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The Vanderbilt University School of Medicine is firmly committed to training future leaders and scholars in medicine. This includes the ability to recognize and understand the various challenges facing medicine as well as the vision and skill to address these challenges. That’s why we’ve created the EMPHASIS PROGRAM – an opportunity for our students to acquire specialized knowledge and experience in a focused area of their choosing.

The EMPHASIS PROGRAM is a unique mode of self-directed study which takes place during the first two years of medical school. We match the students’ area of interest with those of committed faculty mentors, providing them the opportunity to draw from seasoned professionals. Students cultivate knowledge and skill through these mentorship experiences, as well as hands-on research and study in desired areas of focus.

There are eight EMPHASIS focus areas in which students can choose projects: Biomedical Informatics, Community Health Initiatives and Outreach, Global Health, Healthcare and Public Health Research and Management, Laboratory-Based Biomedical Research, Medical Education, Medical Humanities, Ethics, and Policy, and Patient-Oriented Research. Students choose their areas, mentor, and projects during the fall semester of first year, and then use the spring semester to acquire general knowledge and skills within their EMPHASIS area. During this semester, they also work with mentors to design their studies. All students devote eight weeks to their projects during the first and second year while supported by an EMPHASIS stipend. Projects are completed during the second year and, in the spring; students present their work either as posters or oral presentations at our Spring EMPHASIS Forum.

Students who are part of our Medical Scientist Training Program are also featured in this publication. By the time they have completed the second year of medical school, these students will have selected research areas that will lead their doctoral degrees in biomedical research. The abstracts they have provided will serve as roadmaps for their future full-time doctoral studies.

In this publication, you will find abstracts of all projects carried out by the Class of 2012. The broad range of projects reflects the diversity of interests our students bring them to medical school.
In devising the EMPHASIS PROGRAM, Vanderbilt University School of Medicine sought to channel the diverse skills and passions of our students into the pursuit of scholarship and leadership. Believing that this aim is best achieved in the context of a relationship with a mentor, we sought the assistance of faculty in many different disciplines across the medical school, the university, the community, the country, and the globe. The response has been extraordinarily generous, in terms of both time and commitment. Each student has been able to work closely with a mentor for the duration of the program, spanning the first two years of medical school and including eight weeks during intervening summer. As Director of the EMPHASIS PROGRAM, I want to express my thanks to those who willingly accepted responsibility of mentoring these students. The quality of the work reported in this volume is evidence of the effectiveness of this collaboration.

These 112 abstracts represent the posters that were presented at the EMPHASIS Forum at Vanderbilt University School of Medicine on May 2nd and 3rd, 2011. Of these abstracts, 100 represent the work of students who entered the EMPHASIS PROGRAM in the fall of 2008. Twelve abstracts describe research performed by students in Vanderbilt’s Medical Scientist Training Program.

Consistent with the aims of the EMPHASIS PROGRAM, the topic covered in the abstracts are wide ranging. Students explored innovative projects as diverse as medical informatics and healthcare policy. Students carried out complex, cutting edge laboratory investigations and undertook projects on healthcare delivery in developing countries and among the urban poor.

Many of these projects will be reported at scientific meetings and in peer-reviewed publications. Some students plan to continue to work on their projects as they move to the next phase of their medical education. Others may hand their projects off to the next class entering the program. Regardless of future direction these projects take, it is clear the collaboration between students and mentors has provided significant benefit to students, faculty, and the advancement of knowledge. For many, the opportunity to work closely with a faculty member over the past 18 months has forged a relationship that will endure in the incoming years.

The EMPHASIS PROGRAM is the result of many years of discussion and planning. Once initiated, refinement has continued as we have learned from the experience of students and their mentors. However, if we judge the work presented herein, the overarching goal of nurturing scholarship and leadership in our students has already been successful.
Biomedical Informatics

Biomedical Informatics is the scientific field that deals with the storage, retrieval and optimal use of biomedical information for problem solving and decision-making. Vanderbilt Biomedical Informatics is the largest academic department of biomedical informatics in the country, with more than 50 faculty members, a graduate training program, and a portfolio of research and development projects that spans from computational biology and bioinformatics applied to the understanding of biological molecules, through advanced clinical information systems that care for hundreds of thousands of patients at Vanderbilt, to regional health information projects that span many states. Research is focused on all areas of healthcare ranging from computer programs that alert physicians about patient problems to tools that assist basic scientists with bench research. The students’ educational focus is in three general areas of biomedical informatics:

1. Developing, evaluating and refining the computer tools available to clinicians caring for patient
2. Using computer applications and techniques to better enable clinicians to assemble evidence for patient care and research.
3. Managing biologic or genomic information in ways that support discovery of new therapies or that guide basic science research.

“It has been very exciting to observe students as they learn about the field of biomedical informatics. We have had students with a wide range of technical backgrounds who have made landmark contributions to the field. The Emphasis Program is facilitating an exchange of knowledge among our medical students, our faculty, and our graduate students, in a way that has enhanced the intellectual capabilities of all three groups.”

Cindy Gadd is an associate Professor of Biomedical Informatics. She has been the Director of Graduate Studies for Department of Biomedical Informatics graduate degree programs since January 2006 and is the Principal Investigator on our NLM Biomedical Informatics Training Grant, which was recently renewed through 2012. She is an elected Fellow of the American College of Medical Informatics and an active participant in the informatics education initiatives of the American College of Medical Informatics Association. Her primary area of research and publication is the implementation and evaluation of integrated clinical information systems, including electronic health records (EHR) systems, in large health care networks. Since joining Vanderbilt, Dr. Gadd has become a co-investigator in the evaluation of the development, and sustainability of a regional health information exchange and is co-developing ePrescribing evaluation research focused on surrogate prescribers.
ANALYSIS OF COMMUNITY HEALTH CLINICS AND THEIR UTILIZATION OF CLINICAL INFORMATICS

Michael Reyes - Biomedical Informatics

Background Problem
Health information technology (HIT) tools such as electronic medical records (EMRs) are designed to facilitate and improve patient care. Smaller, community based clinics often have unique challenges in successfully incorporating information technology into their practice. These challenges stem from the fact that these smaller practices often lack the staff, information technology, infrastructure, and computer systems seen in larger institutional settings.

Objectives
The goal of this research was to identify the areas where these organizations were benefitting and where they were being constrained by the use of electronic medical records. We were particularly interested in identifying potential challenges that were unique to this clinical setting.

Materials and Methods
For this qualitative research project, two Nashville area community clinics were observed in their interactions with their electronic medical record systems. These observational sessions were used to guide questions for semi-structured interviews that were posed to key personnel.

Conclusions
Resource limited organizations are going to be challenged to find cost effective methods for training both regular staff and volunteer staff on how to effectively utilize information technology. They will have to employ creative solutions to ensure that those interacting with this software have the knowledge to realize the benefits that are associated with EMRs.

Acknowledgements
This project would not have been possible with the support and cooperation of Shade Tree Clinic and Siloam Family Health Center.

Mentor / Department
Kim M. Unertl, PhD, MS - Department of Biomedical Informatics
ANESTHESIA INFORMATION MANAGEMENT SYSTEMS (AIMS) MEDIATE IMPROVED SCIP COMPLIANCE COMPARED TO HOSPITALS WITHOUT AIMS

Ilana Stol-Biomedical Informatics

Background Problem
The Surgical Care Improvement Program (SCIP) is a national attempt to improve care of the patient undergoing anesthesia and surgery by putting specific measures in place to reduce surgical complications. Hospitals now publically report SCIP compliance scores to Centers for Medicare and Medicaid Services (CMS) in various categories based on process measures which map to surgical outcomes. Recent studies utilizing the Nationwide Inpatient Sample have demonstrated that SCIP1 compliance (giving prophylactic antibiotics within 1 hour of skin incision) has been improving over the last five years ranging from 74.8% in 2005 to 88.9% in 2007, (1) However, in the informatics literature, hospitals using an AIMS have reported significantly higher compliance rates approaching 100% (2-3).

Objectives
This study is aimed to assess the association between SCIP1 compliance and AIMS usage in U.S. hospitals.

Materials and Methods
We validated and then distributed a survey to 200 U.S. hospitals to evaluate the association between AIMS use and SCIP1 compliance. We chose a representative sample of U.S. hospitals based on the following variables: Size, Geography, Urban/Rural, and Teaching/Non-Teaching. We mailed the surveys to the Department of Anesthesiology Chair at each hospital, followed up with an online survey, phone calls, and ultimately, a second mailing to those hospitals who did not return a survey. Using the Medicare Hospital Compare database, we collected the 2005-2010 SCIP1 compliance scores from all surveyed hospitals.

Conclusions
Based on past studies such as the one done by O’Reilly in 2006, who showed that AIMS mediated reminders improve performance on specific elements of the SCIP measure, one might expect hospitals with AIMS to outperform those without. Based on our preliminary analysis, we observed a trend towards higher compliance in the AIMS group, but the difference does not reach statistical significance. One might conclude that either AIMS contribute little to managing execution on SCIP measures, or that AIMS users are not taking full advantage of the decision support potential such systems bring. A complete analysis of the entire 2005-2010 data set will be performed.

Mentor / Department
Dr. Jesse Ehrenfeld, Dr. Warren Sandberg Department of Anesthesia, Vanderbilt University
Community Health Initiatives & Health Outreach

Through the Community Health Emphasis Program, medical students develop a substantial set of products that address an unmet community health problem. As they do this, they develop skills in community leadership and scholarship, and helping patients practice positive health behaviors. Students receive training from Center for Health Services in community research strategies including focus groups, in-depth interviews, community needs assessments and grant writing. Nonprofit organizations serve as community partners, helping students develop a strong relationship with the community. Community Health Emphasis Enduring Understandings

• The health of the community plays a critical role in the health of the individual.
• Health may be strongly influenced by a person’s physical, social, political, economic, psychological, or cultural environment
• You think you know the full answer, but you don’t. There are non-medical explanations, resources, and solutions to consider.
• Successful community health programs are interdisciplinary, built from the community level up.

Community Health Emphasis student projects may address
• Health risks/diseases that disproportionately affect underserved populations.
• Obstacles to health and healthcare for the underserved.
• The socio-cultural, historical and medical aspects of caring for an underserved population.
• Principles, approaches and skills needed by medical providers in an underserved community.
• Skills and strategies that motivate patients to practice positive health behaviors
• Diagnosing the health needs of a community and designing plans to meet those needs.

“These students who selected Community Health were, not surprisingly, advocates by nature. They demanded the support of the school in full measure, so that community people would not be left behind in the excitement over bench research or more glamorous emphasis areas. Thus group of Community Health Emphasis students are brilliant, energetic, and helpful to each other step of the way. It was pure pleasure to work with them and to share in their pride as their objectives were met, their papers were accepted for publication, they achieved funding for their community projects, and in some case, became award winners for service to the community.”

Barbara Clinton, m.s.W. is Director of the Center for Health Services at Vanderbilt University. Ms. Clinton is an Adjunct Assistant Professor in both the medical schools and nursing schools at Vanderbilt and has worked as a counselor, a community organizer and a therapist with children. Ms. Clinton helped develop a system of alternative health services for seniors for the state of Georgia and has served as an advisor to former Vice President Al Gore, the Tennessee Commission on Aging, the National Center for Children in Poverty at Columbia University, the Appalachian Rural Science Initiative of the National Science Foundation, and several private foundations.
EVALUATING WOMEN’S BELIEFS ON TOTAL WEIGHT GAIN DURING PREGNANCY

Nkiruka Arinze - Community Health Initiatives and Health Outreach

Objectives

1) To evaluate pregnant women's held beliefs on appropriate weight gain during pregnancy 2) To determine the percentage of women who report having received advice from a healthcare provider on appropriate weight gain during pregnancy 3) To determine the influence provider advice on women's beliefs on appropriate weight gain during pregnancy

Brief Description

-

Conclusions

Despite the collection of this data after the release of the widely publicized 2009 IOM recommendations on appropriate weight gain during pregnancy, overwhelming percentage of the women still reported not receiving advice on appropriate weight gain during pregnancy. The high percentage of women in this study who reported not receiving advice highlights the need for improved education and discussion on healthy gestational weight gain beginning early in pregnancy and continuing at every prenatal visit.

Mentor / Department

Sabina Gesell, Department of Pediatrics
INTERPERSONAL VIOLENCE IN NASHVILLE’S
LATINO COMMUNITY: COMMON THEMES,
COMMON SOLUTIONS

Irène Mathieu—Community Health Initiatives and Health Outreach

Objectives
To elucidate the nature and scope of IPV as well as potential means of diminishing its prevalence among Latino immigrants in Nashville, TN.

Brief Description
This study used community-based participatory research (CBPR) to explore interpersonal violence (IPV), which is a significant public health challenge among Latino immigrants in the context of linguistic, cultural, and legal barriers.

Conclusions
There is both a need and a desire for programming to address IPV in Nashville’s Latino immigrant community, particularly among undocumented people. According to participants, the most effective solutions should involve whole families in constructive dialogue about communication and conflict resolution. Socioeconomic and psychological empowerment of women was also identified as a key component of violence reduction strategies. Migration to the United States is viewed as a potential expansion of women’s rights; however due to language, cultural, and legal barriers, many immigrants remain unaware of how to utilize the social resources available to them in the U.S. These findings corroborate previous qualitative studies describing IPV in Latino immigrant communities. They also serve as a starting point for locally specific IPV interventions.

Mentor / Department
Barbara Clinton (Center for Health Services), Juan Canedo (Progreso Community Center)
IN VolVING UNdERSERVED STuDENTS IN HEALTHY FOoD CHOICES

Daniel Tilden-Community Health Initiatives and Health Outreach

Objectives
19.8% of African-American adolescents boys and 29.2% of African-American adolescent girls are either overweight or obese. In addition, low levels of fruit and vegetable consumption have been correlated with higher rates of diabetes and poor health outcomes. While the underlying causes of these issues are many, poor diets are certainly a contributory factor. Therefore, understanding what factors determine students’ diets, therefore is an important part of combating these troubling trends. While several previous studies have examined parental influences on adolescent fruit and vegetable intake, we seek to understand the role that children and schools play in determining adolescents’ diets.

Brief Description
This study seeks to understand, through a student survey, the quantity of fruit and vegetable intake, when and where they are eaten, and to identify potential protective or predisposing factors in order to guide further study.

Conclusions
It is clear that the vast majority of the study group do not have adequate intakes of fruits and vegetables. Fewer than 2% met the National Cancer Institute’s recommended five-a-day intake level, with fewer than 17% reporting to have consumed an average of two fruits and vegetables per day. Clearly more study is needed to identify interventions that might increase the fruit and vegetable intake for all students in the survey sample. However, among those students with higher average intakes (i.e. meeting the two-a-day threshold), several important trends suggested that student involvement in food decisions might be an important way to increase fruit and vegetable consumption. Students who reported higher intake were significantly more likely to report being involved in food decisions at home (by requesting fruit from the grocery store) and to have healthy snacks available to them at home. These findings suggest that future interventions that put a greater focus on the role adolescents play in guiding their own food consumption might have more success than those that focus on the adults alone.

Acknowledgements
LEAD Academy High School, Tiffany McDole

Mentor / Department
Dr. Tom Cook Vanderbilt University School of Nursing
DENTAL HEALTH EDUCATION TOOLS IN A LOW-INCOME POPULATION

Andrew Wu—Community Health Initiatives and Health Outreach

Objectives
1. Increase knowledge of causes of caries and how to prevent caries in 80% of patients.
2. Increase frequency of positive oral hygiene behaviors in 80% of patients.
3. Determine the percentage use of behavioral intervention tools

Products Developed
Patient Education Materials: 1. “Formula For Good Oral and Dental Health” Patient Education Handout – Colorful and easy-to-remember handout depicting 5 key behaviors to maintain good oral/dental health. 2. Map of Wellness – Laminated, iPad-sized checklist of hygiene habits w/system of rewards for the purpose of patient motivation and goal-setting. 3. Soda3 – a variety of soda bottles and other sugary drink containers containing a representative number of sugar cubes for the respective drink; also includes tables of estimated numbers for cumulative sugar cube sizes and weights measured over different intervals of time. 4. Xylitol gum – 2 month supply packets for patients to help meet adequate daily need for xylitol. 5. Tongue Scraper – New tongue scraper from BreathRX; cheap, effective, and aesthetically appealing

Provider Training Materials: - Powerpoint presentations o “Introduction of ACTPS and the Transtheoretical Model of Behavior Change” ♣ 5 stages of change ♣ 2 intermediate outcomes ♣ 10 processes of change (including mnemonic of all processes and handout detailing the Transtheoretical Model) ♣ Motivational Interviewing o “Introduction and Explanation of Patient Education Materials” o “Concluding Thoughts and Literature Review of Current Therapies for Dental Caries” ♣ Table of Therapies ♣ Xylitol Fact Sheet and Maps of Xylitol Providers in Nashville - Interview Questions and Standardized Answer Key

Brief Description
To design and field test patient education tools and strategies to increase adult patients’ knowledge and improve oral health behavior.

Conclusions
The measured impact of the educational tools could not be obtained, due to lack of clinical record keeping. Soda3 was used the most (7/9) followed by the tongue scraper and xylitol gum. The long-term effects of these items are currently indeterminate. The interviews provided the following information: 1) most patients ranked high for hygiene behavior despite a lack of knowledge about caries; 2) most patients asked questions relating to action items rather than explanations; 3) most patients believe caries is largely caused by a sugary diet; 4) flossing was the most difficult barrier to overcome; 5) brushing daily was the best kept habit; and 6) the most common patient advice was to brush. Four 1-hour presentations presented over four weeks were well-received by the clinic providers. 109 patients were successfully recruited for the pre-intervention group. However, only 16 and 13 patients were recruited for the post-intervention and control groups respectively, which prevented the first two objectives from being completed.
This study should continue in order to recruit more patients for the post-intervention and control groups to evaluate the effects of this intervention.

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All of Interfaith Staff and volunteers

Mentor / Department
Barbara Clinton, Center for Health Services Rhonda Switzer, DMD, Interfaith Dental Clinic
Global Health

The Global Health focus area targets health problems in resource-limited settings, including diseases of poverty and the tropics, and provides students with opportunities to learn first-hand about health issues of international significance. Research projects span a broad range of themes in global health, from medical sciences and clinical investigation to socio-cultural correlates of health and health care delivery. Projects in this area fulfill the practicum requirement of the Vanderbilt Institute for Global Health’s Graduate Certificate in Global Health.

“The primary objective of the Global Health component of the Emphasis program is to nurture a growing number of students interested in global health issues, helping them to assess and understand some of the most pressing public health issues of our time in their socio-economic and culturally specific context. The Global Health focus area serves to introduce these students to the fundamental principles of service, research, planning, and management methodology in resource-limited settings. Our program has fostered the enthusiasm of approximately 60 students who have elected to participate in Global Health in the past five years. A number of students have published their work in international peer-reviewed journals or in more informal ways for general audiences. Students must plan early because overseas projects have increased complexities to obtain final approvals.”

Dr. Heimburger directs the Education and Training portfolio of the Vanderbilt Institute for Global Health (VIGH) and conducts research on nutritional influences on antiretroviral therapy outcomes in HIV/AIDS. Before joining VIGH in 2009, Dr. Heimburger served on the faculty of the Departments of Nutrition Sciences and Medicine at UAB, where his titles included Senior Scientist in the UAB Clinical Nutrition Research Center, Center for AIDS Research, and Comprehensive Cancer Center; Director of the Clinical Nutrition Fellowship Program; and Associate Director of the UAB Sparkman Center for Global Health. During a Fulbright Scholar award-supported sabbatical in Zambia in 2006-7, he initiated nutrition research in a population of Zambians starting antiretroviral therapy for HIV/AIDS. He has served on the Advisory Board of the Fogarty International Center (NIH), the governing Council of the American Society for Clinical Nutrition, a standing Review Group for the National Cancer Institute, the U.S. FDA’s Food Advisory Committee, and a Test Materials Development Committee for the United States Medical Licensing Examination.
PREVALENCE AND SOCIODEMOGRAPHIC RISK FACTORS OF HELMINTH INFECTIONS AMONG ADULTS IN RURAL SOUTHWESTERN KENYA

Jonathan Andereck—Global Health

Background Problem
Rural southwestern Kenya suffers from high soil-transmitted helminth (STH) prevalence. Two studies of a rural village in the Nyanza Province demonstrated a pediatric STH prevalence that fell from 68% in 2007 to 44% in 2010, likely due to increased access to clean water, hygiene and sanitation training, and improved deworming coverage in the schools.

Objectives
We hypothesized that adults (≥18 years) have similarly high prevalence of STH infections and serve as reservoirs for re-infection of the children. We determined the prevalence of STH infection in the adults of this village and assessed socio-demographic factors associated with STH prevalence.

Materials and Methods
We collected stool samples of 323 adults recruited at the local hospital and at four local schools. Basic demographic data were collected before stool sample screening. We used a highly sensitive sedimentation concentration technique for each sample. Concentrated specimens were stained with Dobell’s iodine and examined for ova and parasites by light microscopy at 40x magnification. Adjusted prevalence ratios (PR) were estimated using multivariable regression.

Conclusions
An STH prevalence of 16% was found among adults, approximately one-third of that found among children, and may warrant regular de-worming of adults with risk factors for STH infection.

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Mentor / Department
Aaron Kipp, PhD (Division of Epidemiology, Vanderbilt University Medical Center); Sten Vermund, M.D., PhD (Vanderbilt Institute for Global Health)
DETERMINING THE BARRIERS TO HEALTHCARE ACCESS AND UTILIZATION AMONG SINGLE MOTHERS IN COASTAL KENYA.

Jordan Cohen—Global Health

Background Problem
In Coastal Kenya, there is a great deal of stigma surrounding single motherhood. As a result, single mothers are often discriminated against, shunned, or even ostracized from their communities. This leads to poor education, socio-economic status, and access to health care for these women and inevitably, their children.

Objectives
Two years ago, Jim and Laura Reppart, representatives from the Caris Foundation in Malindi, began a project to empower sixty single mothers. This program linked them to skilled labor training, offered a support system, and provided them with access to health care. My objectives were to determine whether these single mothers reported fewer barriers to accessing health care than their counterparts who were not in the program. Additionally, I looked at patterns of health care utilization among program and pre-program single mothers.

Materials and Methods
I developed a comprehensive survey that asked about barriers to health care and health care utilization. I trained field workers who were women from the same villages as the single mothers to administer the survey. Forty-one women from the empowerment program and 60 women who were about to enter the program were given the survey.

