Efficacy of Intracapsular Tonsillectomy as Demonstrated by Pre- and Postoperative Polysomnogram

Mentor: Heather Nardone, MD

Relationship to Pediatric Health/Background: Intracapsular tonsillectomy is a relatively new technique for removing tonsillar tissue, for the treatment of children with obstructive sleep apnea. Using this technique, approximately 90% of the tonsillar tissue is removed, leaving a small amount of tissue behind as a biologic dressing. This is in contrast to the traditional tonsillectomy technique, where the entire tonsil is removed. While the benefits of intracapsular tonsillectomy, such as decreased rates of post-tonsillectomy hemorrhage and dehydration, have been documented, there remains hesitancy amongst many otolaryngologists to adopt the procedure. Many otolaryngologists question whether this subtotal removal of tonsillar tissue is as effective as traditional tonsillectomy in curing or improving the degree of obstructive sleep apnea. The few articles in the literature that address this topic are limited by very small sample sizes.

Hypothesis: We expect to demonstrate that the efficacy of intracapsular tonsillectomy for the treatment of obstructive sleep apnea in children, as documented by pre- and postoperative polysomnogram, is equivalent to that of traditional tonsillectomy.

Specific Aim: We will examine the degree of improvement in and the cure rate for obstructive sleep apnea in children undergoing intracapsular tonsillectomy, as demonstrated by polysomnogram findings.

Methodology: Retrospective chart review of children undergoing intracapsular tonsillectomy for obstructive sleep apnea. The demographic data, exam findings, and polysomnogram results will be analyzed. In particular, age, gender, comorbidities, BMI, age at surgery, preoperative and postoperative obstructive apnea hypopnea index, mean oxygen saturation level, mean carbon dioxide level will be reviewed and analyzed.
The Use of Cognitive Aids to Improve Trauma Team Performance During Pediatric Resuscitation

**Mentors:** Glenn Stryjewski, MD, MPH and Maria Carmen G. Diaz, MD

**Relationship to Pediatric Health/Background:** Standard team performance during any high stake time critical event such as trauma resuscitation relies upon the experience, knowledge, and recall ability of the trauma team. Multiple care algorithms must be memorized, and consistently reviewed in order to deliver the best, evidence based care. This study will develop cognitive aids designed to assist the trauma team in carrying out key elements of Pediatric trauma resuscitation.

**Hypothesis:** The use of structured evidence based checklists will improve team leader and team performance during Pediatric trauma resuscitation.

**Specific Aim:** Improvement of Trauma Team performance during pediatric trauma resuscitation with the use of novel evidence based checklists.

**Methodology:** A multidisciplinary team of physicians, nurses, and therapists will review existing pediatric trauma guidelines as developed by the American Trauma Society (ATS) and develop 10–15 point checklists for the following pediatric trauma conditions: Blunt abdominal trauma, Penetrating abdominal trauma, Closed head injury.

The new role of the “Checklist” team member will be introduced during simulated trauma resuscitations. The “Checklist” team member will be part of the trauma team and have the specific task of coordinating timely completion of the checklist. Team performance will be evaluated by comparing specific task completion and adherence of ATS guidelines during simulated trauma resuscitations with and without the use of checklists. Outcome measures will be key tasks that must be completed based upon current ATS guidelines. Absolute completion of tasks, quality of task completion, as well as time to task completion will be compared.
Study Fixation Pattern of Normal and Amblyopia Eyes Through Optical Coherence Tomography (OCT)

Mentor: Jing Jin, MD

Relationship to Pediatric Health/Background: Amblyopia is the most common cause of vision impairment in children. It affects 1-5% of the population. Amblyopia is defined as an impaired vision in an eye that otherwise appears normal, or out of proportion to associated structural abnormalities of the eye. OCT is a non-invasive imaging test that uses infrared light waves to take cross-section pictures of retina. Since its first development in 1991, OCT has proven to be an extremely useful technique in the field of ophthalmology to help identify retinal changes that are not readily visible through conventional eye examination.

Hypothesis: There are no differences in central retinal structure and fixation pattern between amblyopia eyes and normal eyes.

Specific Aims: Examine center retina of normal and amblyopic eyes using spectral-domain Optical coherence tomography (OCT) to:
1) Identify potential subclinical retina change in amblyopic eyes
2) Compare fixation pattern of normal and amblyopic eyes.

