specific Aim:

The purpose of this is to establish a database of incident and prevalent cases of JORRP; baseline prior to vaccine introduction and in the early vaccine period.

Methodology:

Retrospective chart review from January 1, 1997 through December 31, 2016 of all patients ages 0-17 with a clinical diagnosis of JORRP. Data collection regarding each subject will include: sex, year of birth/age at visit, race/ethnicity, and status at initial presentation (i.e., incident or prevalent case of JORRP). Data will be used to calculate a total number of prevalent and incident cases each year at AIDHC.



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NSURP Project 6

Title: Factors Affecting Visits to the Pediatric Emergency Department for Urgent and Nonurgent Ocular Conditions

Mentor: Jing Jin, MD, PhD (PI), Julie Reid, MD (co-PI), Jonathan Salvin, MD (co-PI), Dorothy Hendricks, MD (co-PI), Sharon Lehman, MD (co-PI)

Project Description:

Background:

In a study published on May 2017, Stagg et al investigated factors affecting adult patients' visits to the emergency department (ED) due to ocular conditions from 2001 to 2014. The study showed nearly one-quarter of enrollees were diagnosed with a nonurgent condition. They concluded that better educating and incentivizing nonurgent patients to seek care in an office-based setting could yield considerable cost savings without adversely affecting outcomes and allow EDs to better serve patients with more severe conditions. There has been no published study on pediatric patients receiving eye care through ED. We wish to investigate any correlation between the frequency of ED visits for ocular conditions and associated factors among pediatric patients.

Hypothesis:

Pediatric patients' visits to the emergency department for eye diseases are solely determined by ocular pathologies.

Specific Aim:

To evaluate potential factors affecting pediatric patients' visits to the EDs of Nemours A.I.duPont Hospital for Children in Wilmington, Delaware and Nemours Children's Hospital in Orlando, Florida due to ocular conditions.

Our goals are:

1. Provide safe, effective and cost saving care for children with ocular diseases.
2. Identify causes for urgent ocular condition and provide guidance on disease prevention
3. Identify causes for nonurgent ocular conditions and develop education plans for healthcare providers and parents.

Methodology:

Retrospective, longitudinal cohort analysis. Data from January 2007 to September 2017 will be collected from electronic medical records. Factors include medical diagnoses, patients' demographics, socioeconomic condition, presence of comorbidity and geographic location (Delaware, Florida, New Jersey, Pennsylvania, and Maryland). Statistical Analyses will be performed.



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NSURP Project 7

Title: Utilizing Telemedicine to Decrease Costs, Wait Times, and Resource Utilization in the Management of Injured Orthopedic Patients

Mentor: Alfred Atanda, MD (PI), Kenneth Rogers, PhD (co-PI), Ashley Tucker, PA-C

Project Description:

Background:

Involves pediatric patients and their experience in the orthopedic ambulatory care setting as well as in outlying community ERs.

Hypothesis:

1. Telemedicine can be used to streamline patient flow in the orthopedic ambulatory care setting by reducing wait and overall clinic times.
2. Telemedicine can be used to triage acutely injured orthopedic patients to prevent unnecessary ER/hospital transfers.

Specific Aim:

The purpose of this project is (1) to quantify time and cost savings for the orthopedic department and patients when telemedicine is used to provide care as compared to traditional in-person visits.

(2) to quantify time and cost savings for the hospital and patients when telemedicine is used to triage the transport of acutely injured orthopedic patients.

Methodology:

1. Student will track patient flow times and costs both for in-person and telemedicine patients seen in the ambulatory orthopedic clinic during their project duration
2. Student will do retrospective analysis of transport data and work with orthopedic surgeon to determine which transfers could've been avoided if telemedicine had been used to triage the case.



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NSURP Project 8

Title: Lung Nodules in Pediatrics: Presentation, Evaluation and Diagnosis

Mentor: Ambika Shenoy, MD (PI), Laura Greenwald, DO

Project Description:

Background:

The discovery of lung nodules during routine imaging of pediatric patients for other general complaints is a common reason for referral to our pediatric respiratory medicine clinic. However, there is limited medical literature available to diagnose and manage pulmonary (lung) nodules once identified in children. There is also limited literature detailing common causes for lung nodules in children. Often, these are incidental findings which raise stress and anxiety for families. We aim to describe our center's experience by retrospectively reviewing charts of pediatric patients referred to our clinic with incidental pulmonary nodules from discovery and evaluation to diagnoses and treatment.