Conclusions
The empowerment program improved access to care for single mothers by decreasing their barriers to access. The barriers that the program addressed were primarily economic. Women in the program reported hospital fees as less of a barrier, which may be a primary effect of the program paying for all hospital visits. Cost of transportation and distance to facility were also less of a barrier for the post-program single mothers. This is likely a secondary effect of the program, since the women had to provide their own transportation to access these services. The women were more economically stable after going through this program, which allowed them to pay for their own transportation to the hospital. If the program only provided free care without helping the women attain economic self-sufficiency, then they may have not been able to afford transportation and access these services. However, this program used a comprehensive approach that included education and job training to help the women generate income. Once these women attained economic self-sufficiency, they were better able to access health services, improving their standard of living. By expanding this program, more single mothers who have been cast out of society will attain economic stability and access to health care.

Acknowledgements
Jim and Laura Reppart, Angeline, Bill Wester, Rajshri Maintha
Mentor / Department
Bill Wester, Infectious Disease
PROMOTING EXCLUSIVE BREASTFEEDING COMPROMISES AGE-APPROPRIATE COMPLEMENTARY FEEDING WITH READY-TO-USE SUPPLEMENTARY FOOD IN RURAL GUATEMALA: AN ETHNOGRAPHIC USAGE STUDY

Thomas Davis-Global Health

Background Problem
Ready-to-Use Supplementary Food (RUSF) is designed for the prevention of chronic malnutrition. Because successful intervention is dependent on consistent consumption over extended periods, understanding how RUSF integrates into local culture is essential for optimizing usage.

Objectives
This study seeks to identify barriers and motivators associated with RUSF usage within a rural Guatemalan town so that targeted messages can be developed to maximize RUSF effectiveness.

Materials and Methods
Five families consented to participate in five weekly home visits. Ethnographic techniques of participant observation and unstructured interviews were used to characterize how RUSF has integrated into the daily life of participating families. In addition, parents from 18 families participated in one of four focus groups to validate observations across a broader cross-section of the community.

Conclusions
In this culture, meaningful complementary feeding occurs only after breastfeeding is discontinued. We have developed a conceptual framework to encourage mothers to invest a sufficient effort needed to overcome the activation energy preventing successful transition to an age-appropriate balance between breastfeeding and complementary feeding.

Acknowledgements
The authors would like to thank Dr. Peter Rohloff and his team at Wuqu’ Kawoq for facilitating the logistics of the study. We would also like to thank Jillian Currie for her contribution to the development of the conceptual framework.

Mentor / Department
Ted Fischer, PhD - Center for Latin American Studies Doug Heimburger, MD, MS - Vanderbilt Institute for Global Health
YOUTH HIV AND SEX EDUCATION IN NYANZA PROVINCE, KENYA: EFFECTS ON KNOWLEDGE AND ATTITUDE

Mary DeAgostino-Global Health

Background Problem
The Lwala clinic in Nyanza province, Kenya determined a need for an effective sex and HIV education outreach program in local schools to increase understanding of HIV and ultimately reduce HIV prevalence in the region.

Objectives
This study assesses the effectiveness of the “Tuko Pamoja” curriculum chosen by the Lwala Community Alliance as delivered to secondary school students, ages 12 – 24 years, enrolled in Kameji Secondary School.

Materials and Methods
Tuko Pamoja is an HIV, sex, and life skills curriculum designed for youth by Kenya’s Program for Appropriate Technology in Health (PATH), with funding from the United States Agency for International Development (USAID) and the President’s Emergency Plan for AIDS Relief (PEPFAR). This study examined knowledge, attitudes, and beliefs, including perceptions of self-efficacy, prior to and following participation in HIV programming via a questionnaire utilizing items from two previously validated HIV Knowledge, Attitude, and Practice surveys in East Africa.

Conclusions
Ultimately, this research aims to help shape an effective HIV curriculum to reduce the incidence of HIV in the Lwala region. The results provide a unique lens into the importance of understanding the culture of learners prior to program implementation and the translatability of large-scale programs into particular cultural settings.

Mentor / Department
Dr. Emil Petrusa, OTLM
EFFECT OF SUTHERLANDIA ON GLUCOCORTICOIDS AND XENOBIOTIC METABOLISM IN HIV-INFECTED SOUTH AFRICAN ADULTS

Kathleen Doherty-Global Health

Background Problem
Sutherlandia is a flowering shrub native to South Africa that is used in traditional medicines for a wide range of symptoms and diseases, including stress, inflammation and infection. Recent research in cell extracts and animal models has demonstrated inhibitory activities of Sutherlandia and its extracts on enzymes of glucocorticoid synthesis. Because HIV-infection is a known risk factor for adrenal dysfunction, the impact of Sutherlandia on adrenal enzymes could be medically important. Additionally, Sutherlandia has been previously shown in vitro to influence the CYP3A metabolism of antiretrovirals.

Objectives
The primary aim of the study was to investigate the effect of 24-week Sutherlandia consumption on levels of cortisol and DHEAS in sera of HIV-infected South African adults. A secondary aim was to examine Sutherlandia's effects on the CYP3A4 system through measurement of 6ß-hydroxycortisol in urine.

Materials and Methods
The investigation was conducted as a secondary, subsidiary outcome of a larger study, “A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Sutherlandia frutescens in HIV-infected South Africans,” whose aims were to investigate the effects of Sutherlandia on various health measures. Baseline, 12- and 24- week serum (N=36) and urine (N=33) aliquots were gathered from previously collected samples from participants in the larger trial, whose sera and urine had been collected within a 2.5 hour window. Cortisol, DHEAS and 6ß-hydroxycortisol were extracted from the samples and quantified using high-performance liquid chromatography-mass spectrometry.

Conclusions
Regardless of the source of this wide variability, an outcome has been understanding and managing the challenges of executing biomedical research in a resource-limited setting.

Mentor / Department
Dr. William Folk, Ph.D., University of Missouri Biochemistry Department Dr. Douglas Wilson, Edendale Hospital, South Africa Dr. Douglas Heimburger, Vanderbilt Institute for Global Health
COMPARISON OF THE CONTRIBUTING ROLES THAT CELLULAR AND HUMORAL IMMUNITY VERSUS HUMORAL IMMUNITY ALONE PLAY IN DENGUE HEMORRHAGIC FEVER PATHOGENESIS

Joshua Gutierrez - Global Health

Background Problem
Dengue Virus belongs to the Flaviviridae family of viruses, and is a single stranded positive sense RNA virus. Four distinct serotypes exist: DENV1, DENV2, DENV3, and DENV4. Dengue fever results from infection with the virus, and is an arthropod-borne disease spread primarily by the mosquito, Aedes Aegypti. There are currently no effective antiviral options or vaccines available to combat the spread of this disease. The disease can manifest itself in two forms: Dengue Fever and Dengue Hemorrhagic Fever. Dengue Fever is characterized by fever, severe myalgia, severe headache, fatigue, arthralgia, and macular rash. Dengue Hemorrhagic Fever is characterized by thrombocytopenia, capillary leakage, and subsequent proclivity to bleed. Approximately 90% of Dengue Hemorrhagic Fever occurs in the setting of secondary heterologous Dengue Virus challenge; however, the remainder of cases generally occur following primary Dengue infections in infants. During Dengue Hemorrhagic Fever the immune response generated includes a cellular and humoral immune response that not only is inadequate at clearing the virus, but actually promotes viral infection of macrophages and an excessive, out of control, inflammatory response (levels of IFN-g, TNF-a, soluble TNF receptors, IL-6, IL-8, IL-10, and MIP-1b are elevated during Dengue Hemorrhagic Fever compared to Dengue Fever).

Objectives
Establish a murine model of Dengue Hemorrhagic Fever and evaluate the relative roles that B and T cells play in its pathogenesis by comparing a combined humoral and cellular response to a primarily humoral response.

Materials and Methods
- Intraperitoneal infection of C57BL/6 mice with 10^6 PFU DV1 (HW strain), DV2 (16681 strain), or placebo. - Cross-reactivity analysis, draw blood at 7, 15, and 30 days post infection to determine anti-Dengue activity of Abs. - Then one of the following: Homo and heterotypical secondary infection (intraperitoneal) of previously infected mice with 10^6 PFU DV2 Tonga 74 strain - 3 days post infection: blood extraction - 7 days post infection: blood extraction and organ collection - Passive transfer of anti-DENV1, anti-DENV2, or control serum intraperitoneally - 18 hours post transfer: blood extraction to determine Ab titers (ensure they’re sufficient) - 24 hours post transfer: intraperitoneal infection with DENV2 (10^6 PFU) - 3 days post transfer: blood extraction - 7 days post transfer: blood extraction and organ collection - Evaluate hematological and biochemical markers of disease severity characteristic of Dengue Hemorrhagic Fever in humans: thrombocytopenia (platelet count), Renal Failure (BUN and CK levels), Transaminitis (AST and ALT levels), tissue breakdown (LDH and CK levels), bleeding times, and vascular permeability - Also infect 2 C57BL/6 with LPS: 15 mg/kg ip (0.3 mg LPS/mouse assuming each mouse weighs 20 g) - later, coat plates with anti-IFN-gamma Ab
Conclusions
I had the opportunity to develop knowledge regarding and proficiency performing cell passages, maintenance and infection of C6/36 cell lines, calculation of viral titer via plaque assays (plaque forming units), ELISA to evaluate the anti-Dengue activity of Abs from previously inoculated mice (anti-DENV1, anti-DENV2, control), real time PCR, general lab sterility techniques, etc. In addition, I learned that excellent communication is absolutely necessary to ensure a project begins efficiently and runs smoothly. I learned that lab based research requires that the researchers have ample time to carry out their experiments, which are likely required to be repeated due to various challenges. Finally, unforeseen issues I faced in regard to facilities and lab resources demonstrated just how valuable consistency and constancy are in basic science research.

Mentor / Department
Dr. Fernando Polack, Associate Professor in the Division of Infectious Diseases (Department of Pediatrics)
EFFECT OF RADIX ASTRAGALI ON INFLAMMATION AND ANGIOGENESIS

Ka-wai Ho-Global Health

Background Problem
Foot ulcers are a major complication of diabetes mellitus that often results in limb amputation. Previous experiments demonstrate that Radix Astragali (RA), an herb used in Traditional Chinese Medicine to treat diabetes and its vascular complications, promotes diabetic wound healing when used in conjunction with another herb, Radix Rehmanniae.

Objectives
The aim of this study was to determine the anti-inflammatory and angiogenic properties specific to Radix Astragali extracts using established in vitro models.

Materials and Methods
Through simple and highly reproducible assays, it was found that the production of inflammatory mediators decreased as the concentration of RA increased (p<0.05).

Conclusions
From this study, it is evident that Radix Astragali can decrease the inflammatory response and increase angiogenesis, components essential for wound healing in chronic diabetic foot ulcers.

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Mentor / Department
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THE MOORE PEDIATRIC SURGERY CENTER: A NOVEL HYBRID MODEL FOR GLOBAL PEDIATRIC SURGICAL AID

Tyler Merceron-Global Health

Background Problem
Global surgical missions have been criticized for their inability to provide continuity of care. In order to create a sustainable model of surgical care in the developing world, we must (1) develop the infrastructure to provide safe surgical and post-operative care, (2) have a steady supply of resources - both human and medical - and equipment, and (3) include an educational component that involves training of the local team, as well as the visiting team.

Objectives
The goal of this project was to evaluate a new model for providing sustainable, high-quality surgical care in the developing world.

Materials and Methods
A number of surveys were performed to assess the patient population and visiting medical volunteer satisfaction at the Moore Pediatric Surgery Center (MPSC).

Conclusions
The MPSC is a new surgical center that provides free specialty surgical services to children who could not otherwise receive care in Guatemala City, Guatemala. The MPSC is a permanent structure, thus providing a home base for visiting volunteer surgical teams, local Guatemalan medical personnel and patients (for follow-up care). Such a center provides the infrastructure, resources and educational opportunity to provide sustainable and high-quality surgical care in the developing world.

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Mentor / Department
Quentin Eichbaum
Background Problem
There are many challenges to diagnosing and treating of pediatric cancer to low-middle income countries (LMIC). These obstacles make delivery of pediatric oncological care inadequate. To investigate treatment outcomes in a population of pediatric oncology patients, Vanderbilt School of Medicine/Vanderbilt Institute for Global Health has partnered with the University of Zambia School of Medicine/University Teaching Hospital (UTH). UTH is the only government-sponsored medical center in Zambia that provides pediatric oncology care and treatment.

Objectives
The objective of this study is to assess risk factors associated with abandonment of treatment by pediatric oncology patients at UTH in Lusaka, Zambia.

Materials and Methods
This was a retrospective study that looked at a cohort of pediatric oncology patients receiving treatment at UTH between July 2008 and June 2010. Data was collected from an established patient database and review of medical records.

Conclusions
The outcomes of cancer treatment at the only center providing cancer care in Zambia are grim with an overwhelming majority of patients in this study abandoning treatment or dying during treatment. Chief among the many obstacles to successful cancer care in Zambia are access to chemotherapy, logistical facilitation, fiscal support of radiotherapy, and community engagement. Further inquiry is needed to address the effects of these challenges and discovery of approaches to improve outcomes for pediatric oncology patients.

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Mentor / Department
Jeremy Slone, Department of Pediatrics Debra Friedman, Department of Pediatrics
CHARACTERISTICS PREDICTING NICU ADMISSION IN AMMAN, JORDAN

Cristin Quinn-Global Health

Background Problem
Reasons that newborns are admitted to the NICU in Amman, Jordan are currently poorly defined.

Objectives
To compare characteristics of newborns admitted to the NICU to those newborns who are discharged to home.

Materials and Methods
Newborns born within 96 hours at Al Bashir Hospital in Amman, Jordan were prospectively enrolled from February 2010 to July 2011. Demographic information for newborns and their mothers were collected including child’s birth date, child’s birth weight, average daily number of hours mother spends outdoors, mother’s clothing practice, and smoke exposure. Blood samples were obtained from infants by heel stick, placed on filter paper, and then sent to ZRT Laboratory for vitamin D \([25(OH)D]\) measurement. Within this cohort, we conducted a retrospective chart review of newborns who were admitted to the NICU. The questionnaire collected sociodemographic, clinical, and maternal information. We modeled the probability of NICU admission among newborns using logistic regression with splines.

Conclusions
Gestational age, birth weight, type of delivery, and month of birth are the strongest predictors of NICU admission at Al-Basheer hospital.

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Mentor / Department
Dr. Natasha Halasa, Pediatric Infectious Disease; Dr. Najwa Khuri-Bulos, Pediatric Infectious Disease at Jordan University Hospital, Amman, Jordan
THE ASSOCIATION OF VITAMIN D ON BACTERIAL VAGINOSIS IN PREGNANT WOMEN IN RURAL, SOUTHERN INDIA

Megan K. Ryan—Global Health

Background Problem
Bacterial Vaginosis (BV) is a vaginal infection that affects nearly one in three reproductive-aged women and is characterized by the loss of normal vaginal flora. Maternal BV carries a risk of preterm birth in the fetus. Vitamin D has been shown in many studies to play a potential role in the immune system and other studies have shown that Vitamin D Deficiency is associated with Bacterial Vaginosis in pregnant women. Vitamin D Deficiency is a potentially modifiable risk factor for disease. Therefore, treatment of Vitamin D Deficiency among pregnant women could theoretically reduce the prevalence of BV and the prevalence of pre-term labor. Vitamin D supplementation may have a role in new preventive and therapeutic strategies for BV in obstetric populations.

Objectives
The objective of this study is to assess if there is an association of Vitamin D on Bacterial Vaginosis.

Materials and Methods
This was a retrospective study from a much larger, ongoing study. A random sampling of pregnant women was taken from this larger study. I used sera being stored at -70 degrees Fahrenheit to test for total Vitamin D levels using a chemiluminescence assay kit. I also used stored vaginal smears to test for Bacterial Vaginosis. These smears were already stained and were double-blind read using the Nugent Score. Other data was collected from a review of medical records. Statistically, Chi-square and Kruskal-Wallis tests were conducted. An ordinal logistic regression model was fitted for bacterial vaginosis on age, education, Vitamin D and income.

Conclusions
We found no evidence that vitamin D was associated with BV. Further inquiry is needed to determine if Vitamin D levels play a role in maternal health and birth outcomes.

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Mentor / Department
Dr. Heimburger, Department of Global Health Dr. Purnima Madhivanan, Department of Epidemiology at Florida International University
OUTCOMES OF HOSPITALIZED NICU INFANTS IN AMMAN, JORDAN

Priya Sivasubramaniam; Cristin Quinn; Natasha Halasa, MD, MPH; Najwa Khuri-Bulos, MD, CIC, FIDSA; Samir Faouri, MD; Meridith Blevins-

Global Health

Background Problem
In order to evaluate the United Nations millennium development goal to reduce child mortality, a description of outcomes of newborn infants admitted to NICU in the Middle East is needed.

Objectives
We sought to describe characteristics of Jordanian newborns admitted to the NICU and their clinical outcomes.

Materials and Methods
Newborns born at Al Bashir Hospital in Amman, Jordan were prospectively enrolled from February 2010 to July 2011. We focused on the cohort of newborn infants admitted to the NICU and abstracted neonatal and maternal information using a retrospective chart review. Primary outcomes include mortality, antibiotic days, ventilation, oxygen use, and CRP. Clinical data are compared using Wilcoxon rank sum and chi-squared tests. Logistic regression modeling estimates the relationship between hypothesized risk factors and outcomes, adjusting for gestational age effects.

Conclusions
Among this Jordanian population, low apgar and positive CRP were predictors of mortality. All children were administered antibiotics; however, the majority of infants were given a short course of antibiotics.

Acknowledgements
Natasha Halasa, MD, MPH

Mentor / Department
Pediatric Infectious Diseases at Vanderbilt University; Al-Basheer Hospital in Amman, Jordan
COMPREHENSIVE KNOWLEDGE OF HIV AMONG WOMEN IN RURAL MOZAMBIQUE: DEVELOPMENT AND VALIDATION OF A NOVEL SCALE, THE HK-27

Shannon Skinner—Global Health

Background Problem
In 2009, 14% of Mozambican women were infected with HIV, yet only 18% had comprehensive HIV knowledge. Research to understand how poor knowledge might affect HIV-related behaviors has been limited by a lack of rigorously validated measures appropriate for sub-Saharan Africa.

Objectives
To develop and validate a comprehensive HIV knowledge scale for use in Mozambique.

Materials and Methods
A convenience sample of women awaiting prenatal care at two clinics was orally administered a novel HIV-knowledge scale, the HK-27. The HK-27 consists of 27 items adapted from existing scales for a Mozambican context or were generated for this study; items were translated into Portuguese and Echuabo, a common local language. HK-27 scores correspond to the percent of items answered correctly. Validation analyses were stratified by survey language. Kuder-Richardson (KR-20) coefficients estimated internal reliability. Construct validity was examined by testing bivariate associations between HK-27 scores and selected self-reported characteristics. The association between knowledge and self-reported HIV testing was estimated by multivariable logistic regression.

Conclusions
The HK-27 is a reliable, valid measure of HIV knowledge for women in Mozambique. Though significant gaps remain, HIV knowledge was higher than in previous estimates, and associated with HIV testing. Future work should explore the relationship between HIV knowledge and health-related behaviors in low-income settings.

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HIV STIGMA AS A BARRIER TO RECEIVING HIV CARE AT A GENERAL HOSPITAL IN LIMA, PERU: A CASE-CONTROL STUDY.

Carla Valenzuela—Global Health

Background Problem
Poor retention in care may increase the risk of morbidity, mortality, and community HIV transmission. The role of HIV stigma in poor retention has not been well studied in Latin America.

Objectives
The objective of this case-control study was to evaluate the association between HIV stigma and retention in care among HIV patients in Lima, Peru.

Materials and Methods
We evaluated HIV-positive patients who were diagnosed and/or initiated HIV care at a general hospital between 2005-2010, with inclusion based on status of care by March 31, 2011. Those retained in care (n=150) had ≥ 2 documented medical care visits per year and were approached and interviewed privately in clinic during their appointment. Those not retained in care (n=55) had no documented visits for ≥ 1 year; home visits were used to locate them and conduct interviews. The Berger HIV stigma scale was used to quantify the multiple factors of HIV stigma as experienced and perceived by patients within their communities: community enacted stigma (ES), disclosure concerns (DC), negative self-image (NSI), and concern with public attitudes (CPA). Each domain had 5 items with higher scores indicating higher stigma (score range 0-15). Multivariable logistic regression was used to calculate adjusted odds ratios (AOR) and 95% confidence intervals (CI) for being out of care. It was modeled as a continuous variable and linearity assumptions were assessed.

Conclusions
This study suggests that all aspects of HIV stigma, particularly concern with public attitudes, play a role in being out of care.

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Healthcare & Public Research

The student experience in the area of Healthcare and Public Health Research and Management is designed around a research track or management track. Students in the research track complete a hypothesis driven investigation in a field of healthcare research, such as health behavior and education, epidemiology, or outcomes research. Common research methods in this area include chart review, patient surveys, database analysis, qualitative research, systematic review, and clinical trials. The management track involves a healthcare management internship and quality improvement project, in which the student works as part of an interdisciplinary team to improve an aspect of patient care.

Sunil Kripalani, MD, MSc, is Associate Professor in the Department of Medicine, Chief of the Section of Hospital Medicine, and Associate Director of the Effective Health Communication Program. He is an academic hospitalist whose research concerns hospital-based communication, with a focus on transitions of care, health literacy, and medication management. Dr. Kripalani has expertise in the performance of observational research studies (surveys, qualitative research, and secondary data analysis), as well as intervention studies (quality improvement interventions and randomized controlled trials) to inform and improve patient care. His research in health literacy and hospital medicine has been recognized nationally, and he enjoys mentoring medical students and post-doctoral trainees.

Melissa McPheeters, PhD, MPH, Assistant Professor of Obstetrics and Gynecology and Medicine and Public Health, is Co-Director of the Vanderbilt EPC, Deputy Director for Women’s Health Research at Vanderbilt, and Co-Director of the Vanderbilt CTSA Database core. In addition to her research as a healthcare epidemiologist, Dr. McPheeters has more than 15 years of experience in the translation of research to practical and useful products. Dr. McPheeters’ PhD, completed in 2003, was in healthcare and reproductive epidemiology, with an emphasis on the use of epidemiologic analytic methods in large databases – she has continued this work over the past seven years, focusing on expanding approaches to analyses in administrative data, such as hospitalization data, as well as large-scale weighted surveys. Dr. McPheeters is an expert in comparative effectiveness reviews and on epidemiologic study design and analysis, with content expertise in maternal and child health. She has worked at the CDC and at state government in addition to her academic career to so bring a strong public health perspective to her work.
FIRST TRIMESTER ANTIHISTAMINE EXPOSURE AND RISK FOR ADVERSE PREGNANCY OUTCOME

Tiara Aldridge-Healthcare and Public Health Research and Management

Background Problem
Approximately 85% of women use at least one medication during pregnancy—antihistamines are among those most commonly used in the first-trimester of pregnancy. Animal models suggest there are biologically plausible pathways, including uterine contractile and implantation pathways, by which antihistamines could increase the risk of miscarriage and preterm birth. However, knowledge about the effects of antihistamine exposure during pregnancy is poor.