Design: Retrospective/prospective study

Methodology: Review existing and acquires new OCT studies form normal and amblyopic eyes.
1) Obtain measurement of fixation area thickness, volume and topography
2) Analyze the fixation of normal and amblyopic eye including the relative location of fixation point to optic disc, eccentric fixation point and fovea.
Short Term Effects of Orthopedic Surgery on the Walking Activity Patterns in Children and Youth with Cerebral Palsy

Mentors: Justin Connor, MD and Nancy Lennon, MS, PT

Relationship to Pediatric Health/Background: Cerebral Palsy (CP) is the most common cause of physical disability in pediatrics and often leads to significant limitations in mobility and motor function. Helping children with CP to achieve their maximal potential in terms of mobility and motor function requires knowledge of how corrective surgeries impact their daily physical activities.

Over the past two years, we have measured the daily walking activity of children with CP using a portable accelerometer. We collect measures of baseline walking activity and we take periodic measures of activity during post-surgical recovery. The post-op data helps, surgeons, therapists, and families to appreciate how walking function is recovered.

Hypothesis: The hypotheses of this study are 1) that orthopedic surgery to correct gait deformities will result in increased daily walking activity as measured one-year post-operatively by accelerometry; and 2) that age, motor severity, surgical procedures, pain, and physical therapy will influence walking outcomes.

Specific Aims: The primary aim of this project is to determine how orthopaedic surgery effects daily walking frequency, duration, and intensity in children with CP. The secondary aim of this study is to explore differences in walking activity outcomes among children with CP related to age, motor disability, surgical procedures, pain, and physical therapy.

Methodology: The student will learn about the clinical measurements and patient population of the Gait Lab, and specifically the Step Watch™ (SW) activity monitor. H/She will compile and organize the SW data and clinical gait data collected through May 2014. The student will perform multiple paired t-tests and ANOVAs to examine the differences in walking activity pre and post surgery.
Recurrence Following Femoral Derotation in Children With Cerebral Palsy

Mentors: Freeman Miller, MD and Chris Church, MPT

Relationship to Pediatric Health/Background: Internal femoral torsion is a common problem in children with cerebral palsy (CP) resulting in in-toeing and tripping. Alignment can be corrected with femoral derotation osteotomy, but in some cases recurrence occurs with growth.

Hypothesis: 1. Femoral derotation will provide short term correction of internal femoral torsion in children with CP.
2. Over the course of childhood growth following femoral derotation recurrent internal femoral torsion will emerge.
3. Several factors (age at surgery, functional level, severity of pre-operative internal rotation, and variability in dynamic rotation during gait) will predict the probability of recurrence.

Specific Aim: 1. Determine the short term effectiveness of femoral derotation on passive femoral alignment and dynamic positioning during gait.
2. Determine the frequency of recurrence of malalignment over the course of growth.
3. Analyze the predictive ability of several factors to determine the probability of recurrence.

Methodology: In this retrospective review, subjects will be selected that: have CP, underwent femoral derotation, and had gait analyses pre-op (V1), 1-3 years post-op (V2), and 5-10 years post-op (V3) including physical examination and kinematic analysis using 3D motion capture. Passive hip rotation and dynamic femoral position during gait in V1 will be compared to V2 to determine initial correction. Determination of recurrence will be based on additional surgical intervention or the recurrence of static/dynamic malalignment comparing V2 and V3. Age at surgery, functional level (GMFM, GMFCS, Gait Deviation Index), severity of pre-operative internal rotation, and pre-operative variability in dynamic rotation will be used to predict the probability of recurrence.
Combination Testing of the Tubulin Binding Agent, Eribulin with Conventional Chemotherapeutic Agents in In Vitro and In Vivo Models of Pediatric osteosarcoma

Mentors: E. Anders Kolb, MD and Valerie Sampson, PhD

Relationship to Pediatric Health/Background: The Halichondrin B analog, eribulin (Halaven), is FDA approved for second line treatment of breast cancer after anthracycline/taxane therapy. The preclinical testing of eribulin in in vivo xenograft models of sarcoma and acute lymphoblastic leukemia (ALL) has demonstrated high level single-agent activity to provide a rationale for further preclinical evaluation of this drug. In many preclinical and clinical studies of OS, disease stabilization and tumor shrinkage are short-lived and resistance to therapy occurs. Two potential barriers to translational success, dose-limiting toxicities and drug resistance to tubulin-binding agents have been described both preclinically and clinically.

Hypothesis: A multi-agent approach to the study of eribulin may provide therapeutic benefits to pediatric patients with OS.