This study is designed to contribute clinical and diagnostic information to a minimally researched topic in Pediatrics. It is suspected that the majority of incidental lung nodules are the result of underlying infection or another inflammatory process. Unlike in adults, primary lung cancer is rare in pediatrics. Therefore, pulmonary nodules are more likely to represent metastases in children with known extrapulmonary cancers. Similarly, underlying autoimmune diseases are also much less common in children compared with adults. Therefore the adult practice guidelines available for assessing lung nodules, may not necessarily apply to children and provides further justification for our pediatric study.

Hypothesis:

Incidental pulmonary nodules are a benign process in children in the absence of other symptoms of systemic illness.

Specific Aim:

Identify how pediatric lung nodules were first discovered in our patients.

Investigate our patients' clinical symptoms upon presentation in addition to pertinent physical exam findings.

Review diagnostic evaluation following discovery of pulmonary nodules and also list final diagnoses (if any) provided.

Methodology:

Retrospective chart review of ~50 charts of pediatric patients evaluated at our center with incidental pulmonary nodules. Patients' age upon presentation, description of clinical symptoms, frequency of physical exam findings, laboratory studies with average of test results +/- SD, average pulmonary nodules size on Chest radiograph or Chest CT +/- SD, average pulmonary function test value +/- SD and description of pathological findings on biopsy (if completed) will be reviewed.



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NSURP Project 9

Title: The use of Bioness Integrated Therapy System (BITS) as a reliable concussion assessment tool

Mentor: Rochelle Haas, MD (co-PI), Mark Riederer, MD (co-PI), Maya Zayat, PhD (co-PI), Nicole Marcantuono, MD, Bill Emanuele, MD

Project Description:

Background:

A concussion is a type of mild traumatic brain injury that is caused by either a direct or indirect force to the head typically resulting in the onset of impaired neurological function. Current commonly used concussion assessment tools include Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), the King – Devick Test and several standardized neuropsychological assessment tools. The Bioness Integrated Therapy System (BITS; Bioness, Inc.) is a multidisciplinary therapeutic tool used to challenge and assess the physical, visual, auditory, and cognitive abilities of individuals with deficits resulting from neurologic conditions, including traumatic brain injury. BITS is an interactive, easy to administer and score, computerized tool that can be used to assess many factors known to be associated with concussion, including visuomotor coordination, reaction time, visuospatial perception, and visual and auditory processing. To our knowledge, there are no published studies evaluating the BITS as a reliable concussion assessment tool.

Hypothesis:

BITS can be used as a reliable and useful concussion assessment tool.

Specific Aim:

To determine whether BITS can be added to the existing armamentarium available for concussion assessment.

Methodology:

We will perform a retrospective chart review of children and adolescents (ages 9-21y) who were diagnosed with concussion and completed ImPACT testing and/or neuropsychological assessment, as well BITS assessment within the last 24 months. Measurable variables (visuomotor coordination and speed, working memory, etc.) will be compared.

****NOTE: This project will take place at Alfred I. duPont Hospital for Children in Wilmington, DE, with site visits to Nemours locations in Glen Mills, PA and Deptford, NJ. A successful candidate for this position must have a means of transportation between these sites.**



Nemours Summer Undergraduate Research Program
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NSURP Project 10

Title: Foot Deformity and Gait Function in Children with Cerebral Palsy

Mentor: Freeman Miller, MD (PI), Nancy Lennon, MS PT, Kristen Nicholson, PhD

Project Description:

Background:

Good foot position and motion is critical to walking function. In children with cerebral palsy (CP), foot deformities and gait deviations are common; however, treatment of foot conditions can vary widely and lacks strong outcome evidence. Knowledge of the relationship between foot posture, treatment, and gait outcome would allow better-informed surgery decisions for children with CP. In the gait analysis lab, technology such as pedobarograph, and motion capture provides objective data to let us examine these relationships and develop best evidence surgical protocols.

Hypothesis:

1. Foot pressure patterns are related to global gait deviations and walking function in children with CP.
2. Surgical interventions that normalize foot pressure patterns improve walking function in children with CP.
3. Persistent abnormal foot pressure leads to deterioration in gait function in children with CP.

Specific Aim:

1. To define the relationship between foot deformities and gait function over the course of growth in children with CP.
2. To determine the factors that predict successful treatment of foot deformity in children with CP.

Methodology:

Children with CP were enrolled in a prospective longitudinal study at age 2 years. Foot pressure data were collected every 6 months from age 2 to 6 years and then every year until age 18. Gait kinematics were collected every 3 years from age 6 to 18 years. Outcome measures include coronal plane pressure index (foot posture) and the gait deviation index (gait kinematics). Changes over time will be evaluated using an ANOVA. Multiple regression analysis will be used to determine factors associated with change.