Objectives
1. To characterize antihistamine use among pregnant women in a prospective pregnancy cohort
2. To test for association between antihistamine use during pregnancy and adverse pregnancy outcomes

Materials and Methods
Women were enrolled in Right from the Start (2004-2009), a prospective pregnancy cohort. Data about over-the-counter first-trimester antihistamine exposure was obtained from baseline and first-trimester interviews; outcomes (spontaneous abortion [SAB < 20 weeks gestation] and preterm birth [PTB < 37 weeks gestation]) were self-reported and verified by medical records. Cox proportional hazards survival models were used to test for association between antihistamine exposure and SAB risk, while multivariable logistic regression was used to test the association with PTB. Both sets of analyses were performed unadjusted and adjusted for confounders.

Conclusions
Despite pharmacologic properties that suggest antihistamines may influence uterine contraction and pregnancy implantation, we did not detect evidence of association with SAB or PTB outcome. Further investigation of exposure risks during other critical periods in pregnancy, as well as of dose and duration effects, is needed to more completely understand the safety of antihistamine use throughout gestation.

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Vanderbilt University School of Medicine
Emphasis Program-Forum VII-May 2012
Mentor / Department
Dr. Katherine Hartmann, Vanderbilt Epidemiology Center, Department of Obstetrics and Gynecology, Institute of Medicine and Public Health Dr. Digna Velez Edwards, Vanderbilt Epidemiology Center, Institute of Medicine and Public Health, Department of Obstetrics and Gynecology, Center for Human Genetics Research
ACCULTURATION AND OBESOGENIC BEHAVIORS AND FEEDING BELIEFS IN LATINO FAMILIES

Laura Ballenger-Healthcare and Public Health Research and Management

Background Problem
Excess infant weight gain in the first months is associated with increased risk for later obesity. Latinos are disproportionately affected in later prevalence rates. Among Latinos, there has been limited study of the role of acculturation in infant-related nutrition/activity behaviors.

Objectives
Assess the association of Latino caregiver acculturation with feeding/activity beliefs/behaviors in a sample of caregivers of 2-month old infants.

Materials and Methods
Cross-sectional analysis of Latino caregivers of infants presenting for 2 month WCC, participating in a cluster randomized early obesity prevention trial involving pediatric resident clinics at 4 universities. Acculturation was assessed using the Short Acculturation Scale for Hispanics (SASH); low acculturation was defined as mean score ≤ 2.99. Obesogenic behaviors were assessed by caregiver report of infant dietary beliefs/behaviors and sedentary behaviors. Comparison between acculturation and other measures were assessed with chi-square and t-tests. Logistic and linear regression models adjusted for parent age, education, insurance, country of origin, and child age.

Conclusions
Latino acculturation has a complex relationship with obesogenic beliefs and behaviors. Future pediatric obesity prevention interventions among Latinos may require a targeted approach focused on specific high-risk behaviors.

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TIME TO CLINICAL STABILITY FOR CHILDREN HOSPITALIZED WITH PNEUMONIA

Rachel Bloch—Healthcare and Public Health Research and Management

Background Problem
Pneumonia is a prevalent cause of pediatric hospitalization and physiologic and non-physiologic factors may alter disease and hospital course. Assessing course of illness based on physiologic data is valuable for retrospective assessment of illness duration and severity as well as prospective clinical assessment. Appropriate assessment could reduce hospitalization rates, length of stay and decrease healthcare costs in addition to providing a standardized measure to assess pediatric pneumonia course in the hospital setting.

Objectives
To develop a longitudinal outcome based on physiologic data from children hospitalized with community-acquired pneumonia (CAP).

Materials and Methods
From Jan. 2010-Apr. 2011, data on five physiologic variables; temperature, age-based heart rate (HR) and respiratory rate (RR), and need for supplemental oxygen and intravenous (IV) fluids were collected from 338 children hospitalized with CAP at Vanderbilt and enrolled in the CDC Etiology of Pneumonia in the Community (EPIC) Study. Time from admission to resolution of abnormal values for each variable was calculated. A summary measure, Time to Clinical Stability (TCS), defined as the time to resolution of all variables (normal temperature, HR, and RR, and no longer requiring supplemental oxygen or IV fluids) was then calculated and compared with hospital length of stay (LOS) and need for intensive care (ICU).

Conclusions
TCS correlated well with hospital LOS and was longer among those with more severe disease. This objective measure, based on physiologic data, may be advantageous for assessing outcomes for children with CAP. Additional validation is warranted, including exploring factors associated with prolonged LOS after reaching stability.

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Mentor / Department
Derek Williams, Pediatrics
QUALITY ASSESSMENT OF CARDIOPULMONARY RESUSCITATION AT VANDERBILT UNIVERSITY MEDICAL CENTER

Matthew Clark—Healthcare and Public Health Research and Management

Background Problem
Survival from sudden cardiac arrest remains dismally low, even when it occurs in the hospital where trained rescuers are immediately available (1,2). Poor resuscitation technique and inadequate teamwork by rescuers may partially explain sub-optimal survival from in-hospital cardiac arrest. Observational studies of cardiac arrest both inside and outside of the hospital have shown that resuscitations performed by professional rescuers are frequently characterized by technical inadequacies and ineffective teamwork and leadership (2,3,4,5,6). Ensuring high quality cardiopulmonary resuscitation (CPR) therefore represents an important means of maximizing neurologically intact survival from sudden cardiac arrest. To date, there has been no institution-wide effort to assess the quality of CPR at Vanderbilt University Medical Center (VUMC).

Objectives
1. Improve and standardize documentation of resuscitation at VUMC. 2. Assess the quality of resuscitations at VUMC and identify areas of focus for future resuscitation quality improvement (QI) initiatives at VUMC.

Materials and Methods
We created a post-resuscitation with two sections, one consisting of clinical data and the second assessing the respondent’s perception of the quality of resuscitation interventions. The survey was administered through Vanderbilt’s proprietary REDCAP software, a secure, online data collection tool and made available to physicians and nurse practitioners on the clinical desktop. For each patient who survived the initial resuscitation event, the patient’s electronic medical record was accessed to ascertain the patient’s survival to hospital discharge and neurological outcome as assessed by the Cerebral Performance Category (CPC) scale (7).

Conclusions
There are many challenges in the study of in-hospital cardiac arrest and it is difficult to encourage staff to integrate a new documentation and QI tool into their daily work flow. Our limited data is consistent with larger studies suggesting that survival from in-hospital cardiac arrest is poor and in-hospital resuscitations are often of poor quality. Future directions include the creation of a combined documentation and QI tool within StarPanel that is expected to improve participation of housestaff and mid-level providers in the initiative, as well as function as a robust clinical documentation tool for all resuscitations at VUMC.

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Mentor / Department
John McPherson, M.D. Department of Medicine Division of Cardiovascular Medicine
CLINICAL CAUSES OF PREMATURE BIRTH IN THE AFRICAN AMERICAN AND CAUCASIAN POPULATIONS AT A REGIONAL PERINATAL CENTER IN TN

Natasha A. Kassim—Healthcare and Public Health Research and Management

Background Problem
Preterm births account for over 75% of all neonatal deaths in the US and are the leading cause of infant mortality in African Americans. In addition, the rate of African American (AA) premature births (less than 37 weeks gestation) is twice that of Caucasian infants. Despite known adverse outcomes, the preterm birth rate has risen in the US over the past decades. Studies have demonstrated that there is a clear disparity in rates of premature birth between the races; however, it is unknown if this disparity is due to a particular difference in clinical cause of premature birth or higher rates overall of premature birth in the AA population.

Objectives
To examine the clinical causes of premature birth between Caucasian and AA mothers of premature infants. The clinical causes of preterm birth analyzed included abruption, chorioamnionitis, multiple gestations, PIH, PPROM, premature labor, incompetent cervix, maternal diabetes, trauma, and medically indicated for maternal and fetal health.

Materials and Methods
Data was collected from a large level 3 referral center clinical database of preterm infants. We conducted a multinomial logistic regression of N=654 (N=218, AA; N=436, Caucasian) of cause of preterm birth by race, controlling for mother's age and substance abuse.

Conclusions
These results suggest that in our population the patterns of causes of premature birth did not differ by race, and therefore, the prevalence of AA premature birth is not driven by any particular pathway. Our results do not suggest a reason for research directed toward identifying the cause and prevention of preterm birth focus on race.

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Mentor / Department
William F. Walsh, MD, Department of Pediatrics

Vanderbilt University School of Medicine
Emphasis Program-Forum VII-May 2012
VITAMIN D STATUS, SUN EXPOSURE, AND DIETARY INTAKE OF VITAMIN D IN PEDIATRIC HEMATOPOIETIC CELL TRANSPLANT PATIENTS AT TRANSPLANT

Haerin Lee - Healthcare and Public Health Research and Management

Background Problem
Survivors of hematopoietic cell transplant (HCT) are at risk for low bone mineral density (BMD), which is exacerbated by low serum 25OH vitamin D. Greater than 90% of vitamin D comes from sunlight; HCT patients are counseled to avoid unprotected sunlight exposure due to increased risk of secondary skin cancer. HCT patients are therefore advised to consume appropriate amounts of vitamin D or to supplement with vitamin D to protect bone health. In spite of these recommendations, decreased BMD remains a significant problem for many HCT survivors.

Objectives
To compare the serum 25OH vitamin D levels of pediatric HCT patients with those of healthy controls and to explore associations between 25OH vitamin D levels and sunlight exposure and dietary intake/ supplementation with vitamin D.

Materials and Methods
Eligible study patients received allogeneic HCT < age 21 years, with study visits at transplant day ±5. Control subjects were healthy patients < age 21 years without hyperthyroidism, malabsorption, bone problems, diabetes, cancer history, or glucocorticoid requirement. All subjects completed sun exposure and food frequency questionnaires and had a measurement of serum total 25OH vitamin D level. Wilcoxon tests and Pearson chi-square tests were used to compare the groups across several factors. We calculated the Spearman correlation to assess the association between dietary vitamin D intake and serum 25OH vitamin D.

Conclusions
HCT patients have lower serum 25OH vitamin D levels and less sun exposure at transplant than healthy children. Minimal vitamin D supplementation and poor dietary intake of vitamin D is reported in both groups. Dietary vitamin D intake is positively correlated with serum 25 OH vitamin D levels.

Mentor / Department
Dr. Jill Simmons, Pediatric Endocrinology
CHOLEDOCHOLITHIASIS MANAGEMENT VARIATION IN AMERICA: DO RURAL SURGEONS NEED DIFFERENT SKILLS THAN URBAN SURGEONS?

William J. Lee M.S.- *Healthcare and Public Health Research and Management*

**Background Problem**
Choledocholithiasis (CDL) management remains challenging even in the age of advanced laparoscopy and interventional endoscopy. Often, management is dictated by locally available resources and expertise rather than recognized best practices. Our previous work has identified a strikingly consistent variation pattern in CDL management: more operations and less endoscopic interventions are performed in rural communities. In urban areas however, less operations and more endoscopic interventions are performed. The main goal of this proposal is to ascertain why this variation exists and to target potential opportunities for improving access to less invasive techniques of CDL management. We will evaluate why surgeons choose to manage preoperatively discovered CDL either by open common bile duct exploration (OCBDE), laparoscopic common bile duct exploration (LCBDE), or endoscopic retrograde cholangiopancreatography (ERCP). We will evaluate similar responses for CDL discovered incidentally at the time of cholecystectomy. We report here the survey development process and results from a Nashville area pilot study. The national study will be conducted later this year.

**Objectives**
Aim 1 – Evaluate reasons why surgeons choose to manage preoperatively discovered CDL either by OCBDE, LCBDE, or ERCP. Aim 2 – Determine why surgeons choose to manage incidentally discovered CDL at the time of cholecystectomy with OCBDE, LCBDE, or ERCP. Hypothesis – We hypothesize that surgeons in rural communities are more likely to perform operative interventions than their urban counterparts for CDL.

**Materials and Methods**
Iterative focus groups were conducted at our institution over a 6 month period with participation from our minimally invasive General Surgery faculty, senior surgical residents, and medical students to help formulate survey items to address the hypothesis and specific aims. After 6 rounds of refinement, a 22 item survey was developed addressing items of surgical experience, endoscopic experience, resources available, technical factors, training, and demographics. The population of interest to complete this survey will be practicing attending surgeons designated as either ‘General Surgeons’ or ‘Abdominal Surgeons’ in the AMA Physician Masterfile. Access to the AMA Physician Masterfile is facilitated by Direct Medical Data, which acts as the clearinghouse for AMA data. Surgeons in all 50 states and territories of the United States and the District of Columbia will be invited to participate. Currently 24,694 surgeons have valid email addresses within the Masterfile; this represents 76.3% of ‘General’ or ‘Abdominal’ surgeons. Surgeons will be contacted via email and the survey will be completed using Vanderbilt University’s REDCap Survey system. Respondents will be classified into one of six NCHS urban-rural classes based on the location of their primary practice. These classes will be collapsed into 3 groups for analysis: metropolitan areas (NCHS 1–4), micropolitan areas (NCHS
5), and rural areas (NCHS 6). Exploratory analysis will be performed amongst the collected variables to assess consolidation of responses for simplification of analysis. Descriptive statistics will be reported. Chi-square tests and correlations will be calculated as appropriate.

Conclusions
The results of this pilot study provide a first glimpse into CDL management in an urban area of the United States, although these results may reflect an underlying academic bias since all respondents practice in a university hospital or university-affiliated community hospital. The generally accepted treatment for CDL usually involves endoscopic techniques (ERCP) to facilitate clearance of the bile duct of calculi. When ERCP is not feasible or unavailable, operative techniques are employed including LCBDE or OCBDE. The precise role of common bile duct exploration in the age of ERCP still remains to be defined. Usually, patients obtain care near home for benign gallstone pathology as cholecystectomy remains one of the most common procedures performed by general surgeons in the United States. However, CDL management often presents a challenge given the different methods available for treatment, accessibility to these interventions, and costs involved for unnecessary or inefficient care. As such, identifying CDL management differences and the reasons for these differences could help target interventions to reduce this variation and improve care.

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NOISE INDUCED HEARING LOSS: A CONCERN FOR OR STAFF?

Matthew McDonald - Healthcare and Public Health Research and Management

Background Problem
Excessive operating room (OR) noise has received attention from many OR stakeholders in recent literature. Commonly, concerns focus on risk of noise-induced hearing loss (NIHL). NIHL results from sensorineural changes following exposure to loud sounds.

Objectives
We sought to quantify the noise level typical of an operating room in a major medical center during a surgical procedure. This data is essential to better determine the NIHL risk associated with working in a modern OR.

Materials and Methods
Sound Pressure Levels (SPLs) were measured in 28 ORs at VUH using a Larson Davis LxT sound level meter (SLM). Measurements were made using the A-weighted decibel scale and the slow SLM time-averaging function. Equivalent sound levels (Leq) were calculated for each surgery. Surgical procedures were classified into one of three categories (General, Neurosurgery, and Orthopedics) based on which surgical service performed the procedure. Procedures performed by a service other than Neurosurgery or Orthopedics were placed in the General group. Mean Leq and 95% bootstrapped confidence intervals were calculated.

Conclusions
Our data predict that the Leq during surgery is far below the 90 dB-A level known to cause NIHL. Additionally, groups studying other hospitals have generated results similar to ours. Based on these data, the risk of NIHL from OR exposure is likely negligible. However, the noise levels we observed may significantly affect OR staff communication and job performance.

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Mentor / Department
Michael Pilla Department of Anesthesiology
DOES SCENE PHYSIOLOGY PREDICT HELICOPTER TRANSPORT ADMISSION

Andrew Medvecz-Healthcare and Public Health Research and Management

Background Problem
Helicopter transport (HT) is necessary in the management of civilian trauma, but its significant expense underscores the need to minimize overuse and inefficiency.

Objectives
The objective of this study is to determine if on-scene physiologic criteria predict appropriate triage in HT trauma patients.

Materials and Methods
This is a retrospective review of adult patients flown from the scene of injury scene to the emergency department (ED) of a Level 1 trauma center by a university HT service from Jan 2006 to Dec 2010. Demographics, mechanism of injury, scene revised trauma score (RTS), distance, trauma alert level, payor status, ED and hospital disposition and injury severity scores (ISS) were collected, with similar data on patients admitted to trauma by ground transport (GT) for comparison. Proper triage criteria were defined through the ACS Committee on Trauma. Analysis with chi-squared, Wilcoxon and logistic regression identified predictors.

Conclusions
Physiologic criteria did not predict triage status in HT admissions. Although >40% of HT patients were over-triaged, they were more severely injured and required greater institutional resources than GT patients, supporting over-triage by a HT program may be appropriate.

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Mentor / Department
Oscar Guillamondegui, MD MPH, Division of Trauma and Critical Care, Department of Surgery
LONG-TERM OUTCOMES AFTER REVISION NEURAL DECOMPRESSION AND FUSION FOR SAME LEVEL RECURRENT LUMBAR STENOSIS: DEFINING THE EFFECTIVENESS OF SURGERY.

Stephen Mendenhall—Healthcare and Public Health Research and Management

Background Problem
Lumbar spinal stenosis is a disabling pathology experienced by a growing number of patients in the U.S. Decompressive laminectomy for lumbar stenosis is the most common operation performed in the aging population, with favorable clinical outcomes reported in many studies. Meta-analyses conducted by Turner and colleagues, show successful outcomes with surgery in two-thirds of patients with spinal stenosis. Herno et al reported good surgical results in 68% of patients after a mean follow-up period of 12 years. In spite of this, up to 20% of patients undergoing primary surgery for spinal stenosis do not experience sustained symptomatic pain relief. Failure of therapy may result from epidural fibrosis, recurrent disc herniation, spinal instability, inadequate surgical technique or a combination of the aforementioned factors, resulting in failed back surgery syndrome (FBSS), a common potential complication of lumbosacral surgery that consists of a constellation of conditions that describe recurrent/persistent low back pain. Over the past decade the prevalence of lumbar spine surgery has increased dramatically, concurrently, the incidence of revision surgery has increased, with reported success rates varying widely from 18% to 80%. The preponderance of published studies assessing outcomes after re-operation for spinal stenosis have mostly been small, retrospective case series, investigating outcomes after revision discectomy or revision decompression for recurrent disc herniation. Furthermore, success rates reported in prior studies utilized physician-assessed patient outcome instruments, which no longer suffice in this era of comparative effectiveness research. Hence, the long-term clinical outcomes in patients with same-level recurrent spinal stenosis without a finding of recurrent disc herniation remain poorly studied. Given the paucity of published studies reporting outcomes in this patient population, we set out to assess, using validated patient-assessed instruments, the long-term effectiveness of revision neural decompression and instrumented fusion in patients with recurrent same-level lumbar stenosis.

Objectives
To assess the long term outcomes of revision surgery using validated patient reported outcomes measures.

Materials and Methods
Fifty-three patients undergoing revision neural decompression and instrumented fusion for same level recurrent stenosis-associated back and leg pain were included in this study. Baseline and two-year LP-VAS, BP-VAS, Oswestry Disability Index (ODI), Zung-self reported depression score (ZDS), time to narcotic independence, time to return to work, health-state utility [EuroQol (EQ-5D)] and physical and mental quality of life (SF-12 PCS & MCS) were assessed.
Conclusions
Our study suggests that revision neural decompression and instrumented fusion for recurrent same level stenosis provides significant improvement in all patient-assessed outcome metrics, and should be offered as a viable treatment option.

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I would like to thank David Shau for much help and collaboration on this project. Additionally, I would like to thank Dr. Matthew McGirt for the opportunity to advance the field of Neurosurgery.

Mentor / Department
Dr. Matthew McGirt; Department of Neurosurgery
IMPACT ON DIABETIC KETOACIDOSIS (DKA) PATIENT OUTCOMES THROUGH IMPLEMENTATION OF A PEDIATRIC DKA GUIDELINE FOR REFERRAL HOSPITALS

Jenny M. Raab - Healthcare and Public Health Research and Management

Background Problem
Diabetic ketoacidosis (DKA) is a condition that affects pediatric diabetic patients. The care of pediatric DKA patients differs significantly from adult diabetic patients. Referring Emergency Departments frequency of pediatric DKA patient visits are low, and thus they often do not provide optimum care for these patients.

Objectives
We distributed a pediatric specific DKA guideline to referring emergency departments (ED) for patient management. Patients transferred to our Pediatric Emergency Department (PED) were examined for morbidity and mortality before and after utilizing this DKA protocol.

Materials and Methods
In February 2009, a DKA guideline was distributed to EDs who referred their pediatric DKA patients to the Children’s Hospital at Vanderbilt PED (VCH). This guideline discouraged the use of any insulin or sodium bicarbonate prior to the patient’s arrival to VCH. A retrospective chart review was conducted for patients transferred with DKA from 2/2008 - 4/2011. Data analysis was performed on presentation to the outside hospital (OSH), presentation to VCH, and DKA-related outcomes. Outcome measures were glucose on arrival to VCH-ED, treatment of cerebral edema, greatest drop in glucose per hour, adherence to the new guideline, and number of hours on an insulin drip at VCH.

Conclusions
Pediatric DKA patients transported from OSH were often treated with an insulin bolus or infusion thus increasing their risk for hypoglycemia and cerebral edema. More education needs to occur to help reduce the incidence of these events.

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Mentor / Department
Mark Meredith, Pediatric Emergency Department
PEDIATRIC CANCER AND FAMILY ADJUSTMENT

Jennifer Rahn—Healthcare and Public Health Research and Management

Background Problem
As the number of childhood cancer survivors increases, special importance needs to be focused on the quality of life of the survivors and their families. Stress from a diagnosis affects not just the child, but rather the entire family unit. It is not unreasonable to expect that what families bring to the situation at the outset will determine how they cope with cancer and its consequences.