Specific Aim: To compare the efficacy of multi-agent therapy of eribulin, irinotecan and temozolomide single-agent eribulin therapy in in vitro in osteosarcoma cell lines. We will determine the effects on aberrant pathway signaling (e.g. IGF-1R, EGFR, mTOR) and altered microtubule associated proteins which represent mechanisms of resistance to the anti-cancer effects of treatments.

Methodology: We will treat OS cell lines with sequential or simultaneous combinations of eribulin, and irinotecan and temozolomide administered as a single-agent. The impact of drug treatments on cell viability, cell cycle, apoptosis, microtubule sedimentation and tubulin polymerization will be determined.

We expect to provide strong biological rationale to inform decisions for the evaluation of eribulin in early-phase clinical trials in pediatric patients with this disease.
Cell Instructive Materials for Engineering Vascular Grafts

Mentor: Robert Akins, PhD

Relationship to Pediatric Health/Background: Procedures to repair, bypass, or re-open diseased or malformed cardiovascular (CV) tissues are routine and often very successful. Hundreds of such procedures are performed at Nemours each year. Significant problems still exist, however, with many procedures leading to stenosis and fibrosis of the manipulated tissues. Substantial morbidity develops in a large number of patients, and approaches to improve outcomes are needed.

The Akins lab is working to develop cost-effective, easy-to-use, injectable biomaterials for engraftment on the abluminal surface of at-risk CV tissues. These materials will attenuate maladaptive responses and support long-term CV healing. The lab is testing PEG polymer-based hydrogels with tunable mechanical, biological, and chemical properties that could be adjusted to the specific needs of individual patients.

The student will perform experiments to examine the effects of PEG hydrogel modulus on human aortic adventitial fibroblasts (AoAFs) and the role of RhoA signaling in AoAF responses.

Hypothesis: Increasing hydrogel modulus drives AoAFs to a proliferative phenotype associated with RhoA signaling. This hypothesis will be tested in the following Aim.

Specific Aim: Determine the effects of hydrogel modulus on the phenotype of encapsulated adventitial fibroblasts.

Methodology: AoAF will be encapsulated in established hydrogels and evaluated using well-established microscopic and biomolecular assays to determine modulus/phenotype correlations and to interrogate RhoA activity (inhibited by exoenzyme C3-transferase) as a mechanism for observed effects. We anticipate that culture within our FGF-containing hydrogels1-3 will influence AoAFs to a myofibroblast-like phenotype as a result of differential Rho signaling associated with alterations in substrate modulus.
Growth Factor Signaling in Pediatric Brain tumor Development

Mentor: Sigrid Langhans, PhD

Relationship to Pediatric Health/Background: Medulloblastoma is the most common malignant brain tumor in children and usually forms in the cerebellum, the part of the brain that controls movement, balance, and posture. Although survival rates are improving, approximately one-third of patients with medulloblastoma remain incurable. In addition, current treatments such as surgical resection, radiotherapy, and chemotherapy, have serious side effects, including deficits in IQ, memory, and language, impaired growth, and increased risk of secondary cancers. Understanding the molecular mechanisms how medulloblastoma develops will aid in developing much needed safer drugs to treat this devastating disease.

Hypothesis: Aberrant activation of TGF-β signaling in cerebellar granule cells prevents neuronal differentiation and promotes cell proliferation thus contributing to the development of medulloblastoma.

Specific Aim: To define the role Transforming growth factor (TGF)-β signaling in normal cerebellar granule cells (the cells from which medulloblastoma is thought to derive) and during tumor development.

Methodology: We will test cerebellar granule cell differentiation in TGF-β-treated and control cells using standard molecular and cell biology methods including immunoblot, qPCR, cell culture and immunofluorescence microscopy.
Gene Pathway Analysis in Costello Syndrome Fibroblasts

Mentor: Katia Sol-Church, PhD

Relationship to Pediatric Health/Background: Costello Syndrome (CS) is a rare condition resulting in failure to thrive, intellectual disabilities, short stature, coarse facial features, skeletal abnormalities, and congenital heart disease. CS patients have an increased risk for malignancies, specifically embryonal rhabdomyosarcoma. CS is caused by heterozygous gain of function activating mutation in the HRAS oncogene.

Hypothesis: We hypothesized that novel crosstalk between important signaling pathways contributes to the different pathogenicity of the germline mutations in CS patients.

Specific Aim: The goal of this project will be to complete an ongoing study and identify, via microarray expression analysis, genes differentially expressed that will provide clues to new pathways relevant to this syndrome. These differentially expressed genes, once validated by Western blot analysis may reflect on important constitutive cell signaling differences between normal and disease state that could be of clinical importance.