Objectives
The primary objective is to examine whether family conflict mediates relations between stress during treatment and adjustment within the family unit. Furthermore, we will determine the level of conflict in the family unit at the time of diagnosis and observe how it changes over the course of the first year and what effect it has on each member of the family unit. We also will look for any stressors that contribute to greater family conflict and disruption of family roles as well as any protective factors that decrease family conflict.

Materials and Methods
Through StarPanel, families were identified who met the inclusion criteria: patient is 2-10, family speaks English, and patient has no physical or developmental delay. Families were approached within the first 2 months of a child’s diagnosis. Questionnaire packets were distributed with the primary caregiver completed packets every month for 12 months and the secondary caregiver completing packets at months 1, 6, and 12. The family also participated in a video-recorded in-person visit where family conflict was assessed through tasks such as Lego-building. The caregivers also participated in 2 audio-recorded telephone interviews to talk about their feelings of anger and sadness around the child’s diagnosis.

Conclusions
Though conclusions have not been drawn, we hypothesize that increased initial family conflict will result in greater amounts of stress during the course of treatment.

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Mentor / Department
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SURVEILLANCE AND PHARMACIST INTERVENTION FOR VULNERABLE HOSPITALIZED GERIATRIC PATIENTS ON HIGH-RISK MEDICATION REGIMENS

Carmen Rodriguez—Healthcare and Public Health Research and Management

Background Problem
Clinical decision support systems are useful tools to discourage the use of potentially inappropriate medications (PIMs) in the geriatric inpatient population. These interventions have had variable success, in large part because geriatric medication decisions are difficult and not always amenable to resolution via a computerized prompt.

Objectives
To develop an electronic dashboard which facilitates surveillance and pharmacist intervention among geriatric inpatients who are prescribed PIMs, to pilot the tool, and to measure provider satisfaction with the intervention.

Materials and Methods
We created an electronic PIMs dashboard that identifies patients in Vanderbilt University Hospital who are age 65 or older and have been prescribed at least one PIM (based on Beer’s criteria). The dashboard synthesizes and displays information about the prescription of 240 PIMs, with a score quantifying the anticholinergic burden and the 48-hour narcotic and benzodiazepine doses. It also shows demographics, care providers, and links to the patient's chart. Thus, the dashboard supports efficient review by a clinical pharmacist, who contacts the care provider when a change in therapy is recommended. A survey was developed based on interdisciplinary research to measure provider satisfaction of the intervention.

Conclusions
We successfully developed a dashboard integrated into the electronic health record that allowed focused pharmacy review of medication appropriateness among geriatric inpatients. The pharmacist’s time was greatly leveraged by this tool, the majority of recommended changes were made, and the intervention was highly acceptable to providers.

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Mentor / Department
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REVERSAL OF LEGAL BLINDNESS FROM DYSTHYROID OPTIC NEUROPATHY THROUGH SKULL-BASED APPROACH TO THE ORBITAL APEX

Nishma Sachedina—Healthcare and Public Health Research and Management

Background Problem
Thyroid Eye Disease (TED) is the leading cause of unilateral and bilateral proptosis in adults. The most severe manifestation of the disease is dysthyroid optic neuropathy (DON) resulting in loss of vision. DON affects 5% of TED patients.

Objectives
To investigate the utility of combined orbital and skull-based endoscopic surgical decompression of the optic nerve in patients rendered legally blind from dysthyroid optic neuropathy.

Materials and Methods
Retrospective, non-comparative, interventional case series. Consecutive patients diagnosed with DON from extraocular muscle enlargement causing apical crowding of the optic nerve who presented for treatment over an eight-year period were included. Pre- and postoperative measurements of visual acuity, color vision, pupil response to light, extraocular movements, and intra-ocular pressure were assessed and compared.

Conclusions
Blindness from DON is potentially reversible with emergent decompression of the skull base component of the orbital apex and optic canal through a combined endoscopic and orbital approach to the optic nerves.

Mentor / Department
Dr. Louise Mawn, Vanderbilt Eye Institute
THE ASSOCIATION OF ACUTE KIDNEY INJURY AND MORTALITY IN CHILDREN ON ECMO

Sarah Scott - Healthcare and Public Health Research and Management

Background Problem
Extracorporeal membrane oxygenation (ECMO) is used for life threatening cardiopulmonary failure in the pediatric population unresponsive to conventional therapies. Acute kidney injury (AKI) is a frequent co-morbid finding during ECMO, the incidence of which is currently underestimated based on previously published definitions of AKI. A recent consensus definition of AKI published by the Acute Kidney Injury Network (AKIN) is used to define AKI based on changes in serum creatinine from baseline or urine output, as opposed to absolute values.

Objectives
The purpose of this study is to describe the incidence of AKI during ECMO using recent AKIN criteria and describe its effects on mortality.

Materials and Methods
This is a retrospective observational cross-sectional study of patients admitted to Vanderbilt Children’s Hospital on ECMO from 01/2009-07/2011. Patient information collected included MRN, DOB, date and age at ECMO initiation, diagnosis leading to ECMO, mode of ECMO (VV/VA), ECMO duration, serum creatinine (SCr) before and during ECMO, renal replacement therapy (RRT) use, and patient survival. AKIN staging was done by a previously reported method and determined with a delta creatinine between the highest SCr reached during ECMO and the lowest SCr measured either before or after the ECMO run. AKIN level “0” - no kidney injury; “1” delta SCr of 150-200%; “2” 200-300%; “3” >300%. 50 patients were included in this study.

Conclusions
Previously reported incidence of AKI during ECMO ranged from 22-71% in neonates and 12-30% in pediatric patients, which is less than this study. Our future study will focus on the CDH cohort on ECMO to determine if AKI is an independent predictor of mortality.

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Mentor / Department
Geoffrey Fleming - Pediatric Critical Care
FACTORS INFLUENCING 2-YEAR HEALTH CARE COSTS IN PATIENTS UNDERGOING REVISION LUMBAR FUSION PROCEDURES

David Shau - Healthcare and Public Health Research and Management

Background Problem
Revision lumbar fusion procedures are technically challenging and can be associated with tremendous health care resource utilization and cost. There is a paucity of data regarding specific factors that significantly contribute to increased cost of care.

Objectives
The authors set out to identify independent risk factors predictive of increasing 2-year direct health care costs after revision lumbar fusion.

Materials and Methods
One hundred fifty patients undergoing revision instrument-assisted fusion for adjacent-segment disease (50 cases), pseudarthrosis (47 cases), or same-level stenosis (53 cases) were included in this study. Patient demographics, comorbidities, preoperative health states as assessed by patient-reported outcome questionnaires and perioperative complications were collected and analyzed. Two-year back-related medical resource utilization and direct health care costs were assessed. The independent association of all variables to increasing cost was assessed using multivariate linear regression analysis.

Conclusions
Revision lumbar fusion can be associated with considerable 2-year health care costs. These costs can also vary widely among patients, as evidenced by the 2.6-fold overall cost range in this series. Although comorbidities and preoperative severity of disease states contribute to cost of care, the primary drivers of increased cost include perioperative complications such as surgical site infection, return to the operating room, and readmission during the global health period. Measures focused on health service improvement will be most successful in reducing the cost of care for patients undergoing revision lumbar fusion.

Mentor / Department
Dr. Matt McGirt; Department of Neurosurgery
DEVELOPMENT OF A PEDIATRIC HEMATOLOGY-ONCOLOGY INFECTIOUS DISEASE DATABASE

Monique Simpson-Healthcare and Public Health Research and Management

Background Problem
Pediatric patients with malignancy, Langerhans cell histiocytosis (LCH) or Hematophagocytic lymphohistiocytosis (HLH) often receive immunosuppressive drugs that place them at high risk for infection. A number of questions remain unanswered with regard to the care of this population when they present, to the Emergency Room or hematology/oncology outpatient clinic, with concern for infection during their treatment. There is benefit in the development of a robust parent database of these patients, with the capacity to answer a number of questions related to the current standard of patient care within this population. These questions include whether certain lines are more likely to become infected, whether certain pathogens have an increased frequency of occurrence in this population, and what treatments are best suited to target the most commonly isolated pathogens.

Objectives
This database was created, under IRB# 101020 in order to collect the following information within the cohort of pediatric hematology-oncology patients, who were newly diagnosed with malignancy from 2007 to 2009: a. To establish exact dates for infectious disease complications b. To trace central line usage (duration, type, etc) c. To record all bacterial and fungal pathogens isolated d. To record information concerning bacteremia at diagnosis, and during neutropenic and non-neutropenic episodes

Materials and Methods
All new diagnoses of malignancy, LCH or HCH between 2007 and 2009 were captured in the Redcap database and information was collected for episodes through the end of 2010. Patients met criteria of being under the age of 23 at first presentation, and were both diagnosed and treated for malignancy, at Monroe Carell Jr. Children’s Hospital at Vanderbilt. Total number of participants eligible for this study over this time period is 346. Demographic information was then captured in the database, this includes their age, race and ethnicity, as well as their type and date of diagnosis. Other information stored in the database includes their medical exposures, such as: types and numbers of central line placements, past diagnoses of cancer, treatment outcomes, stem-cell transplants received and blood culture history, as well as the pathogens isolated from these blood cultures. The blood cultures were then further grouped, with all cultures taken within seven (7) days of one another merged into episodes. These episodes were then classified as being neutropenic (ANC <500), non-neutropenic (ANC > 500) or at diagnosis (within 7 days of diagnosis). The information was housed in a password protected Redcap database and all information exported from the database was de-identified for analysis.

Conclusions
This database could potentially be expanded in the future. The addition of both anterograde and retrograde data from the electronic medical record (Starpanel) would serve to fortify this resource for future use. Existing data is likely to lead to additional investigations of clinical
questions concerning infectious disease in the pediatric hematology-oncology population here at Vanderbilt; especially with regard to febrile episodes at diagnosis and during neutropenic or non-neutropenic episodes later in their treatment course.

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Laboratory-Based Research

Experiences in the Laboratory Based Biomedical Research Area of the Emphasis Program are focused on hypothesis driven investigation primarily based within a laboratory environment. Each student becomes an active participant in a research program and completes a clearly defined project. During the first year, the lab-based explorer becomes acclimated with new protocols, becomes an integral member of the team and becomes well versed in the foundational literature in his/her chosen field of focus. By summer the student is ready for full-time research making ever evolving modifications to the research plan while attending occasional relevant seminars with the cohort of students in the lab-based research area. Guiding students as they move through the project selection phase with its wealth of potential mentors and research areas toward their transformation into skillful and meticulous contributors at the bench is rewarding and fascinating for Co-Directors Lillian Nanney, Ph.D., and Michael Laposata, MD, Ph.D. Some students select projects based on collection of human samples and subsequent analysis at the lab bench. Others select in vivo work with unique animal models. Still others conduct in vitro analysis using sophisticated molecular tools. As students immerse themselves in experiential learning, each begins to take ownership and pride in expected and unexpected accomplishments. By the end of second year most students are making plans for national poster presentations and several polish off portions of manuscripts. A select number of students develop a real affinity for lab-based investigation and quickly seek and find new mentors and projects and maintain a sustain research experience throughout medical school. A few become fully committed and plan for a Medical Scholars year or enter the MSTP program. Few become fully committed and plan for a Medical Scholars year or enter the MSTP program. Every student hones his/her abilities to critically evaluate journal articles. Each has an opportunity to improve their interpersonal skills while experiencing the synergistic power of collaborative research. All students come to realize that the thrill of success in lab research is balanced with formidable challenges. Each student develops a much richer appreciation for the behind-the-scenes effort and serendipity that fuels discoveries that shape the future of medicine.

Vanderbilt University School of Medicine Emphasis Program-Forum VII-May 2012

Dr. Michael Laposata is the Edward and Nancy Fody Professor of Pathology and Medicine at Vanderbilt University School of Medicine. He is the pathologist-chief at Vanderbilt University Hospital and director of clinical laboratories. He received his M.D. and Ph.D. from Johns Hopkins University School of Medicine and completed a postdoctoral research fellowship and residency in Laboratory Medicine (Clinical Pathology) at Washington University School of Medicine in St. Louis. He took his first faculty position at the University Of Pennsylvania School Of Medicine in Philadelphia in 1985, where he was an Assistant Professor and director of the hospital’s coagulation laboratory. In 1989, he became Director of Clinical Laboratories at the Massachusetts General Hospital and was appointed to faculty in pathology at Harvard Medical School. In 2005, he was recognized by the Institute of Quality in Laboratory Medicine of the Centers for Disease Control and Prevention for this innovation. Dr. Laposata is the recipient of 14 major teaching prizes at Harvard, the Massachusetts General Hospital, and the University Of Pennsylvania School Of Medicine. His recognitions include the 1989 Lindback award, a teaching prize with competition across the entire University of Pennsylvania system; the 1998 A. Clifford Barger mentorship award from Harvard Medical School; election to the Harvard Academy of Scholars in 2002, and to the Vanderbilt University School of Medicine Academy for Excellence in Teaching in 2009; and the highest award - by vote of the graduating class - for teaching in years 1 and 2 at Harvard Medical School in 1999, 2000, and 2005.

Lillian Nanney, Ph.D., is the director of Plastic Surgery Research Activities, Co-Director of the Skin Disease Research Center, and the Founder and Director of Vanderbilt's Institutional Immunohistochemistry Core Laboratory. She directs efforts to study a broad spectrum of conditions ranging from poor or delayed skin repair (burns, chronic wounds, mouse models of injury) to undesirable hyper proliferative growth conditions that include malignancy. She teaches full-time in Medical Gross Anatomy course and was the 2005 award recipient for best teaching in a small group setting. Dr. Nanney’s contributions extend to the national level where she recently served as the national president of the Wound Healing Society.
MACROPHAGE LRP1 PREVENTS ATHEROSCLEROSIS BY MAINTAINING NORMAL CHOLESTEROL HOMEOSTASIS

Annie Ahn—Laboratory-Based Biomedical Research

Background Problem
LRP1 is a member of the LDLR family, and its deletion in murine macrophages leads to accelerated atherosclerosis. LRP1 deletion also impairs ABCA-1 mediated cholesterol efflux from macrophage foam cells. Thus, LRP1 is atheroprotective in mice. Prosaposin is an LRP1 ligand that is cleaved to sphingolipid activator proteins (saposins) in the lysosome. Saposins regulate glycosphingolipid metabolism, which in turn affects cholesterol trafficking.

Objectives
Our objective was to determine whether macrophage LRP1 deletion influences GSL trafficking by altering prosaposin disposition.

Materials and Methods
Peritoneal macrophages (Mφ) from MφLRP+/+ and MφLRP1-/- mice were incubated with acetylated LDL for cholesterol loading. Cells, media, and cell lysates were used for immunoblotting, RT-PCR, cholesterol efflux assays, and fluorescence microscopy.

Conclusions
MφLRP1 deletion leads to abnormal GSL metabolism by altering prosaposin trafficking for maturation to saposins. Normal GSL trafficking is important to maintain normal cholesterol homeostasis, and thus alteration of the former will affect the latter. This may explain the impaired cholesterol efflux by LRP1-/- macrophages despite overexpression of ABCA1.

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Mentor / Department
Dr. Sergio Fazio, Department of Cardiovascular Medicine
USING DNA SAMPLES LINKED TO AN ELECTRONIC MEDICAL RECORD TO VALIDATE A SNP SIGNATURE PREDICTIVE OF CLINICAL OUTCOME IN ADVANCED NSCLC PATIENTS TREATED WITH BEVACIZUMAB.

J. Scott Beeler- Laboratory-Based Biomedical Research

Background Problem
Lung cancer is the leading cause of cancer deaths in the United States with non-small cell lung cancer (NSCLC) being responsible for greater than 80% of all lung cancer deaths. Bevacizumab is an anti-VEGF monoclonal antibody that was the first targeted therapy to demonstrate a survival benefit in advanced NSCLC patients when combined with cytotoxic chemotherapy. Unfortunately, this therapy is linked to fatal adverse outcomes including hemorrhage, gastrointestinal tract perforation, and pulmonary embolism. To date, there is no way to predict which patients will receive benefit from bevacizumab therapy.

Objectives
A subset pharmacogenetic analysis of patients enrolled in the phase III clinical trial that led to FDA approval of bevacizumab identified a combination of germline single nucleotide polymorphism (SNPs) in angiogenesis-related genes that predicted benefit in patients receiving bevacizumab therapy. Synthetic Derivative (SD) and BioVU are unique Vanderbilt resources that link electronic medical records to a repository of patient DNA. Using these systems to validate this SNP signature in an independent cohort would have the potential to significantly improve patient outcomes.

Materials and Methods
Patients were identified by searching the medical records of SD for primary lung cancer diagnosis and treatment with a specific chemotherapeutic regimen. Cases were patients who underwent bevacizumab, carboplatin, and paclitaxel (BCP) treatment, while controls only received carboplatin and paclitaxel (CP).

Conclusions
We anticipate that our results will determine if the SNP signature predicts which patients are likely to benefit from the addition of bevacizumab to cytotoxic chemotherapy. Our findings demonstrate the utility of using a DNA database linked to electronic medical records to conduct retrospective studies that may shed light on the relationship between genomic data and therapeutic interventions.

Mentor / Department
David P. Carbone, M.D., Ph.D. Department of Cancer Biology & Medicine, Vanderbilt University Vanderbilt-Ingram Cancer Center
HIGH VITAMIN C, NORMAL OXIDATIVE STRESS, AND NORMAL BEHAVIOR IN A MOUSE MODEL OF SVCT2 OVEREXPRESSION

Jennifer Best (Vanderbilt University School of Medicine), Fiona Harrison, James May, Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt University Medical Center-Laboratory-Based Biomedical Research

Background Problem
Most animals, including mice, synthesize their own vitamin C (VC), an essential antioxidant. Because of its tight regulation, it is difficult to increase VC dramatically through dietary intake. In order to increase VC concentrations in tissues and to study its antioxidant effect, we have created a new transgenic mouse with global overexpression of the sodium vitamin C transporter SVCT2.

Objectives
The present study focused on biochemical and behavioral characterization of this new mouse.

Materials and Methods
SVCT2 mRNA was measured using q-PCR, and ascorbate levels were measured using HPLC. Behavioral assessments were performed using the Y maze, Elevated zero maze, Rotarod, and Inverted screen to measure spatial working memory, anxiety, motor coordination and strength respectively. Oxidative stress was measured through malondialdehyde assay.

Conclusions
These data suggest that we have successfully created a transgenic mouse with overexpressed and functional SVCT2. A 1-3 fold increase in VC was found to have no adverse effect in terms of oxidative stress on the organs and possibly even a protective function in the kidney. The transgenic mice showed normal behavior, except in the inverted screen test, which might have been due to a motor strength deficiency in that particular group. This mouse may be useful in future studies that require increases of ASC at the cellular level, and therefore could be used in disease models as well as to study the role of ASC in response to pharmacological agents.

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James May, Fiona Harrison

Mentor / Department
James May, Fiona Harrison, Department of Diabetes, Metabolism, Endocrinology, VUMC
GENOTYPE PHENOTYPE CORRELATIONS IN HYPERTROPHIC CARDIOMYOPATHY

Alejandro de Feria - Laboratory-Based Biomedical Research

Background Problem
Hypertrophic Cardiomyopathy (HCM) is a common inherited cardiovascular disease (prevalence 1:500) that is characterized by varying degrees of left ventricular hypertrophy. Individuals that have HCM are at increased risk for developing symptoms of heart failure (primarily diastolic dysfunction) and experience life threatening cardiac arrhythmias. The two most common genes mutated in HCM patients are β-myosin heavy chain (MYH7), and myosin-binding protein C (MYBPC3) and isolated familial data suggested that MYH7 mutations caused a more severe phenotype than MYBPC3 mutations.

Objectives
The goal of this study was to analyze the HCM patients that were genotyped in the Vanderbilt Center for Inherited Heart Disease (CIHD) and determine if mutation status impacts the phenotypic characteristics of disease.

Materials and Methods
Data was analyzed through a retrospective chart review in which CIHD patient charts were scanned for genetic testing results, maximum left ventricular wall thickness, left ventricular outflow tract gradient, family history of sudden death, syncope, ICD implantation and age at diagnosis.

Conclusions
HCM patients with sarcomeric gene mutations have distinct phenotypic differences compared to HCM patients that do not carry sarcomeric gene mutations. However, HCM patients that carry different types of sarcomeric mutations have similar phenotypes in the CIHD clinic.

Acknowledgements
Jason Becker M.D.

Mentor / Department
Charles Hong M.D., Ph.D., Jason Becker M.D., Yan Ru Su M.D.
NOX1 AS A MEDIATOR OF HYPERPLASIA IN HYPOXIC PULMONARY ARTERY SMOOTH MUSCLE CELLS

Jacob DeVolder—Laboratory-Based Biomedical Research

Background Problem
Pulmonary hypertension in newborns is marked by significant remodeling of pulmonary arteries, which can result in hypoxemia, respiratory failure, and right-sided heart failure. The NOX family of enzymes plays a suspected role in many vascular diseases. Specifically, NOX1 has been shown to increase in the resistance-level pulmonary arteries of piglets with hypoxia-induced pulmonary hypertension as well as piglet pulmonary artery smooth muscle cells (PASMCs) cultured in hypoxia for 72 hours. Hypoxia is etiologically linked to pulmonary hypertension.

Objectives
Eliciting the role of this enzyme in the remodeling of the arterial wall may provide a new target of therapy for newborns with pulmonary hypertension. This study investigated the contribution of NOX1 to arterial remodeling as a mediator of hyperplasia in PASMCs.

Materials and Methods
PASMCs from resistance-level pulmonary arteries of newborn piglets were cultured in normoxia and hypoxia. Cell counts were determined at 24, 48, 72, and 96 hours by direct counting with a hemacyctometer. Western-blots analysis for PCNA was also performed after 72 hours. Data were compared using an unpaired t-test.

Conclusions
These data do not suggest that increases in NOX1 would result in hyperplasia of the smooth muscle cells in the pulmonary arterial wall. This is not to say that hyperplasia does not occur in vivo. There are a number of scenarios not replicable in this in vitro study. NOX1 signaling, for instance, may recruit cells into the vessel wall to transdifferentiate. The remodeling may also be due to hypertrophy rather than hyperplasia.

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Mentor / Department
Candice Fike, M.D., Division of Neonatology
STRUCTURAL ANALYSIS AND ELUCIDATION OF THE INHIBITORY MECHANISM OF A ROTAVIRUS VP6-SPECIFIC HUMAN ANTIBODY USING CRYOELECTRON MICROSCOPY

Ilyas Eli—Laboratory-Based Biomedical Research

Background Problem
Rotavirus (RV) is the leading cause of acute dehydrating diarrhea in infants and young children worldwide. Although several licensed vaccines exist for RV, the immune correlates for protection against RV are not well-defined. Structurally, RV is a triple-layered virus with an inner VP2 layer, an intermediate VP6 layer and an outer VP7 layer with intermittent spikes of VP4. While RV VP4 and VP7 proteins induce neutralizing antibodies in humans, the highest titers of human antibodies binding to RV proteins after infection are directed against the VP6 protein. Our laboratory previously isolated naturally-occurring RV VP6-specific human monoclonal antibodies that exhibit an unusual dominant pattern of antibody VH1-46 variable gene segment usage, suggesting recognition of an immunodominant epitope on VP6.

Objectives
The current study focuses on elucidating the mechanism of inhibition of RV by one of these VP6-specific mAbs, designated RV6-26, which was shown previously to inhibit RV intracellularly in African green monkey kidney epithelial (MA-104) cells. It is not clear where in cells this antibody binds to RV in order to mediate its antiviral effect.

Materials and Methods
RV6-26 was expressed recombinantly as a Fab antibody. RV double layered particles (DLPs) were prepared and purified using MA-104 cells for cryo-EM. The complexes of RV-DLPs with RV6-26 Fab were vitrified and imaged using a 300kV EM. 3300 particle images were collected and processed using IMAGIC and FREALIGN image reconstruction software and analyzed using the Chimera software.

Conclusions
While asymmetric binding of the RV6-26 Fab suggests some global conformational changes to the DLP VP6 layer, the DLP-Fab does not resemble the conformationally altered transcriptionally-inactive TLP form. However, the binding pattern of RV6-26 Fab at the five-fold pore suggests that the mode of inhibition of RV6-26 Fab is through a physical blockade mechanism preventing egress of RV mRNA during viral transcription. These studies provide insight into the structural basis of inhibition of rotavirus replication by these common human VP6-specific antibodies.

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Mentor / Department
James E. Crowe, Jr, M.D. Department of Pathology, Microbiology and Immunology Department of Pediatrics, Division of Infectious Diseases
IN VIVO MOLECULAR IMAGING OF RNA BIOMARKERS IN RETINAL VASCULAR DISEASE

Andrew Y. Gordon - Laboratory-Based Biomedical Research

Background Problem
Molecular imaging strategies for early detection of retinal vascular diseases are needed for improving clinical diagnosis, timeliness of therapeutic intervention, and assessment of therapeutic response. Approaches for molecular imaging of the retina have been limited by a lack of molecularly targeted imaging agents capable of targeting disease biomarkers in vivo with sufficient sensitivity and safety.

Objectives
To address the need for clinically-relevant retinal molecular imaging agents, hairpin DNA functionalized gold nanoparticles (hAuNP) featuring optical contrast agents and RNA-specific nucleic acid targeting sequences were developed to noninvasively image any messenger RNA or microRNA biomarker in the retina. The goal of this study was to evaluate the utility of hAuNP for longitudinal imaging of mRNA and microRNA biomarkers in an animal model of laser-induced choroidal neovascularization (LCNV), with the long-term goal of developing imaging agents for clinical detection of subclinical and advanced CNV.

Materials and Methods
hAuNP designed to specifically target the CNV-relevant mRNA biomarkers HIF1-alpha and VEGFR2, as well as the microRNA 23-24-27 family members, were evaluated using in vitro endothelial cell cultures and mouse models of LCNV. Nonspecific control hAuNP and hAuNP targeting housekeeping mRNA transcripts were utilized in parallel as negative controls and normalization of emission signal, respectively.

Conclusions
hAuNP are promising nanoscale imaging agents which can be utilized in conjunction with clinically-available ophthalmic imaging instrumentation for noninvasive, high sensitivity, and high specificity imaging of RNA disease biomarkers in retinal vascular disease. The nanoparticle is readily amenable for imaging virtually any RNA target in living tissues, and may also be valuable for elucidating molecular mediators of retinal disease in preclinical studies.

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Mentor / Department
Ashwath Jayagopal; Vanderbilt Eye Institute
IDENTIFICATION OF A NOVEL PREDICTOR OF NEURAL FATE IN RESPONSE TO ENERGETIC CHALLENGE

Kimberly N. Grelli - Laboratory-Based Biomedical Research

Background Problem
The isocitrate dehydrogenase (IDH) isoforms are well known for their role in the Kreb’s cycle, but recent genetic analysis has revealed a high level of somatic mutations in the IDH enzymes of patients with glioblastomas. These IDH mutations promote cellular survival and hyper-proliferation in hypoxic environments through the stabilization of hypoxia inducible factor 1α (HIF1α). IDH regulation may be a conserved mechanism to promote survival under physiological stress as we observed a 30% decrease in IDH3 associated with acute ischemic injury in vivo and in vitro that also resulted in increases in HIF1α.

Objectives
To further elucidate cellular signaling in response to hypoxia, the goal of this work was to analyze the independent effects of energetic and oxidative stress on IDH expression.

Materials and Methods
HT-22 neural cells were exposed to either a selective energetic challenge by utilizing a galactose enriched media or a selective oxidative challenge evoked by depletion of cystine. Cellular proliferation and survival were quantified using an MTT assay and protein expression of the IDH isoforms, mitochondrial enzymes, and HIF were analyzed by immunoblotting.

Conclusions
The IDH family of proteins rapidly responds to changes in mitochondrial energetic status, but not to oxidative stress. These data suggest that upregulation of the IDHs in neural cells serves to maximize ATP production via oxidative phosphorylation, promoting survival following energetic stress when oxygen or glucose is limiting. Therefore, the IDHs may serve as first-line, rapid response enzymes, which may represent an unrecognized means of neuroadaptation during energetic stress.

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Mentor / Department
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INVESTIGATION OF THE STRUCTURE AND FUNCTION OF ADAMTS10

Calvin Gruss—Laboratory-Based Biomedical Research

Background Problem
Primary open angle glaucoma (POAG) is a leading cause of vision loss and blindness. Elevated intraocular pressure is a strong risk factor for glaucoma development and progression [1]. The only proven treatments for POAG patients involve reduction of intraocular pressure by inhibiting aqueous humor production, or bypassing the diseased trabecular meshwork. Fibrillin monomers assemble to from microfibrils in the presence of fibronectin to make this meshwork. Microfibrils regulate TGFβ signaling pathways and poor TGFβ regulation results in increased Smad2 phosphorylation and downstream events. The ADAMTS10 protein is expressed at particularly high levels in the trabecular meshwork.

Objectives
The objective of this project is to determine the role of ADAMTS10 in microfibril formation as well as in the formation of the extracellular structure (trabecular meshwork) of the eye.

Materials and Methods
Human dermal fibroblasts were cultured in this experimental setup. A gene silencing experiment was performed on the cultured cells in which ADAMTS10 function was knocked down using siRNA fragments. The selected siRNA terminated expression of ADAMTS10. The results of the experiments were then quantified following TGFB stimulation by measuring the cellular expression of Smad2 and pSmad2 using Western blots. This protocol was followed for both silenced cells, as well as control populations.

Conclusions
Therefore ADAMTS10 may not play a significant role in the regulation of Smad2 phosphorylation or the knockdown levels required to illustrate the effect are greater than those attainable by siRNA transfection protocols.

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Mentor / Department
John Kuchtey, PhD; Rachel Kuchtey, MD, PhD Department of Ophthalmology
COMPARATIVE PROTEOMIC SIGNATURES OF HUMAN CLEFT LIP TISSUE

Pawina Jiramongkolchai - Laboratory-Based Biomedical Research

Background Problem
Cleft lip and/or palate (CLP) is a common craniofacial abnormality with an incidence of 1 in 700 live births. A multifactorial disease, CLP is often accompanied by other congenital malformations. Up to 25% of CLP patients have cardiac defects. There are hundreds of identified genes that have been linked to CLP, with mutations in IRF6 having a strong association with CLP. IRF6 is linked to popliteal pterygium syndrome (PPS), a disorder characterized by the maldevelopment of the face, skin, heart, and genitalia. While IRF6 is required for keratinocyte differentiation and proliferation, its specific mechanism of function is unknown.

Objectives
Our objective was to assess the gene expression profile of lip tissue from three groups of CLP patients: non-syndromic CLP (NSCLP), syndromic CLP with cardiac malformations (SCLP), and PPS. We hypothesized that we could identify novel protein signatures between the three groups.

Materials and Methods
15 snap-frozen epithelium specimens from CLP patients (9 NSCLP, 5 SCLP, 1 PPS) were collected from Vanderbilt Children’s Hospital. The samples were examined using histology guided matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). Protein signatures were compared between the groups.

Conclusions
While the lip epithelium proteomic signature did not distinguish NSCLP patients from SCLP patients, unique protein signatures were found comparing PPS patients with NSCLP patients as well as PPS patients and SCLP patients. These alterations in the gene pathways found consistently between PPS and NSCLP/SCLP patients may suggest unique roles for IRF6. We will next focus on protein identification and RNA sequencing of these tissues to elucidate the pathways regulating IRF6 expression in CLP patients.

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Mentor / Department
Dr. Steven Goudy, Department of Otolaryngology
DISCOVERY OF A NOVEL KIR4.1 POTASSIUM CHANNEL INHIBITOR: IMPLICATIONS FOR TREATMENT OF RETT SYNDROME

Rishin Kadakia—Laboratory-Based Biomedical Research

Background Problem
Rett (RTT) syndrome is an X-linked developmental condition that presents with a spectrum of neurological symptoms, including breathing difficulties, which is the most common cause of death amongst RTT patients. A recent study on an RTT mouse model suggests that the breathing abnormalities may result from an overexpression of Kir4.1, an inward rectifying potassium (Kir) channel, in the central nervous system.

Objectives
The molecular pharmacology of Kir4.1 is limited to a handful of neurological drugs such as the SSRI, fluoxetine. The ultimate aim of this project is to develop a selective inhibitor of Kir4.1, which will be vital in determining the therapeutic potential of Kir4.1 as a target protein for therapy in RTT.

Materials and Methods
A high-throughput screen (HTS) of 3,655 molecules using a fluorescence-based thallium flux assay was performed in a 384-well plate format at the university’s HTS center. Thallium flux assays and whole-cell patch clamp electrophysiology were used to characterize a novel Kir4.1 inhibitor termed VU717 identified in the screen, as well as other inhibitors of Kir4.1.

Conclusions
High-throughput screening has been used to discover a moderately potent inhibitor of the Kir4.1. We are currently assessing VU717’s selectivity within the Kir channel family, using site-directed mutagenesis to define its mechanism of action, and preparing to perform a screen of more than 300,000 small molecules for additional chemical modulators of Kir4.1. This work may lead to the development of drug-like compounds that can be used to probe the therapeutic potential of Kir4.1 in RTT syndrome patients.

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Mentor / Department
Dr. Jerod S. Denton, Department of Anesthesiology
DETECTION OF THRESHOLD RETINOPATHY OF PREMATURITY USING THE PINT-ROP GROWTH MODEL

Anupam Kumar - Laboratory-Based Biomedical Research

Background Problem
Retinopathy of prematurity (ROP) is blinding disease of the eye.1-2 The central defect in ROP is a failure of vascular development. Areas of avascular retina become metabolically active and relatively hypoxic. This hypoxia leads to subsequent retinal neovascularization, bleeding, fibrosis and eventual traction retinal detachment.

Objectives
To report the effectiveness of the PINT-ROP growth model in detecting cases of previously diagnosed threshold retinopathy of prematurity (ROP) at a single study center.

Materials and Methods
Retrospective chart review. Infants treated with laser therapy were identified retrospectively by billing diagnosis. The PINT-ROP growth model was used to determine if infants with threshold ROP requiring laser therapy would have been predicted with this model.

Conclusions
Growth models are used to attempt to reduce the need for ROP screenings for infants at low risk for developing severe disease. The PINT-ROP model failed to identify all infants requiring laser therapy in this cohort of children, possibly due to the older gestational age at birth. Standard screening guidelines for infants at risk for ROP should not be altered for infants born at gestational age greater than 28 weeks based upon these findings.

Mentor / Department
Dr. David Morrison, Vanderbilt Eye Institute
A MINIATURE B-SCAN FORWARD-IMAGING OCT PROBE TO GUIDE REAL-TIME LASER ABLATION

Zhuoyan Li—Laboratory-Based Biomedical Research

Background Problem
Optical coherence tomography (OCT) has emerged as an important ophthalmologic imaging tool to evaluate structures within the eye. However, there is currently not a functional OCT that is able to image real-time microsurgical ablation. Therefore, our group has developed a miniature 25-gauge B-scan forward imaging OCT probe as a guidance tool for mid-infrared (IR) laser ablation studies. A number of medical procedures have utilized pulsed lasers for ablating biological tissue. An experimental tunable free electron laser (FEL) has emerged as a promising tool to ablate soft tissue with minimal collateral damage. The laser has been discovered to be most efficient at a strong amide I band absorption wavelength of 6.10 μm which is at a water-absorption peak. Tissue that has been treated with this wavelength include articular cartilage, fibro-cartilage, skin, cornea, and optic nerve sheath. A robust hollow-glass waveguide intraocular probe capped with a calcium fluoride window has been developed to deliver this mid-infrared energy. The following experiments were conducted combining the miniature B-scan forward imaging OCT probe and the hollow-glass waveguide to evaluate real-time imaging of gelatin, corneal, and retinal tissue ablation.

Objectives
To determine whether a miniature B-scan forward-imaging OCT probe can be combined with a laser to guide real-time incisions of gelatin and ocular tissues.

Materials and Methods
A miniature 25-gauge B-scan forward-imaging OCT probe was developed. It was combined with a 250 μm hollow-glass waveguide that was capped with a calcium fluoride window to permit delivery of 6.1 μm laser energy. The laser beam was aimed so that it was coplanar with the OCT scanning probe. The Raman-shifted alexandrite laser system delivered 6.1 μm at 10 Hz with an output energy of 0.5-0.6 mJ/pulse. To demonstrate real-time imaging of tissue ablation with the combined forward-scanning OCT probe and mid-infrared laser, a gelatin mixture (10% by weight), and porcine retinas and corneas were prepared. A preset number of pulses was delivered to the respective tissues with real-time imaging by the miniature B-scan forward-imaging probe attached to an 840 nm spectral domain OCT system (Bioptigen Inc, Durham, NC). The ablation studies were observed and recorded in real-time. The corneas and retinas were prepared for histological analysis.

Conclusions
A combined miniature OCT probe and laser can monitor real-time tissue laser ablation. The incision depth is measurable with the OCT probe. The novel instrument has the potential of effectively guiding surgeries by simultaneously imaging and ablating tissue.
Mentor / Department
Karen Joos, Vanderbilt Eye Institute, and Jin-hui Shen, Vanderbilt Eye Institute
PLATELET DERIVED MALONDIALDEHYDE ADDUCT FORMATION ON HDL AND LDL

Ryan McGrath - Laboratory-Based Biomedical Research

Background Problem
Cardiovascular disease is the most common cause of death in America and it is estimated that in 2010 785,000 Americans had a new coronary attack, and 470,000 will have had a recurrent coronary attack. The most prominent cause of cardiovascular disease is atherosclerosis, or the deposition of lipid-rich plaques on blood vessel walls. It has long been known that high-density lipoprotein (HDL) plays a cardioprotective role in the progression of atherosclerosis. The cardioprotective effects of HDL come from its ability to extrude cholesterol from existing plaques and deposit it in the liver and steriodogenic organs to be excreted or used in making steroid hormones respectively. By doing so, HDL helps to prevent the growth and rupture of atherosclerotic plaques that may go on to occlude blood vessels resulting in cardiovascular events such as myocardial infarctions and strokes. This is contrary to the action of low-density lipoprotein (LDL), which allows for transport of dietary cholesterol in the bloodstream to be deposited in atherosclerotic plaques. Oxidative stress has been shown to predispose individuals to cardiovascular disease progression, with elevated oxidative stress being associated with the development of atherosclerotic plaques. The exact mechanisms underlying atherosclerotic plaque development and elevated oxidative stress are not fully understood. These signaling pathways remain elusive in part due to the difficulty of studying the very short-lived and difficult to measure, reactive oxygen species. Malondialdehyde (MDA) is a highly reactive organic compound that is often used to measure oxidation as MDA will covalently bond with lysine residues resulting in long-lived products. Recently MDA has been shown to bind to lysine residues on apolipoprotein A-1 present in HDL which blocks the ability of HDL to perform cholesterol efflux, suggesting a direct link between oxidative stress and cardiovascular events. However, the exact source and cause of formation of HDL bound MDA is yet unknown. Thromboxane synthase in the human platelet also produces MDA as a byproduct to thromboxane A2 production during cleavage of prostaglandin H2. We now have evidence that suggests that when given arachidonic acid to promote inflammatory pathways, platelets will produce MDA that forms MDA-lysine adducts on HDL and LDL proteins. Additionally, we show that this pathway of MDA adduct production is cyclooxygenase-1 (COX-1) dependent and is susceptible to inhibition by the COX-1 inhibitor aspirin.

Objectives
The origin of the MDA oxidative species is still not well understood. Our hypothesis is that platelet derived MDA is contributing to MDA-lysine adducts on HDL by a pro-inflammatory pathway. By using arachidonic acid to stimulate platelet rich plasma to produce MDA, we can then isolate the HDL and LDL proteins to investigate the ability of the platelets to produce MDA-lysine adducts. Additionally, we will be investigating the ability of aspirin to block this process by blocking the platelet’s ability to produce MDA. By digesting and purifying single amino acids that are derived from isolated HDL and LDL proteins, the level of lysine adducts can be observed using mass spectrometry. When control and treated groups are compared, we expect to see an increase in MDA-lysine adducts in the presence of arachidonic acid treatment.
Furthermore, we expect to be able to significantly decrease the level of MDA adduct production with the administration of aspirin.

**Materials and Methods**

Sample collections: Human blood is drawn from healthy volunteers who do not smoke, and have not taken any cycloxygenase inhibitors for at least ten days, and are not on any other medications. Approximately 120 ml of blood is drawn in the presence of sodium citrate, apyrase, carbaprostacyclin, and SQ to prevent clotting and inappropriate platelet activation. Blood is then spun at 900 rpm to obtain platelet rich plasma. Platelet activation: Platelet rich plasma from a single volunteer is then split into three groups at approximately 10 ml of platelet rich plasma per treatment group. A control group receives 5 µl of ethanol. An arachidonic acid treated group receives 100 µM arachidonic acid and is incubated at 37°C for 2 hrs. An aspirin and arachidonic acid group is treated with 200 µM aspirin and incubated at 37°C for 40 min, after which the plasma is treated with 100 µM arachidonic acid and incubated at 37°C for 2 hrs. All samples are then centrifuged at 3,200 rpm for 10 min to separate platelets from plasma. Samples of 50 µl are taken and measured for thromboxane levels by standard thin layer chromatography. Butylated hydroxytoluene at 5 mg / 100 ml, 3 mM trolox, 1mM pyridoxamine and 1 mM ethylenediaminetetraacetic acid are immediately added after removal of platelets to prevent any production of oxidative species that are not deriving from the platelets. Ultracentrifugation: Platelet poor plasma is then separated using ultracentrifugation to separate VLDL/IDL, LDL and HDL using 24 hr, 24 hr, and 48 hr spins respectively at 48,000 rpms at 4°C. Standard potassium bromide solutions were used to adjust densities of plasma and a corresponding overlay to perform ultracentrifuge separations. Protein concentration: After ultracentrifugation, protein levels of all samples were determined using a standard Thermo Scientific BCA protein absorbance assay. Volumes corresponding to 1 mg of protein were taken from each treatment group in duplicate and protein was precipitated by 10% TCA as volume percent. Samples were spun at 10,000 rpm for 10 min and supernatant was removed. Pellets were then treated with ice-cold acetone spun at 10,000 rpm for 10 min and supernatant was removed. Pellets were then treated with diethylether and spun at 10,000 rpm for 10 min. Pellets were then dried under argon and re-suspended in PBS. Protein digestion: All samples were sonicated and heated to 95°C and allowed to cool to room temperature. Pronase is then added to every sample at 1 mg pronase in 100 µl water for every 1 mg of protein of sample and incubated at 37°C for 24 hrs. Pronase is inactivated by heating samples to 95°C for 10 min and allowed to cool to room temperature before adding 0.5 µl of 500 mM aminopeptidase and incubated at 37°C for 24 hrs. After aminopeptidase incubation, samples are again heated to 95°C for 10 min and allowed to cool to room temperature. Protein purification: Five nanograms of C13-MDA-lysine crosslink standard is added to every sample prior to protein purification to standardize MDA-lysine adduct quantification in LCMS data. Samples are purified using 1 cc Oasis HLB column and dried under nitrogen flow, diluted in 0.1% formic acid solution, and filtered using a 0.22 µm nylon Spin-x centrifuge tube spun at 6,000 rpm for 5 min. High-pressure liquid chromatography: Samples are run through a Thermo Scientific Aquasil C18 5µm reverse phase column. By measuring for the presence of the radioactive C13-MDA-lysine crosslink standard the separation of impurities is monitored via a liquid scintillation counter. Portions of samples are then concentrated using 1 cc Oasis HLB columns and samples are dried under nitrogen. Liquid chromatography mass spectrometry: Purified samples are injected into a Thermo Scientific TSQ Vantage Quadrupole Mass Spectrometer and using Xcalibur software mass spectrometry data is

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collected. All measured MDA-adduct signal in each sample is divided by the signal for the C13-MDA-lysine crosslink standard of known concentration to quantify experimental results. Statistics: All statistics were performed using a paired student’s t-test with \( p \leq 0.05 \) being considered statistically significant.

**Conclusions**

With evidence linking the formation of MDA-adducts to the dysfunction of HDL and possibly LDL, it is important to understand the origins and causes of this process. Earlier research has suggested that the production of MDA-adducts is derived from a non-specific oxidative stress. However, if an exact mechanism can be isolated, therapies can be designed to prevent the destruction of functional HDL and LDL by oxidative species and maintain proper handling of cholesterol. There has long been a link between inflammation and cardiovascular disease, however these mechanisms are not yet fully understood. Our research suggests that human platelets activated by pro-inflammatory stimuli are able to produce MDA at concentrations that are sufficient to create significant elevation in the production of MDA-adducts on both HDL and LDL proteins. Using thromboxane A2 production as a marker for MDA production, we show that an aspirin treatment that is sufficient to block thromboxane production stimulated by arachidonic acid is also sufficient in blocking MDA-adduct formation (figure 1). This would strongly suggest that a COX-1 dependent pro-inflammatory pathway in the platelets could play a role in the formation of MDA-adducts on HDL and LDL proteins. Taken together, these findings could not only provide a direct link between inflammation and cardiovascular events, but may also shed light on the long known, but not fully understood, cardio-protective effects of long-term of COX-1 inhibition by aspirin therapy.