Methodology: The summer student will learn all aspects of tissue culture as well as isolating DNA, RNA, and protein from cell pellets. A critical aspect of this study will be to analyze the significant microarray genes into specific pathways and gene clusters using bioinformatics programs. The student will also learn how to validate the identified significant genes and pathways using western blot analysis of protein samples from CS fibroblasts.
Cell Cycle Specific Post-Translational Modifications of MeCP2

Mentor: Asmita Kumar, PhD

Relationship to Pediatric Health/Background: Precise amounts of the protein product of the epigenetic regulator, Methyl CpG binding Protein 2 (MECP2) gene are necessary for proper growth and development. Too much or too little MeCP2 protein results in MECP2 duplication syndrome and Rett Syndrome, respectively. Both these disorders result in a wide range of neurological deficits including intellectual disability. Therefore, research has mainly been focused on studying the function of MeCP2 in neurons even though the protein is produced everywhere in the body. Our body is made up of both dividing and non-dividing cells. Cells like fibroblasts can grow and divide in a cyclical manner to accomplish growth and to replenish the body from the loss of damaged/dead cells while the latter group consisting of neurons cannot.

Hypothesis:

Specific Aim: We are interested in investigating how MeCP2 regulates cell growth and division. Specifically, we are examining what parts of the cell cycle are regulated by MeCP2 and how. Our studies reveal that MeCP2 levels oscillate during the cell cycle.

Methodology: We are therefore interested in identifying the post-translational modifications of the protein, namely, phosphorylation and ubiquitination that are associated with its degradation when it is not needed. This project relies on proteomic and molecular biology approaches to address this question. These studies are aimed to help us better understand what the function of MeCP2 is and may even help identify targets for therapeutic interventions.
Serum Lipid, Leptin, IL-4 and IFN-gamma as Biomarkers of Racial/Ethnic Variance in Childhood Overweight and Obesity

Mentor: Laurens Holmes, PhD, DrPH

Relationship to Pediatric Health/Background: Serum lipids, and leptin had been demonstrated to be associated with excess body fat and adiposity, and IFN-gamma and IL-4 had been indicated to inversely correlate with leptin in preclinical data. IFN-gamma like cytokine IL-4 may correlate inversely with leptin and serum lipid but directly with IL-4, and may decrease the risk of childhood overweight and obesity (BMI).

Hypothesis: (1) There is no correlation between leptin, serum lipid, IFN-gamma and IL-4. (2) There are no racial/ethnic and sex variances in the distribution of serum lipid, leptin, IFN-gamma, and IL-4. (3) Racial/ethnic and sex differences in childhood BMI is unexplained by IL-4, serum lipid, leptin and IFN-gamma.

Specific Aims: (1) To examine the correlation between IL-4, IFN-gamma, leptin and serum lipid. (2) To determine whether or not there are variances in the distribution of these biologic molecules across diverse pediatric populations. (3) To correlate these biomarkers with diverse populations BMI.

Methodology: (1) Study Design: A cross-sectional study involving simultaneous data collection on serum lipid, leptin, IL-4, IFN-gamma, BMI, insurance, sex, race/ethnicity, age, and other confounders. (2) Patient Sample: Consecutive patients from the Nemours Medical records. (3) Biologic Specimen: Immunologic Laboratory: cytokines (IL-4) and IFN-gamma isolation and analysis. Clinical Biochemistry Laboratory: serum lipid and leptin. (4) Statistical Modeling: Summary statistics; mean and SEM, median, and IQR; frequency and percentage. Hypothesis specific analysis: Pearson Coefficient, Spearman rank coefficient for correlation analysis, while ANOVA, kruskal Wallis, GLM, GEE will be used for the distribution of these biomarkers by race/ethnicity and sex.
Can Racial/Ethnic differences in Waist and neck Circumference Explain the Variability in Asthma Severity in Diverse Pediatric Patient Population?

Mentor:  Kirk Dabney, MD

Relationship to Pediatric Health/Background:  Racial/ethnic disparities had been observed in asthma morbidity and mortality. Utilization of healthcare services and adherence to treatment had been shown to play a role in severe cases, and in uncontrolled asthma. The determinants of variances are multiple. Since obesity/overweight had been implicated in asthma predisposition, we propose to examine factors that may predispose some racial/ethnic groups to asthma severity.

Hypothesis: (1) There are no racial/ethnic disparities in asthma severity. (2) Asthma severity is not associated with waist circumference (WC) and NC. (3) NC and WC do not explain the racial/ethnic variance in asthma severity.