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**Mentor / Department**

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SARCOIDOSIS MYCOBACTERIAL ESAT-6-SPECIFIC TH-17 CELLS DEMONSTRATE REDUCED CELLULAR FUNCTION

Kristen Ploetze - Laboratory-Based Biomedical Research

Background Problem
Sarcoidosis is an idiopathic granulomatous disease defined by the presence of localized collections of activated macrophages and predominantly Th-1 CD4+ lymphocytes in affected tissues(1). While nearly any organ may be affected, most deaths are due to progressive pulmonary disease(2). Though most of the CD4+ cells within the sarcoidosis granuloma have a Th-1 immunophenotype, Th-17 CD4+ cells are also present in granulomas from patients with sarcoidosis(3).

Objectives
Many patients with sarcoidosis demonstrate antigen-specific immunity to mycobacterial virulence factors. Th-17 cells are crucial to the immune response to mycobacterial infection, and have recently been shown to be present in greater numbers in the peripheral blood and bronchoalveolar lavage fluid (BALF) of sarcoidosis patients than healthy controls. It is unclear whether Th-17 cells in sarcoidosis are specific for mycobacterial antigens, or whether they have similar functionality to control Th-17 cells.

Materials and Methods
Flow cytometry was used to determine numbers of Th-17 cells present in the peripheral blood of patients with sarcoidosis, the percentage of Th-17 cells that were specific to the mycobacterial virulence factor ESAT-6, and IFN-γ and PD-1 expression in Th-17 cells following polyclonal stimulation. Additionally, flow cytometry was used to compare numbers of Th-17 cells in pulmonary and cutaneous sarcoidosis.

Conclusions
Patients with sarcoidosis have mycobacterial antigen-specific Th-17 cells peripherally and at sites of active involvement, but the Th-17 cells may have reduced functionality compared to Th-17 cells from healthy controls.

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Mentor / Department
Wonder P. Drake; Department of Pathology, Microbiology and Immunology
C-TYPE NATRIURETIC PEPTIDE IS A POTENT ENDOGENOUS MEDIATOR OF DUCTUS ARTERIOSUS (DA) RELAXATION THAT STIMULATES A FEED-FORWARD MECHANISM TO PERPETUATE PDA

Quentin Reuter-Laboratory-Based Biomedical Research

Background Problem
Natriuretic peptides (NP) are released from the heart and endothelium in response to volume overload. They act through guanylyl cyclase receptors Npr1 (ANP, BNP) and Npr2 (CNP), resulting in diuresis and vasodilation. Infants with patent DA (PDA) have increased levels of ANP and BNP. The L-to-R shunt of PDA overloads the heart causing release of NPs, but it is unknown whether NPs play a pathophysiologic role in maintaining a PDA.

Objectives
We hypothesized that NPs, acting on Npr1 and 2, have direct vasodilatory effects on DA tone, both in vitro and in vivo.

Materials and Methods
QPCR for Npr1, 2, and 3 was performed on DAs of d15 to P1 mice. Pressure myography examined the effect of NPs on DA tone in vitro. We compared preterm vs term and WT vs Npr KO DAs treated with NPs, in fetal and newborn O2. Physiologically closed P1 DAs were treated with NPs. In vivo studies included ELISA of serum NP levels in mouse models of PDA (PGE-treated newborns and Cox1/Cox2 dKO offspring) vs. control newborns; and imaging of DAs in newborns treated with PGE2, ANP, BNP, or CNP, vs. control. Data were analyzed by t-test, ANOVA, or linear mixed models regression.

Conclusions
All three NPRs are expressed in the fetal and newborn DA. CNP>>ANP, BNP, via specific NPRs, dilated the mouse DA in vitro, and maintained in vivo patency. During congestive failure, CNP may be a potent mediator of PDA. Our findings suggest that NPs could be used to maintain a PDA in infants with cyanotic heart lesions, and NPR antagonists could help close a PDA refractory to treatment.

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Mentor / Department
Jeff Reese, Dept. of Pediatrics
GENERATING LEUKEMIA: ETOPOSIDE QUINONE AS A POISON OF TOPOISOMERASE IIβ

Nicholas Anthony Smith—Laboratory-Based Biomedical Research

Background Problem
Etoposide is a topoisomerase II poison that has been employed for decades to treat human cancers (1). Unfortunately, 2–3% of patients treated with etoposide eventually develop leukemias associated with 11q23 chromosomal rearrangements (2). While the molecular basis for etoposide-induced leukemogenesis is not fully understood, it is associated with enzyme-mediated DNA cleavage. Humans encode two topoisomerase II isoforms, α and β (1). Evidence suggests that topoisomerase IIβ may play an important role in generating leukemic chromosomal translocation (2,3). In humans, etoposide is metabolized by CYP3A4 to etoposide catechol, which can be further oxidized to etoposide quinone (4,5). Patients with specific mutations in the CYP3A4 display a lower incidence of etoposide-related leukemia (6). Therefore, we characterized the effects of etoposide quinone on topoisomerase IIβ.

Objectives
Our primary objective was to assess the ability of etoposide quinone to poison topoisomerase IIβ. We also sought to contrast the mechanism of action of etoposide quinone with that of etoposide.

Materials and Methods
The effects of etoposide and etoposide quinone on human topoisomerase IIβ activity were studied using in vitro DNA cleavage and re-ligation assays. The effects of the ATP cofactor and reducing agents that revert etoposide quinone to the catechol also were examined.

Conclusions
The oxidizing environment in hematopoietic tissues can result in a high concentration of etoposide quinone in these cells. The high activity of the quinone toward topoisomerase IIβ supports the hypothesis that etoposide quinone may play a role in the induction of leukemic chromosomal translocations.

Mentor / Department
Jo Ann Byl and Neil Osheroff. Biochemistry
THE EFFECT OF BMAL1 ON CIRCADIAN CORTICOSTERONE RELEASE

Daniel Sun - Laboratory-Based Biomedical Research

Background Problem
In nearly all mammals, behavioral and physiological rhythms are regulated by a master circadian pacemaker located in the paired suprachiasmatic nuclei (SCN) of the anterior hypothalamus. A transcription-translation molecular feedback loop underlies these diurnal rhythms. Bmal1 is an integral component of this mechanism; in homozygous Bmal1 knockout mice, we observe complete abolition of circadian rhythms. Peripheral tissues have peripheral clocks that operate via the same mechanism. For example, the StAR protein, which is involved in steroid production, is controlled by the adrenal circadian clock. In global Bmal1 knockouts, sex hormone production is impaired due to abolition of rhythmicity, resulting in infertility. When Bmal1 is knocked out in adrenal tissue only, circadian production of sex hormone is dampened, but not abolished.

Objectives
My project seeks to investigate the result of global and hypothalamic-specific knockouts of Bmal1 on corticosterone release. We hypothesize that disrupting circadian rhythms will abolish hormones which are under hypothalamic control, such as corticosterone. To test this, we will subject our Bmal1-deficient mice to stress and observe their plasma corticosterone.

Materials and Methods
My project seeks to investigate the result of global and hypothalamic-specific knockouts of Bmal1 on corticosterone release. We hypothesize that disrupting circadian rhythms will abolish hormones which are under hypothalamic control, such as corticosterone. To test this, we will subject our Bmal1-deficient mice to stress and observe their plasma corticosterone.

Conclusions
These data confirm our hypothesis that Bmal1 is essential for circadian release of corticosterone. In future experiments, we will delete Bmal1 from hypothalamic tissue only and perform the same circadian corticosterone assay. In addition, we will subject both cohorts of animals to stress tests to observe any HPA axis deficits.

Mentor / Department
Dr. Louis Muglia, Pediatrics
THE ROLE OF HEMATOPOIETIC PROGENITOR CELLS IN IMMUNE TOLERANCE

Analise B. Thomas—Laboratory-Based Biomedical Research

Background Problem
Type 1 Diabetes, a chronic disease of global immune dysfunction that affects over ten million people worldwide, could be cured with islet transplantation; however, this procedure relies on life-long immunosuppression in transplanted individuals with attendant side effects including islet toxicity. To permit clinically successful islet transplantation, immune tolerance must be established in the recipients, a daunting challenge given their pre-existing autoimmunity. This challenge is highlighted in the murine model of Type 1 diabetes, the NOD mouse, in which no protocol to induce allogeneic tolerance has ever been established. Previous studies have focused on the effects of tolerogenic therapies on the peripheral immune system. The contribution of bone marrow stem cells to tolerance induction and autoimmunity has not yet been elucidated.

Objectives
We aimed to investigate the novel hypothesis that HSC turnover within the bone marrow (BM) is a target of tolerance-inducing therapies that is disrupted in T1D.

Materials and Methods
HSCs were identified using flow cytometry by staining with antibodies against Sca-1, cKit, a lineage panel, and CD45RB. BM HSC activity was confirmed by colony forming cell (CFC) assay in which BM cells were plated in methylcellulose media with differentiation factors and colony formation was determined on day 7. To test HSC mobilization, pre-diabetic NOD and B6 female mice were treated with G-CSF (2.5mg/dose twice daily x4 days) or the tolerance inducing agent anti-CD45RB (100ug/dose on days 0,1,3,5,7). Interruption of sympathetic function was performed with 6-OH dopamine given in two doses (2mg/dose at day -4 and 5mg/dose at day -2 before anti-CD45RB treatment).

Conclusions
Tolerogenic therapy enhances marrow stem cell frequency and function in tolerance-susceptible B6 but not NOD mice. Interruption of sympathetic input to the bone marrow also overrides anti-CD45RB mediated mobilization. These studies suggest a framework in which mobilization of bone marrow stem cells may be a key first step in tolerance induction. Processes that disrupt this function, such as injury of the autonomic nervous system, may prevent tolerance induction and drive autoimmunity.

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Mentor / Department
Daniel J. Moore, M.D., Ph.D., Department of Pediatrics
MANGANESE-ENHANCED MRI: RETINAL CALCIUM UPTAKE IN A RAT MODEL OF GLAUCOMA

James Tsahakis - Laboratory-Based Biomedical Research

Background Problem
Increased intraocular pressure in glaucoma is associated with disrupted Ca2+ homeostasis in both the retina and optic nerve. As both a Ca2+ analogue and MRI contrast agent that shortens T1 relaxation times, Mn2+ can be used as a surrogate marker for activity-dependent signaling.

Objectives
We used Mn2+-enhanced MRI (MEMRI) to investigate changes in Ca2+ activity following short-term elevations in intraocular pressure (IOP) in a rat model of glaucoma.

Materials and Methods
We elevated IOP by injection of polystyrene microbeads into the anterior chamber of the left eye of Brown Norway rats; the right eye received an equivalent volume saline injection to serve as a control. IOP was measured for a period of either 6 or 20 days, after which each eye was imaged in vivo with a 4.7T 31-cm bore Varian DirectDrive MRI scanner 4 hours following intraperitoneal injection of MnCl2 (60 mg/kg). We compiled MEMRI T1 maps of the retina from multiple cross-sectional scans per animal.

Conclusions
Modest elevations in IOP over even a limited period (6-20 days) increase MEMRI signals in the retina as measured by decreased T1 relaxation times. Since shorter T1 values indicate increased Mn2+ uptake, our results suggest that limited elevations in IOP increase homeostatic retinal Ca2+ activity. How this activity changes over longer periods of IOP elevation is important for understanding the contribution of Ca2+-dependent mechanisms to progression of neurodegeneration in glaucoma.

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Mentor / Department
David J. Calkins, Ph.D; Vanderbilt Eye Institute
HEDGEHOG SIGNALING PATHWAY ACTIVITY AND THE PROLIFERATION OF GLIOMAS

Ato Wallace - Laboratory-Based Biomedical Research

Background Problem
The activity of the hedgehog-signaling pathway has been implicated as essential for embryological cell proliferation and differentiation. More recent studies have also demonstrated hedgehog signaling pathway activity in malignant tumors especially grade II and II gliomas.

Objectives
Malignant gliomas are highly lethal primary brain tumors whose growth are regulated by the Hedgehog signaling pathway. The Hedgehog pathway inhibition has thus emerged as potential therapeutic target for patients with malignant glioma. In this study, we evaluated the effects of a small molecule inhibitor on glioma cell proliferation in an animal model for primary human gliomas

Materials and Methods
Primary brain tumor was obtained from patient and placed into immunocompromised mice to create primary orthographic xenographs. The mice were then treated with cyclopaamine and vehicle approximately 3 months following the xenograph when they began to show symptoms of tumor (they exhibit weight loss). Their brains were then obtained, sectioned and fixed in paraffin and placed on slides. The slides were evaluated using various biochemical markers, including: vimentin, Ki67, and Brdu

Conclusions
The result therefore is that small molecular inhibition of the hedgehog signaling pathway poses limited efficacy towards tumor genesis.

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Mentor / Department
Dr. Michael Cooper, Vanderbilt University Medical Center, Department of neurology, movement disorder division
THE USE OF CONNECTIVE TISSUE GROWTH FACTOR (CTGF) TO ENHANCE ISLET TRANSPLANTATION

Brian Wright-Laboratory-Based Biomedical Research

Background Problem
Islet transplantation as a therapy for Type 1 diabetes has shown promising results but still remains limited due to loss of beta cell viability, poor or failed islet revascularization, and islet toxicity from immunosuppression. Connective tissue growth factor (CTGF) is a secreted protein endogenously expressed in mouse embryonic beta cells but not detected after post-partum day 3. CTGF is re-expressed in islets of pregnant mice. Our group has shown that CTGF is important for embryonic beta cell proliferation, while others have shown that it promotes angiogenesis. Thus, CTGF treatment may increase islet survivability during and after transplantation via increased beta cell replication and improved vascularization.

Objectives
We hypothesize that CTGF treatment may alleviate some of these barriers to successful islet transplantation. To this aim, we sought to quantify the change in islet revascularization following increased expression of CTGF.

Materials and Methods
To determine whether increased CTGF could enhance islet vascularization, we used transgenic mice in which CTGF expression can be induced specifically in insulin-expressing cells (RIP-rtTa; TetO-CTGF, bigenic). Expression of PE-CAM, a protein found in blood vessel endothelial cells, was assessed in islets from control and CTGF over-expressing mice.

Conclusions
Although preliminary, these results suggest that over-expression of CTGF over a one-week period increases islet vascularization, while a period of five weeks does not. Further studies are being conducted to evaluate islet revascularization from DOX administration in both control and bigenic mice following islet transplantation. Such studies will help elucidate any role that CTGF could play in increasing islet survivability during and after transplantation.

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Uma Gunasekaran, Michelle Guney, Maureen Gannon, Vanderbilt University School of Medicine

Mentor / Department
Maureen Gannon, Molecular Physiology and Biophysics, and Cell and Developmental Biology
FUNCTIONAL ORGANIZATION OF FEATURE-BASED ATTENTION IN MACAQUE V4

Soo-Ryum Yang—Laboratory-Based Biomedical Research

Background Problem
Macaque V4 contains discrete domains of cortical cells that preferentially respond to features such as color and orientation (Tanigawa et al. 2010 Nat. Neurosci.). Such functional organization of feature representation raises the question of whether feature-based attention is similarly organized in domain-based manner.

Objectives
In this study, we wanted to determine whether feature attention enhances correlation between domains involved in attended feature.

Materials and Methods
To explore this, we used intrinsic optical imaging to record neural responses from V4 of two monkeys (J and L) while they performed feature-change discrimination tasks. Monkey J detected a color change (either reddish vs. bluish) of a grating by attending to its color, and monkey L detected a paired change in both orientation and the color (bluish and counter-clockwise vs. yellowish and clockwise) by attending to both the orientation and color. Non-attentive control conditions involved central fixation with no feature change. Domains (selective for colors, orientations, luminance, non-selective) were identified by optical imaging and examined pairwise. For each unique domain pair, reflectance values at the initial dip of one domain were correlated with those of the other domain across all trials using Spearman’s rank correlation. The correlations during attention vs. fixation were compared.

Conclusions
In summary, our findings suggest that correlational enhancement is exclusively limited to feature domain pairs relevant to the attended feature(s). Thus, unlike spatial attention in which attention is mediated via response enhancement, feature-based attention involves an increase in correlational activity among relevant domains. Thus, our data suggest a domain-based model for feature attention—where functional connections of relevant domains are selectively increased for enhanced perceptual processing of specific features. This may be a mechanism by which feature attention is implemented across large cortical topography at the exclusion of other irrelevant but competing feature representations.

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Robert Friedman, Kayla Yelle, Pratik Talati

Mentor / Department
Anna Wang Roe, Department of Psychology Hisashi Tanigawa, Department of Psychology
Medical Education

This educational experience is designed to introduce students to theory and practice in the learning and teaching of medical students, residents, practicing physicians and patients as well as provide an opportunity to develop a project in an area of interest. Students will be provided with opportunities to examine the practice of education in a wide variety of health care settings. Students will have opportunities to examine

- How learning occurs in medical school, residency, and practice
- How students can develop reflection and self-assessment skills to develop an approach to lifelong learning that can be used throughout their medical careers
- What teaching strategies help medical students, residents, practicing physicians, and patients learn
- Assessing the progress of student, resident, or patient learning
- Curriculum development in specific content areas

The student experience will introduce them to the community of scholars at Vanderbilt and elsewhere who study and work in the field of medical education. Each student will work with a mentor who will provide direction to the student as he or she determines an area of focus, develop a project proposal, implement the project proposal, present findings, and prepare findings for publication. In addition, students in the Medical Education area will be expected to participate in ongoing educational activities such as Medical Education Grand Rounds, Medical Education Journal Club, and CORE Conversations dealing with issues in medical education research.

“Working with students in the Emphasis Program has been one of the highlights of my work at Vanderbilt. It has been an honor and a privilege for me to share their excitement and satisfaction as they worked through and accomplished their projects. I look forward to working with the students who choose the Medical Education area this year.”

Don Moore, Ph.D. is a Professor of Medical Education and Administration, Director, Division of Continuing Medical Education at Vanderbilt University School of Medicine, and Director, Education and Evaluation, Graduate Medical Education. He has devoted a considerable amount of his professional career examining, writing and speaking about continuing medical education and a number of other related areas such as: practice-based CME, planning and assessing CME, and how Physicians learn. His research interests also include the role of CME in physician change, office systems for CME, and the impact of CME on health care outcomes.
HUMANIZING ANATOMY: HOW INSIGHT INTO THE LIFE OF THE DONOR CAN INFLUENCE A STUDENT’S EXPERIENCE IN ANATOMY, AND HOW PROVIDING THIS INSIGHT CAN BENEFIT THE FAMILY.

Alicia Cutillo-Medical Education

Brief Description
The aims of this study were to implement a program in which first year medical students could learn more about their anatomical donors, by either meeting with a family member or receiving a biography, and to assess how such a program would influence both the students and family members’ experience with anatomical donation.

Mentor / Department
Dr. Lynn Webb, Medical Education and Administration
EFFECT OF EDUCATIONAL SYSTEM ON MEDICAL STUDENT ACQUISITION OF SURGICAL SKILLS

Barry Kang - Medical Education

Brief Description
To compare alternative methods of surgical education, specifically through an instructional video, against the traditional model of direct supervision from a surgeon in teaching medical students how to suture.

Acknowledgements
Vanderbilt Surgical Skills Lab

Mentor / Department
Dr. John Nesbitt Thoracic Surgery
ASSESSING THE RECEPTION AND IMPACT OF THE COLLEGE COLLOQUIUM AT VANDERBILT SCHOOL OF MEDICINE

Carmela Kiraly - Medical Education

Brief Description
Surveys, observations, and faculty evaluations will be used to analyze the relationships among several themes pertinent to the reception and impact of the College Colloquium on its pilot students: cognitive flexibility, empathy, learning style, and attitude toward the course itself.

Acknowledgements
Regina Russell, OTLM Scott Demonbreun, OTLM Scott Rodgers, Student Affairs Mario Davidson, Biostatistics

Mentor / Department
Quentin Eichbaum, Associate Dean and Professor of Medical Education
MEDICAL EDUCATION AS A MEANS TO ACHIEVE PUBLIC HEALTH GOALS: ARE BREASTFEEDING CURRICULA ADEQUATE?

Michele Ann Luhm Vigor - Medical Education

Objectives
Breastfeeding (BF) is considered best practice for infant feeding. However, little is known about BF education in US medical schools. This study describes the current state and effectiveness of BF education, based on a representative sample of US medical schools.

Brief Description
This study utilizes a national survey of fourth-year allopathic medical students to describe the current state of breastfeeding education in US medical schools, focusing on confidence in the clinical skills needed to promote best practices for infant feeding and to support breastfeeding patients.

Conclusions
The data supports the notion that the amount and quality of curricular time devoted to BF is insufficient in preparing future physicians to support BF. As a result, students have low confidence in the clinical skills they need to promote and support BF. Our findings about BF in medical education illustrate the need for medical schools to design curricula that align with public health goals, so that physicians can serve a more effective role in promoting these goals and seeing them realized.

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Mentor / Department
Bonnie Miller, MD, Senior Associate Dean for Health Sciences Education, Vanderbilt University School of Medicine; Mavis Schorn, PhD, CNM, FACNM, Assistant Dean for Education, Vanderbilt University School of Nursing
ANIMATING INTERDISCIPLINARY CONCEPTS IN LUNG FUNCTION AND PATHOPHYSIOLOGY: A NOVEL PLATFORM FOR THE INTEGRATION OF CORE CONTENT FOR VANDERBILT MEDICAL STUDENTS

Voranaddha Vacharathit-Medical Education

Brief Description
Studies from different fields suggest that animations are more effective than conventional chalk-on-blackboard lectures or static images in PowerPoint presentations, especially in teaching complex or multidisciplinary concepts. For students first introduced to the material as well as the more visual learners, animations, when properly designed, can present concepts through a new perspective and act as a platform for the integration of ideas in ways that may not be apparent through discontinuous lecture modules. At present, however, medical animations that integrate cross-disciplinary concepts are rare – those specifically designed for medical students so that they may, for instance better understand the pathophysiological basic sciences behind diagnostic test results are even scarcer. Even when animations are used, there is virtually non-existent data on the effectiveness of using them to teach medical students since most of what is known comes from other fields that do not have the same ultimate goal of enhancing students’ ability to apply knowledge to real clinical scenarios. For these reasons, the study we now propose is crucial and timely in the ever evolving education scene. We propose a multi-stage project to: 1) create an animated platform interconnecting interdisciplinary ideas and integrating clinical diagnostics with a cohesive explanation of how basic pathological perturbations affect normal physiology the clinical presentation; 2) evaluate the e-learning module via a two-tailed data-matched randomized controlled trial in VMSIs with different Kolb’s learning styles. The animated platform will be evaluated in the following areas: a) Retention of concepts b) comprehension of conceptual cross-talk between different disciplines c) ability to apply concepts learned, for instance through a focused differential diagnosis of a patient. If successful, this proof-of-concept could pave way for future integrative endeavors and animated e-learning modules. The effectiveness study we propose would be one of the first in the field of medical education.