Specific Aims:  (1) To examine the prevalence of asthma severity in our patient population (2) To compare waist and neck circumference (NC) between cases and controls.

Methodology: (1) Study Design: A case-control design will be used to determine whether or not NC is associated with asthma severity in our patient sample. (2) Patient Sample & Sampling Technique: Asthma patients with severity of symptoms will be identified from the EMR and classified as cases. The controls will be comparable to cases except for severity and will be frequency matched with cases. Data on pulmonary function, medication use, ED visit, race, ethnicity, sex, age, BMI and will be collected at baseline and compared between cases and control, The NC and WC will be measured for all participants. (3) Statistical Modeling: Summary statistics: mean, SEM, median, IQR, frequency, and percentage. The hypothesis-specific analysis will involve log binomial regression model, and GEE (random and fixed effects).
Quantitative Evidence Synthesis (QES) of Racial/Ethnic Variances in Mortality Outcomes in Pediatric sports Concussion

Mentor: Diane Fitzgerald, RN

Relationship to Pediatric Health/Background: Pediatric sports concussion (PSC) is more prevalent than reported in literature, and mortality outcomes vary by health disparities indicators. The factors leading to the observed variances are not fully understood. Understanding the determinants of variances may enhance prevention intervention across diverse pediatric populations.

Hypothesis: There are no racial/ethnic disparities in PSC prevalence and mortality outcomes.

Specific Aims: (1) To examine the prevalence and cumulative incidence, and factors that result in excess PSC among racial/ethnic minorities. (2) To determine if excess mortality outcomes are reliable measures in the published literature.

Methodology: (1) Study Design: A quantitative systematic review, termed quantitative evidence synthesis (QES) will be used to extract data from published literature that meet the inclusion and data quality criteria. (2) Search Techniques: The pubmed search engine will be used to identify literature on sports related pediatric concussion injuries and mortality, 1966 – 2013. The following search terms will be employed: “pediatric concussion” and “sports” “incidence”, “prevalence”, “cumulative incidence”, “injuries”, “mortality”, “death”, “race”, “ethnicity”, African Americans”, “Blacks”, Whites” “Caucasians” , “Hispanics”. (3) Study/Data Quality: To be included in the QES, studies will be assessed for (a) clear statement of purpose/objective,(b)sample size, (c) bias and confounding, (d) analytic techniques and inference (4) Statistical Modeling: Summary statistics will be performed using mean, SEM (paramedic), median, IQR (non-parametric), frequency, and percentage (discrete). The hypothesis- specific analysis will involve heterogeneity test prior to the decision to use the fixed effect or random effect method. Forest plot will be used for summary estimates by race/ethnicity.
Racial/Ethnic and Sex Differences in Pediatric Pedestrian Motor Vehicular Trauma (PPMVT): Ecologic Decomposition analysis Using Delaware Trauma Registry (2004-2010)

Mentor: Laurens Holmes, PhD, DrPH

Relationship to Pediatric Health/Background: Pediatric trauma outcome impacts on years of potential life lost (YPLL) and racial/ethnic minorities and males are adversely affected. The Institute of Medicine has observed a direct correlation between optimal insurance and higher socioeconomic status as enhancers of optimal prognosis, as well as survival prolongation. Understanding the determinants of variances in race/ethnicity and sex with respect to incidence and mortality outcomes may facilitate data-driven intervention mapping in addressing health disparities therein.

Hypothesis: (1) There are no racial/ethnic and sex variances in the cumulative and annual incidence and mortality outcomes of PPMVT. (2) Racial/ethnic and sex disparities in PPMVT are unexplained by insurance status, ISS, comorbidity and trauma prognostic factors.

Specific Aims: (1) To examine the distribution of PPMVT by zip code as geographic locale, race/ethnicity, and sex; (2) To determine sex, and racial/ethnic variance in PPMVT while controlling for insurance status, injury severity score (ISS) comorbidities and other prognostic factors.

Methodology: (1) Study Design: A retrospective cohort study of prospectively collected data from the Delaware Trauma Registry (DTR) on PPMVT. (2) Patient Sample: Consecutive patient from the DRT with the available data will be eligible for inclusion. (3) Statistical Modeling: Summary statistics will be performed using mean, SEM (paramedic), median, IQR (non-parametric), frequency, and percentage (discrete). The hypothesis- specific analysis will involve poison regression and generalized linear model. The GEE (random and fixed model) will used to examine the complex ecologic model of the association between race/ethnicity and sex variance in PPMVT.