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Mentor / Department
Dr. Cathy Pettepher (Cancer Biology), Dr. John Newman (Pulmonary Medicine), Dr. Mario Davidson (Biostatistics)
Medical Scientist Training Program

The central goal of the Medical Scientist Training Program (MSTP) at the Vanderbilt University School of Medicine is to train leaders in academic medicine. Our program is based on solid clinical and research training and is designed to foster the development of independent scientific careers.

The MSTP is a joint endeavor between the Vanderbilt University School of Medicine and the Vanderbilt University Graduate School. Students usually complete the first two years of Medical School, pursue graduate studies for three to four years, then return to Medical School to complete the final two years of clinical training. Successful completion of the program leads to both the M.D. and Ph.D. degrees.

Full-time laboratory research is performed in three rotations from the summer prior to the first medical year through the summer following the first year of Medical School. These cumulative research experiences serve as the Emphasis project for MSTP students.

“The laboratory rotations that comprise the Emphasis experience are incredibly important for our students. They gain exposure to a variety of research opportunities and select a mentor, training environment, and scientific project best suited to their professional development.”

Terence S. Dermody, M.D., is the Dorothy Overall Wells Professor of Pediatrics and Microbiology and Immunology, Director of the Division of Pediatric Infectious Diseases, Director of the Lamb Center for Pediatric Research, and Director of the Vanderbilt Medical Scientist Training Program (MSTP). Dr. Dermody came to Vanderbilt in 1990 after completing his medical degree at Columbia University in New York, a residency of internal medicine at Presbyterian Hospital in New York, and fellowships in infectious diseases and virology at Brigham and Women’s Hospital and Harvard Medical School in Boston. Dr. Dermody is a physician scientist with clinical interests in pediatric infectious diseases and research interests in viral pathogenesis. He has been directing the MSTP since 2003.
TISSUE SPECIFIC FUNCTION OF TSC PROTEIN IN THE PATHOGENESIS OF TUBEROUS SCLEROSIS

Laura Armstrong- MSTP

Background Problem
Tuberous Sclerosis is an autosomal dominant disease with an incidence of 1 in 6000. TSC causes benign tumor growth (hamartomas) in the kidneys, lung, heart, skin and brain as well as causing epilepsy in most patients and learning disabilities or autism in many. In 85% of patients there is an identifiable heterozygous mutation in the genes TSC1 or TSC2, making this an accessible disease to use to study the role of the mTOR pathway in brain development. Though the neurological manifestations are the most common symptoms in these patients the neuropathology is still unknown. In most organs the tumors have acquired a second mutation in TSC1/2, presumably leading to unhindered growth. In contrast, hamartomas in the brain appear to consist of cells with only one mutation, the same heterozygous germline mutation as the non-tumor neurons. The Ess lab has recently shown in a zebrafish model that cells which acquire a second mutation may influence neighboring neurons in a non-cell-autonomous manner, suggesting an alternative mechanism for the neurological abnormalities seen in TSC patients.

Objectives
This research will explore the tissue specific role that the TSC proteins play in the pathogenesis of disease and determine whether neurons homozygous for TSC1/2 mutations alter migration and function of adjacent heterozygous neurons.

Materials and Methods
Using induced pluripotent stem (iPS) cells generated from patients with Tuberous Sclerosis, I plan on generating kidney cells and neurons and measuring differences in mTOR pathway activation. Similarly, neurons generated from iPS cells with homozygous TSC1/2 mutations will be grown in vitro alongside heterozygous neurons and their reciprocal influence will be studied.

Conclusions
To be determined

Acknowledgements
Vanderbilt University Medical Scientist Training Program

Mentor / Department
Kevin Ess, Cell and Developmental Biology
TRANSCRIPTIONAL REGULATION OF DENDRITIC BRANCHING OF NOCICEPTOR NEURONS IN C. ELEGANS

Elana Feingold-Link-MSTP

Background Problem
Organisms across phylogeny utilize mechanosensitive neurons to sample their environment. The proper balance of different mechanosensitive cells allows the organism to respond to a myriad of environmental stimuli, ranging from a light mechanical brush to a harsh painful hit. Imbalance of this network could result in an organism that is hyper or hypo sensitive to pain.

Objectives
To identify the molecules required to establish the network of mechanosensitive cells we used Caenorhabditis elegans, which has a simple network of mechanosensitive neurons. Here we show that transcription factors ZAG-1 and AHR-1 are required to restrict post-embryonic light-touch neurons from becoming nociceptive neurons.

Materials and Methods
We show that AHR-1 and ZAG-1 interact with MEC-3 to control the branching pattern of sensory neurons.

Conclusions
Together our results define an intrinsic transcriptional network that maintains the balance of mechanosensitive neurons and thus controls behavior incited by mechanical stimulus.

Acknowledgements

Mentor / Department
David Miller, PhD Department of Cell and Developmental Biology
RECOMBINANT EXPRESSION OF THE NATIVE GOODPASTURE AUTOANTIGEN, THE ALPHA 3 NC1 DOMAIN OF COLLAGEN IV

A. Scott McCall-\textit{MSTP}

Background Problem
The NC1 (Noncollagenous-1) domain of the alpha 3 chain of collagen IV contains the epitopes recognized by the autoantibody responsible for Goodpasture autoimmune disease. The immunodominant epitope (Ea) of the Goodpasture autoantigen is formed upon dissociation of the native hexamer complex into monomer and dimer subunits, and it resides within subdomain A of the monomer subunit.

Objectives
An understanding of the 3D structure of the epitope and conformational changes that underlie epitope formation may provide insights into the etiology of the Goodpasture disease. Potentially, these structural features can be defined by NMR spectroscopy, using 15N and 13C labeled recombinant NC1 domain.

Materials and Methods
A Baculovirus expression vector in SF9 insect cells, was evaluated for preparation of the alpha 3 NC1 monomer (MW 25 KDa) and its subdomain A (MW 12.5 KDa).

Conclusions
The findings establish an experimental strategy for using NMR spectroscopy to delineate the mechanism of epitope formation and assembly of the 3D structure of the alpha 3 NC1 domain.

Mentor / Department
S. Kent Dickeson, and Billy G. Hudson
SCREENING CANDIDATE MOLECULES FOR AMYLOID IMAGING: DEVELOPMENT OF A HIGH-THROUGHPUT ASSAY

Richard A McClure-MSTP

Background Problem
Despite a myriad of efforts, a reliable screening diagnostic for AD, prior to the onset of symptoms, has remained elusive. PET-based imaging of β-amyloid (βA) plaques remains an ideal diagnostic methodology as it facilitates the imaging of low density targets while minimizing side effects due to the picomolar concentrations of tracer needed.1 Currently, only Pittsburgh Compound-B has been shown capable of differentiating between normal brains and those affected by AD.2 In addition, studies have shown that reliance on transgenic mouse models may be inappropriate for identifying PET tracers for amyloid imaging.3 In summary, development of novel radio-labeled ligands for detection of βA plaques in-vivo has proven challenging and continues to suffer from a distinct paucity of screening methodologies necessary to refine candidate molecules prior to further investigation in humans. Our study will provide one such screening methodology and potentially lead to the discovery of a new class of compounds capable of functioning as PET tracers for amyloid imaging. Not only would the discovery of such a PET tracer represent a breakthrough in the early detection of AD, it would also yield a means with which to evaluate potential therapeutics by providing a non-invasive and reliable approach to diagnosing AD prior to the onset of symptoms.

Objectives
The immediate aim of this research is the development of a high-throughput assay capable of screening candidate molecules for their ability to bind βA plaques. If successful, this novel assay could provide a means for identifying new classes of molecules capable of serving as diagnostic Positron Emission Tomography (PET) tracers of the hallmark lesion of Alzheimer’s disease (AD). The anticipated long-term outcome of this research is the identification of a novel βA plaque binding molecule which can then be radio-labeled and utilized to screen patients for the early detection of AD using PET-based amyloid imaging.

Materials and Methods
Staining with thioflavin remains the most reliable methodology for visualizing βA plaques via fluorescence microscopy.6 In the presence of βA, the fluorescent emission of thioflavin is dramatically increased when compared to thioflavin not complexed with plaques. By employing the 5XFAD mouse model, a brain lysate containing numerous βA plaques can be created in animals aged less than 8 months. By combining thioflavin with this amyloid lysate, the thioflavin emission is maximized and serves as a stable indicator of βA-binding when measuring via fluorescence spectroscopy. Molecules capable of binding βA plaques can then be identified through their ability to competitively bind βA plaques resulting in an attenuation of thioflavin emission due to the reduction of thioflavin-βA plaque complexes. This advantage of using this assay is that it can be optimized to achieve compatibility with plate readers facilitating a very high through-put screening of candidate molecules.
Conclusions
Preliminary data suggest that Promethazine is capable of binding βA plaque. Furthermore, confirmation of our ability to identify a novel βA plaque binding molecule via the use of the High-throughput Amyloid Thioflavin Competitive-binding Optical (HATCO) assay, supports the hypothesis that potential probes for amyloid imaging can be identified through high-throughput methodologies.

Mentor / Department
Wellington Pham Department of Radiological Sciences
IDENTIFYING MECHANISMS OF ACQUIRED RESISTANCE TO EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS IN NON-SMALL CELL LUNG CANCER

Catherine Meador-MSTP

Background Problem
EGFR mutant lung cancers are highly sensitive to EGFR tyrosine kinase inhibitors (TKIs). However, disease progression occurs after about a year. Mechanisms of resistance in ~30% of cases remain unknown.

Objectives
The goal of this project is to utilize deep sequencing of DNA from multiple isogenic pairs of drug-sensitive and –resistant EGFR mutant cell lines coupled with functional studies to identify novel mechanisms of acquired resistance.

Materials and Methods
Genomic DNA from isogenic pairs of drug-sensitive and –resistant EGFR mutant cell lines (e.g. PC-9, HCC827, and HCC4006) was subjected to whole genome paired-end sequencing on an Illumina Genome Analyzer Ix platform. 100 bp reads were aligned to the Human Genome (UCSC hg19) using ELAND (Version 2). FastQC (Version 0.9.1) was used to perform a quality control check of the raw data, and reads were analyzed by Dr. Zhongming Zhao’s group for insertions/deletions/single nucleotide variants (SNVs). Putative mutations were validated by direct sequencing.

Conclusions
Novel mutations specific to resistant cells have already been identified. Functional studies will be carried out by siRNA knock-down of uniquely mutated genes in resistant cells, to determine their effect on erlotinib sensitivity. Results could identify novel mechanisms of resistance as well as shed light on how to distinguish among ‘driver’ mutations that affect biology and ‘passenger’ mutations that occur stochastically without biological impact.

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Mentor / Department
William Pao, M.D., Ph.D., Department of Cancer Biology
DEFINING THE METABOLIC LINK BETWEEN KRAS MUTATIONS IN COLORECTAL CANCER AND THE WARBURG EFFECT

Kelli Money-MSTP

Background Problem
Previous experiments in the Beauchamp and Liebler laboratories have shown a connection between colorectal cancer cells harboring a K-Ras mutation and an altered state of metabolism known as the Warburg effect, a metabolic state that supports proliferation by decreasing the Krebs cycle and oxidative phosphorylation and increasing aerobic glycolysis and lactate formation. Previously collected proteomics data from a K-Ras mutated colorectal cancer cell line (DKO-1) showed increased expression of several glycolytic enzymes, including a form of pyruvate kinase seen in embryological development (PKM2).

Objectives
We sought to investigate how blocking the Ras pathway or reducing glycolytic enzymes would affect tumor cell behavior.

Materials and Methods
DKO-1 cells were evaluated in comparison to the same cancer cell line without a K-Ras mutation (DKS-8) for glycolytic profile, invasiveness and survival in normal and low glucose conditions. Major downstream K-Ras signaling pathways (ERK and PI3K) were disrupted to investigate the role of K-Ras in PKM2 upregulation. PKM2 was knocked down to investigate its effects on tumor cell behavior alone and combined with ERK and/or PI3K inhibition.

Conclusions
Although inhibition of ERK and PI3K does not lead to decreased levels of PKM2, combined inhibition of ERK and PKM2 does show an additive effect with DKO-1 cell susceptibility to induced apoptosis.

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Dan Beauchamp Lab Vanderbilt MSTP

Mentor / Department
Dan Beauchamp, Departments of Cancer Biology and Cell and Developmental Biology
TRIGLYCERIDE PRODUCTION IN CETP TRANSGENIC MICE

Brian T. Palmisano- MSTP

Background Problem
Cholesterol ester transfer protein (CETP) is present intracellularly and in the serum. In the serum, CETP is known to exchange cholesterol ester (CE) and triglyceride (TG) between various lipoproteins. CETP action on high-density lipoprotein (HDL) enriches HDL with TG. C57Bl/6 mice do not express CETP, and transgenic mice expressing human CETP express CETP in the serum. Transgenic mice expressing rhesus monkey CETP are used as a model here because both intracellular and extracellular CETP is expressed, whereas the human CETP transgenic mice only express serum CETP. Long term high fat diet feeding has been shown to make C57Bl/6 mice insulin resistant, but female CETP transgenic mice remain insulin sensitive as measured by a hyperinsulinemic euglycemic clamp. Male CETP transgenic mice become insulin resistant as with the C57Bl/6 controls. Canonical insulin action inhibits VLDL-TG production in the normal liver, but TG production in these CETP transgenic mice is not known. We aim to measure the VLDL-TG production in male and female CETP transgenic mice using dual isotope of [3H]cholesterol and [14C]palmitate tracer infusion.

Objectives
To determine the VLDL-TG production in male and female mice CETP transgenic mice using dual isotopic labeling of substrates.

Materials and Methods
Mice: Age matched rhesus CETP transgenic mice (female n=3, male n=3) were put on a high fat diet for >160 days. All animals were fasted 5 hours prior to the study. Animals were attached to the infusion pump an hour before the infusion was started. Time zero refers to the beginning of the infusion. Infused Tracers: [3H]Cholesterol and [14C]palmitate were infused along with donor red blood cells. Serum Analysis: Specific activity (SA) of TG-[3H]glycerol using a dual label scintillation counter of folch extracted serum and a free glycerol assay (Thermo). Tissue Analysis: Tissue SA was measured using a dual label scintillation counter and a colorimetric triglyceride assay (Thermo).

Conclusions
High variability in endpoint fat storage in tissues will require further experiments with higher doses of radioactivity and longer experiment duration. Higher radiation doses will also improve the signal to noise ratio of the serum triglyceride production. These results could support that female CETP transgenic mice produce triglyceride faster than male counterparts. Future measurements of triglyceride clearance rates will facilitate calculations of net triglyceride mobilization in these mice.

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David Cappel, Melissa Martinez, Lin Zhu, Christopher Emfinger
Mentor / Department
John Stafford, Department of Molecular Physiology & Biophysics, Department of Medicine - Diabetes, Endocrinology & Metabolism
MECHANISMS OF ALTERED STRIATAL DOPAMINE NEUROTRANSMISSION IN NEURONAL RICTOR NULL MICE

India Reddy-MSTP

Background Problem
Akt is a protein kinase that is activated through phosphorylation at two key residues: threonine-308 and serine-473, the latter of which is catalyzed by mTORC2 (mammalian target of rapamycin 2). Decreased Akt signaling in humans appears to confer greater susceptibility to schizophrenia while Akt1- deficient mice exhibit amphetamine-induced prepulse inhibition (PPI) deficits, a measure that serves as an ‘endophenotype’ of schizophrenia. Conversely, antipsychotic treatments of animal models stimulate Akt in the striatum, a brain region enriched in dopaminergic terminals and relevant to bipolar disorder and schizophrenia. This evidence has led to a model that links deficits in Akt signaling to disruption of dopamine-associated networks, although the mechanism by which this occurs is unclear.

Objectives
Through this project, I sought to determine relevant changes to neurotransmitter systems in a genetic mouse model of Akt dysfunction.

Materials and Methods
In order to create this model, we eliminated the gene encoding the mTORC2 subunit protein, Rictor, in neurons through Cre-lox-mediated recombination.

Conclusions
The Rictor null mouse thus reveals itself as a model to study the dynamic interactions between noradrenergic and dopaminergic neurotransmitter systems in order to elucidate mechanisms behind schizophrenia.

Acknowledgements
I would like to acknowledge Mike Siuta and Amanda Poe for their contributions to this project.

Mentor / Department
Aurelio Galli, Ph.D., Department of Molecular Physiology and Biophysics
THE ROLE OF B LYMPHOCYTE RECEPTOR SIGNALING IN B LYMPHOCYTE MEDIATED IMMUNE REGULATION

Blair Taylor Stocks-MSTP

**Background Problem**
Islet transplantation represents a clinical solution to type 1 diabetes (T1D); however the obligatory immunosuppression that follows the operation significantly limits the widespread use of this procedure. Clinically applicable islet transplantation for T1D will therefore depend on restoring immune tolerance in graft recipients.

**Objectives**
While transplantation tolerance is easily achieved in normal strain mice (B6), no protocol has been successful in non-obese diabetic (NOD) mice. We hypothesize that defective B-lymphocyte function in NOD mice may lead to an inability to restore tolerance. Recent evidence suggests that monoclonal antibody to CD45RB restores immune tolerance in a B-lymphocyte dependent manner. In the present study, we examined B-lymphocyte receptor (BCR) signaling in anti-CD45RB treated, tolerance-susceptible B6 and tolerance-resistant NOD mice.

**Materials and Methods**
Age matched wild type B6 and NOD mice were injected with saline or an anti-CD45RB mAb every other day for five days. On day six, mice were sacrificed and spleens were harvested. To assess B lymphocyte signaling in the “activated” state, unsorted splenocytes were exposed to an anti-IgM antibody for 10 minutes. Cytoplasmic pSyk and pPLCγ2 levels form the unsorted splenocytes were evaluated via flow cytometry by measuring changes in mean fluorescent intensities.

**Conclusions**
Preliminary data suggest that anti-CD45RB mAb treatment may alter splenic B-lymphocyte signaling by increasing Syk and PLCγ2 phosphorylation as detected in NOD mice, however further experimentation is required to confirm these initial data. Overall, identification of alterations in BCR signaling may reveal how antigen-specific tolerance is induced, how B lymphocytes function during tolerogenesis, and new pathways to correct fundamental deficits in the biology of the diabetes-prone immune system.

**Mentor / Department**
Dan Moore, MD, PhD Department of Pediatrics Department of Pathology, Microbiology, and Immunology
SMALL MOLECULE ACTIVATORS OF HSSRS IN STAPHYLOCOCCUS AUREUS INHIBIT GROWTH UNDER RESPIRATION OR OXYGEN RESTRICTED CONDITIONS

Matthew Surdel-MSTP

Background Problem
Staphylococcus aureus is a bacterial pathogen that contributes to significant morbidity and mortality. In order to colonize the host, S. aureus must obtain nutrients, such as iron and heme, both of which are essential cofactors in respiration. To gain access to human heme and iron, S. aureus uses the iron-regulated surface determinant system (Isd). S. aureus also has the ability to endogenously produce heme. The combination of these two mechanisms allows S. aureus to meet its heme and iron requirements. Too high of a concentration of intracellular heme is, however, toxic to the bacteria. To prevent toxicity, S. aureus utilizes the heme sensor system (HssRS) to induce the expression of the heme-regulated transporter (HrtAB), relieving heme toxicity. A high throughput screen (HTS) was performed and identified thirteen small molecule activators of HssRS. The most potent HssRS activator has been shown to increase endogenous heme synthesis and is particularly toxic to fermenting staphylococci.

Objectives
Based on these observations we hypothesize that HssRS activation is intimately tied to the respiratory state of the bacteria. The goal of this study is to test the responses of S. aureus to the other top compounds from the HTS under respiration and oxygen dependent growth conditions. Doing so will help elucidate the pathways through which these molecules produce their effects within S. aureus, thereby potentially identifying novel therapeutic targets for microbial growth inhibition and providing fundamental insights into staphylococcal physiology.

Materials and Methods
Activation of HssRS will be verified through the use of a XylE reporter assay. Growth under respiration and oxygen dependent conditions will be tested in the presence of these compounds to determine the extent of growth inhibition. Assays such as intracellular heme quantification assays may be used to help elucidate the mechanism through which these molecules exert their effects.

Conclusions
To be determined.

Mentor / Department
Eric Skaar, PhD, MPH, Department of Pathology, Microbiology & Immunology
GENETIC AND IMAGING TECHNIQUES TO INVESTIGATE THE HIPPOCAMPUS IN PSYCHOSIS

Pratik Talati-\textit{MSTP}

\textbf{Background Problem}
The hippocampus is a medial temporal lobe structure responsible for learning and declarative memory. It is composed of the cornu ammonis (CA), which is subdivided into CA1-4, and the dentate gyrus. Of note, the CA3 region is responsible for pattern completion (using a partial cue to retrieve the extended representation) while the dentate gyrus is responsible for pattern separation (distinguishing between similar memories at different times). It has been shown that smaller hippocampal volumes are evident in patients with schizophrenia. Recent evidence suggests that loss or dysfunction of CA3 inhibitory GABAergic interneurons is implicated in psychosis, which can result in abnormal hippocampal activation to generate many of the features of psychosis. To evaluate this hypothesis, imaging and genotyping studies will be conducted on patients with psychotic disorders.

\textbf{Objectives}
The main aim of my project is to obtain high-resolution MRI maps of hippocampal volume and correlate them with functional studies. Cerebral blood volume experiments will complement the studies to investigate differential pathology in the CA1-4 regions of the hippocampus to elucidate the mechanism of the disease. These experiments will be supplemented with single nucleotide polymorphisms (SNPs) to determine key genes that correlate with hippocampal volume.

\textbf{Materials and Methods}
Imaging: Subjects will undergo a 3T and 7T T1-weighted MRI to align the 3T image with the higher resolution 7T image. The transformation will then be used on 7T T2-weighted images to allow for high-resolution tracing of the hippocampus. The images will then be correlated with functional data (obtained based on a memory-dependent task) and cerebral blood volumes (via administration of a Gadolinium-based contrast). Genotyping: Single nucleotide polymorphisms will be run for on an assay using DNA collected from patients. Genes of interest will be investigated using available literature.

\textbf{Conclusions}
This research aims to elucidate whether there is a dysfunction in the GABAergic inhibitory neurons in the hippocampus, which would determine whether hippocampal pathology would be a useful criteria for diagnosing psychotic disorders.

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\textbf{Mentor / Department}
Stephan Heckers, M.D., MSc., Department of Psychiatry
**Patient Oriented Research**

The area of Patient-Oriented Research addresses:

1. The mechanisms of human disease,
2. Therapeutic interventions,
3. Clinical trials,
4. The use of new technologies for the diagnosis, treatment, or prevention of disease, and
5. The emotional, social, development and behavioral mechanisms of health and disease.

In addition to standard randomized clinical trials, patient-oriented methodologies also include self-perception measures (e.g., patients completing questionnaires), interviews, and focus groups. The core of this focus group is the scientific study of human participants to understand the cause of disease, health, and function. This understanding contributes to therapy and prevention. Clinically derived scientific knowledge, laboratory science, and patient-oriented science are core disciplines of the medical profession.

“The Emphasis Program provides me a unique opportunity to nurture aspiring medical students in the field of clinical research. The motivation to learn from each clinical encounter, fostered by the patient oriented research of the Emphasis Program, is likely to transform each participating student into a life-long learner, effective problem-solver, and compassionate thinker. To paraphrase William Osler, ‘No matter trifling the clinical question at hand, answer it with a feeling that is demands the best that it is in you, and when done look it over with a critical eye, not sparing a strict judgment of yourself.’ Through the auspices of the Emphasis Program, I wish to inculcate such a spirit of reflection in each medical student.”

--Jayant Shenai, M.D.

Jayant Shenai, M.D. is the Director of Educational Affairs for the Division of Neonatology, Vanderbilt Children’s Hospital. His primary research interests include vitamin A in relation to chronic lung disease in pre-term infants and related clinical applications. As the Editor-in-Chief of Neo Reviews Plus, he contributes to the Self Assessment Program for neonatologists developed by the American Academy of Pediatrics. He participates in the grant review process at the National Institutes of Health as a member of the Study Section of Reproductive Biology. He is an Amos Christie Award winner for his outstanding teaching accomplishments and was a 2006 recipient of an Excellence in Teaching award for his contribution to continuing medical education.
IMPACT OF SECONDHAND SMOKE EXPOSURE ON SEVERITY OF PEDIATRIC PNEUMONIA

Anna Ahn—Patient Oriented Research

Background Problem
Smoking is a risk factor for adverse respiratory outcomes in adults. However, the impact of secondhand smoke (SHS) exposure on the severity of pediatric pneumonia has not been fully characterized.

Objectives
To assess the relationship between SHS exposure and disease severity among children hospitalized with community-acquired pneumonia (CAP).

Materials and Methods
We examined the impact of SHS exposure on disease outcomes among 337 children (0-18 years, median 2.5 years) hospitalized with CAP at Vanderbilt Children's Hospital from Jan. 2010-Apr. 2011 and enrolled in the CDC Etiology of Pneumonia in the Community (EPIC) study. SHS exposure was defined according to the number of household smokers: non-exposed (0 smokers); low level exposure (1 smoker); and high level exposure (2 smokers or more). Outcomes included hospital length of stay (LOS), need for supplemental oxygen, intensive care (ICU) admission, and mechanical ventilation.

Conclusions
High level SHS exposure is associated with increased CAP severity. Further study into the impact of this common environmental exposure on pediatric CAP is the focus of ongoing efforts.

Mentor / Department
Kathryn M. Edwards, M.D. and Derek J. Williams, M.D., M.P.H., Department of Pediatrics
PRIMARY EXCISION COMPARED WITH RE-EXCISION OF EXTREMITY SOFT TISSUE SARCOMAS– IS ANYTHING NEW?

Vignesh Alamanda- Patient Oriented Research

Background Problem
Soft tissue sarcomas (STS) are rare and are commonly excised outside of a sarcoma center without appropriate preoperative planning. Studies have shown varying results in survival and outcome when comparing patients undergoing re-excision to patients undergoing a single, planned excision.

Objectives
The goal of this study was to examine the differences in outcomes, if any, including death, local recurrence, and distant metastases due to the sarcoma, of both single excision and re-excision patients from 2000-2006.

Materials and Methods
This retrospective study evaluated 278 patients treated for STS of the extremities between January 2000 and July 2006. One hundred-seventy six patients had a primary excision while 102 patients had a sarcoma re-excised. Survival Curves for disease free survival, metastasis free survival, and local recurrence free survival were calculated using competing risk analysis for both groups.

Conclusions
There were no differences in death, metastases or local recurrence between the two groups after adjusting for high risk variables. Survival advantages previously seen in the re-excision group serve as proxy for tumors that have a better survival profile.

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Mentor / Department
Ginger E. Holt, MD - Dept of Orthopaedics and Rehabilitation
ROUTINE MULTIPLEX MUTATIONAL PROFILING OF MELANOMAS FACILITATES ENROLLMENT IN GENOTYPE-DRIVEN THERAPEUTIC TRIALS

Elizabeth Berry - Patient Oriented Research

Background Problem
Knowledge of tumor gene mutation status is becoming increasingly important for the treatment of cancer.

Objectives
We report here the spectrum of somatic mutations found in melanoma samples at Vanderbilt Ingram Cancer Center (VICC) and show that knowledge of tumor mutation status directly impacted clinical care by targeting patients to mutation-specific clinical trials.

Materials and Methods
Tumor mutation testing was completed using the previously described SNaPshot method of multiplex PCR, multiplex primer extension, and capillary electrophoresis. The melanoma specific SNaPshot panel detects 43 common somatic point mutations in 6 genes (BRAF, NRAS, KIT, GNAQ, GNA11, and CTNNB1) potentially relevant to existing and emerging targeted therapies in melanoma. Clinical characteristics and outcomes were assessed in the first 150 patients whose tumors were genotyped in the Vanderbilt molecular diagnostics lab under an IRB approved protocol (MEL #09109).

Conclusions
This study demonstrates that adoption of a genetically-informed approach to the treatment of melanoma has already had an impact on clinical trial enrollment and prioritization of therapy for patients with this disease.

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Mentor / Department
Jeffrey Sosman1, William Pao1, Christine M. Lovly1 1Vanderbilt-Ingram Cancer Center, the Department of Medicine/Division of Hematology-Oncology, Vanderbilt University School of Medicine
CRYOPRECIPITATE TRANSFUSION DOES NOT INCREASE PLASMA FIBRINOGEN LEVELS IN CHILDREN FOLLOWING CARDIAC SURGERY

Isaac M. Chocron - Patient Oriented Research

Background Problem
Cryoprecipitate transfusion is frequently used to treat the consumptive coagulopathy associated with cardiac surgery, purportedly by elevating plasma fibrinogen levels. However, the impact of post-bypass cryoprecipitate transfusion on fibrinogen levels has not been characterized in the pediatric cardiac surgery population.

Objectives
The purpose of this study was to examine the effect of post-bypass cryoprecipitate transfusion on plasma fibrinogen concentrations in a cohort of children undergoing cardiopulmonary bypass.

Materials and Methods
We reviewed 57 patient records for which appropriate data were available. Transfusion data for these patients were then studied to assess the impact of post-bypass cryoprecipitate transfusion on plasma fibrinogen levels upon arrival in the ICU. To evaluate whether alterations of plasma fibrinogen were a result of dilution, we also assessed the impact of post-bypass platelet transfusion on postoperative platelet count. Transfusion of plasma and cryoprecipitate were ordered without knowledge of intraoperative lab values. Mann-Whitney U test was used to determine significant difference between groups. This study was approved by the IRB.

Conclusions
In this retrospective study, we show that intraoperative cryoprecipitate transfusion has a negligible effect on postoperative fibrinogen levels. This is likely not a result of dilution from ongoing transfusion, since platelet counts rose significantly as a result of platelet transfusion. The ineffectiveness of cryoprecipitate in this setting may indicate an ongoing consumptive state.

Mentor / Department
Brian S. Donahue Pediatric Cardiac Anesthesiology
RETROSPECTIVE ANALYSIS OF THE ROLE OF AGE AND SUTURE SITE ON REPEAT CRANIOFACIAL RECONSTRUCTION FOR NON-SYNDROMIC CRANIOSYNOSTOSIS: A 10-YEAR EXPERIENCE.

Javier Cifuentes-Patient Oriented Research

Background Problem
Treatment for syndromic and non-syndromic craniosynostosis remains primarily surgical. However, complication rates and re-operation rates vary. Previous studies have reported outcomes of surgical treatment for craniosynostosis, yet much remains to be elucidated about factors contributing to the need for re-operation.

Objectives
The purpose of this study was to critically assess long-term outcomes for craniofacial reconstruction for non-syndromic craniosynostosis with a focus on age of initial operation and suture site.

Materials and Methods
A retrospective review was conducted on all non-syndromic cases of craniosynostosis from 2000 through 2009. Demographic information, surgical factors, post-operative complications, and need for re-operation were assessed. Logistic regression and bivariate analyses were performed.

Conclusions
We report our objective outcome findings. We report our considerations for surgical management of craniosynostosis particularly with respect to age at initial surgery, race, and suture site. The results suggest the presence of a racial difference in surgical outcome, although this may be influenced by a variety of other factors. The influence of other factors needs to be further analyzed so that a more precise protocol can be suggested.

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VITREOUS METABOLOMIC PROFILING IN PATIENTS WITH DIABETIC RETINOPATHY

Allison Ferreira—Patient Oriented Research

Background Problem
Diabetic retinopathy is a microvascular complication of diabetes mellitus (DM). It is the primary cause of legal blindness among adults aged 20-74 in the United States. In the United States, approximately 26 million people live with diabetes,1 and the number of adults with DR is projected to triple to 16 million by the year 2050. At a clinical population level, the risk of retinopathy is increased by poor glycemic control, increased blood pressure, and elevated lipids. However, at the individual level, it is not yet possible to predict who will develop DR.

Objectives
The objective of this project is to quantitatively examine the physiologic microenvironment that characterizes DR. We are testing the central hypothesis that a collection of specific metabolic factors influences an individual’s risk for developing DR. The specific aim of this project is to identify the metabolic profiles associated with risk of retinopathy among type 2 diabetics in serum and vitreous. We have processed and analyzed previously-ascertained serum and undiluted vitreous samples from 39 DR patients and 41 non-diabetic controls at the time of vitrectomy surgery. We have determined metabolomic profiles for both serum and vitreous samples for all patients using DC-FTMS. Our goal is to identify specific collections of metabolites and pathways that are associated with DR.

Materials and Methods
Metabolomic analysis with liquid chromatography-Fourier-transform mass spectrometry was performed on frozen vitreous samples collected from 19 PDR patients and 44 non-diabetic controls at the Vanderbilt Eye Institute. Data were collected by a Thermo LTQ-Orbitrap Velos mass spectrometer from mass/charge ratio (m/z) 85 to 2000 over 20 minutes. Peak extraction and quantification of ion intensities were performed by an adaptive processing software package (apLCMS). Individual features were matched to the Madison Metabolomics Consortium and Metlin metabolomics databases. A Benjamini and Hochberg False Discovery Rate (FDR) of 0.05 was employed to account for multiple testing. Principle component analysis and orthogonal partial least squares discriminatory analysis were performed to isolate metabolic features that differentiate PDR patients from controls.

Conclusions
These data can be used to design metabolomic analyses targeting metabolic pathways that are differentially regulated in patients with proliferative diabetic retinopathy. Identifying biochemical profiles that are characteristic of diabetics who develop DR will yield new insights into the underlying pathophysiology of DR, pointing to new directions for therapies to treat or prevent DR-related vision loss.

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Mentor / Department
Milam A. Brantley Jr., M.D., Ph.D., Ophthalmology
ALTERED ACYL TO DESACYL GHRELIN RATIO EARLY AFTER ROUX-EN-Y GASTRIC BYPASS SURGERY

Anna Garcia - Patient Oriented Research

Background Problem
Patients undergoing Roux-en-Y gastric bypass (RYGB) surgery demonstrate increased insulin sensitivity within 2-7 days of the procedure, before substantial weight loss has occurred. Additionally, ~30% of patients discontinue their anti-diabetes medication upon hospital discharge. Mechanisms for such improvements are not well-defined. Ghrelin is an orexigenic hormone produced predominately by P/D1 cells of the fundic stomach that regulates food intake and energy balance. Recent studies indicate that acyl ghrelin (AG) induces insulin resistance and desacyl ghrelin (DAG) may counteract the negative effects of AG on insulin sensitivity. AG has an octanoyl group at Ser-3 and is a ligand for GHS-R1a, while DAG has no known receptor.

Objectives
We hypothesize that a decrease in AG and an altered ratio of AG to DAG occurs after RYGB and contributes to early improvements in insulin sensitivity.

Materials and Methods
To test this hypothesis, fasting blood samples were collected from 16 patients on the day of RYGB surgery and at the postoperative visit to the surgical weight loss clinic (7-10 days later) for quantification of AG, DAG, insulin, and glucose levels. A serine protease inhibitor, Pefabloc SC, was added to the blood sample for AG measurement to ensure stability of the octanoyl group. Plasma insulin and glucose levels were measured to estimate insulin sensitivity by HOMA-IR.

Conclusions
This decrease in the form of ghrelin known to exert the hormone’s appetite stimulating and insulin desensitizing effects may contribute to the rapid improvement in satiety and insulin sensitivity following RYGB.

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Anna Garcia, BSPH; Joseph Antoun, PhD; Ronald H. Clements, MD; Brandon Williams, MD; Pamela Marks-Shulman MS, RD, CCRP; Naji Abumrad, MD; and Robyn Tamboli, PhD; Vanderbilt University School of Medicine, Department of Surgery.
PREDICTING THE RECOVERY OF COMPLETE ATRIOVENTRICULAR BLOCK FOLLOWING CONGENITAL HEART DISEASE SURGERY

Nina Hu-Patient Oriented Research

Background Problem
Complete atrioventricular block (CAVB) can complicate congenital heart disease surgery, and current guidelines recommend permanent pacemaker implantation if AV block is not expected to recover or persists for at least 7 days postoperatively.

Objectives
This study analyzed patients with CAVB following congenital heart surgery to determine factors that predict whether patients will recover conduction or require a permanent pacemaker.

Materials and Methods
Pediatric patients who underwent congenital heart surgery at Vanderbilt between September 2007 and October 2011 were prospectively enrolled. Patients who experienced postoperative CAVB were assessed daily for intermittent recovery of conduction until they demonstrated either 1:1 AV conduction recovery or permanent pacemaker implantation.

Conclusions
A slight majority of patients with CAVB following congenital heart surgery recover full AV conduction, with intermittent conduction observed in most cases by POD 2. There is an association between early postoperative presence of JET and full recovery of AV conduction.

Mentor / Department
Prince Kannankeril, Department of Pediatric Critical Care Medicine
OPTIMAL LEAD LOCATION FOR DEEP BRAIN STIMULATION TREATMENT OF POST-TRAUMATIC TREMOR

Neil Issar—Patient Oriented Research

Background Problem
Deep brain stimulation (DBS) surgery has emerged as an important treatment modality for patients with post-traumatic tremor. However, ambiguity regarding the optimal lead location persists. Most cases support the ventral intermediate (VIM) thalamic nucleus as the optimal target, but there is evidence to suggest that DBS of the zona incerta (ZI), the nucleus ventral oralis anterior/posterior (VOA/VOP), and/or a combination of these targets may provide superior tremor control.

Objectives
We reviewed the cases of six patients with disabling post-traumatic tremor treated with DBS of the VIM, ZI, and globus pallidus internus (GPi) in order to identify the optimal lead location for DBS treatment of post-traumatic tremor.

Materials and Methods
We performed a retrospective analysis of all patients with post-traumatic tremor treated by the Vanderbilt DBS group in the past four years. We reviewed all available records of these patients’ trauma histories, presurgical assessments, surgical procedures, and subsequent tremor responses. The final patient in this group had been treated initially with VIM DBS in 2000 but suffered ineffective long-term tremor control. His subsequent surgery, performed in 2011, allows direct comparison of VIM and ZI DBS therapy in a single subject.

Conclusions
Unilateral or bilateral Vim DBS and bilateral GPi DBS are effective and safe treatment modalities for intractable post-traumatic tremor. Stimulation of the ZI may have some advantages over the VIM target in this population.

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Mentor / Department
Joseph S. Neimat, M.D., M.S. (Department of Neurosurgery)
MERCURY IN TOTAL PARENTERAL NUTRITION: A POTENTIAL SOURCE OF EXPOSURE IN PRETERM INFANTS

Karola Jering - Patient Oriented Research

Background Problem
Mercury is a ubiquitous pollutant in the environment with well-established neurotoxic effects. Preterm infants are more vulnerable to environmental neurotoxic agents than children or adults since they have an immature and highly permeable blood-brain barrier and since they are in a critical window of brain development. Thus exposure to mercury at levels present in the general population might have deleterious effects on neurodevelopment in this sensitive patient population.

Objectives
We seek to evaluate the pre- and postnatal exposure to Hg in preterm infants, admitted to the neonatal intensive care unit (NICU) at Vanderbilt (2010-11). We initially hypothesized that Hg levels in preterm infants would be related to maternal levels. We further postulated that should infants be exposed to Hg through breast-milk, their Hg levels would increase.

Materials and Methods
This study is a prospective evaluation of pre- and postnatal mercury (Hg) exposure in 60 preterm infants with gestational age of <30 weeks and birth weight <1500g, cared for at Vanderbilt NICU during 2010-2011. Infants with prenatally diagnosed genetic or metabolic diseases were excluded from this study. Mercury levels were quantified from maternal hair samples and infant urine samples using high-resolution inductively coupled plasma mass spectrometry and were normalized against urine creatinine. Infant urine samples were collected within the first week of life and at post-conceptual age of 34-36 weeks. Additionally, we collected information on maternal demographics, the infants’ gestational age, birth weight, the length of their NICU stay, the number of days spent on a ventilator, on supplemental oxygen and on total parenteral nutrition (TPN) as well as their primary source of nutrition in the NICU.

Conclusions
Preterm infants at the Vanderbilt NICU showed increasing levels of urine Hg over the course of their NICU stay, correlated to the time spent receiving TPN. The infants might be exposed to Hg contamination, possibly associated with the TPN preparation process. Estimated body burden in a 1,000g infant receiving two weeks of TPN was 16ng/mL, well below the threshold for toxicity in adults (200ng/mL). Nevertheless, this exposure to Hg is concerning given the infants’ high vulnerability to neurotoxic agents.

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**Mentor / Department**
Dr. Nathalie Maître, Neonatology
SKIN BIOPSIES AS A PREDICTOR FOR GRAFT VERSUS HOST DISEASE IN PEDIATRIC STEM CELL TRANSPLANT PATIENTS

Charissa Kahue- Patient Oriented Research

Background Problem
Graft-versus-host disease (GVHD) is an important complication responsible for significant morbidity and mortality in stem cell transplant (SCT) patients. In SCT, the donor’s allograft (the ‘graft’) replaces the patient’s (the ‘host’) immune system. The graft can later interpret the host’s normal tissues as foreign, leading to an immunologic attack against host tissues including skin, liver, and gastrointestinal mucosa. GVHD affecting the skin manifests as rashes and blisters in the acute phase (<100 days post-transplant) and as lichenoid/sclerodermatous changes in the chronic phase (>100 days). Pathology grading of skin biopsies for GVHD ranges from grades I (mildest, with rash) to IV (most severe, with necrosis and bullae formation). Vanderbilt Children’s Hospital (VCH) has transplanted 371 pediatric patients since 2001. SCT patients receive extensive post-procedure follow-up care and monitoring, which for some patients includes skin punch biopsies at 100 days post-transplant to screen for findings indicative of GVHD. It is not known whether a negative biopsy has predictive value of future GVHD burden.

Objectives
We sought to determine if there is an association between GVHD and skin pathology at day 100 post-SCT.

Materials and Methods
We conducted a retrospective chart review using the Vanderbilt StarPanel system and examined the medical records and skin biopsy pathology reports of pediatric patients who underwent SCT at VCH from 2001-2011.

Conclusions
We are continuing to investigate the future utility of skin biopsies as clinical predictors of GVHD. Timely identification and reduction of risk factors can alleviate disease burden and potentially improve patient outcomes. Since screening biopsies are expensive and most patients have clinical symptoms of GVHD at the time of biopsy, we will examine the true utility of performing them as protocol measures.

Mentor / Department
Jennifer Domm, MD Department of Pediatric Hematology-Oncology

Vanderbilt University School of Medicine
Emphasis Program-Forum VII-May 2012
IN VIVO FLUORESCENCE AND DIFFUSE REFLECTANCE SPECTROSCOPY IN STEREOTACTIC BRAIN BIOPSIES

Harish Krishnamoorthi—Patient Oriented Research

Background Problem
Stereotactic brain biopsies are critical for sampling deep brain tumors to determine pathology, grade, as well as location of the tumor core and margins. Guided by CT and MRI, a needle is inserted through a small pore in the cranium and driven to the tumor location, where a biopsy is taken. However, due to imaging resolution limits, imprecise guidance can lead to repeat biopsies and incorrect samples.

Objectives
A technique that can function alongside the stereotactic biopsy needle for optimal guidance would reduce the sampling errors of the process. Optical spectroscopy, specifically diffuse reflectance and fluorescence spectroscopy, is an emerging imaging modality with the ability to provide biochemical data about various tissues, particularly in differentiating between normal and abnormal lesions. Here, we show that fluorescence and diffuse reflectance can be used to guide stereotactic brain biopsies and provide valuable information about tumor margins by acquiring data at possible biopsy locations before tissue is removed.

Materials and Methods
An optical probe designed to fit in the biopsy needle cannula was guided to the presumed tumor core, where fluorescence and diffuse reflectance measurements were made. The probe was pulled out 1 mm and optical measurements were re-taken. This was repeated until optical data was sampled in presumed normal white matter. After processing and normalizing, tumor spectra were compared with normal brain tissue spectra.

Conclusions
With such results, optical spectroscopy has the potential to aid stereotactic brain biopsies by precisely guiding the needle to the tumor center and providing enhanced information about the tumor margins.

Mentor / Department
Anita Mahadevan-Jansen, Department of Biomedical Engineering
DECREASING PACKED RED BLOOD CELL UTILIZATION WITH COMPUTERIZED PROVIDER ORDER ENTRY AND DECISION SUPPORT IN A TERTIARY CARE CHILDREN’S HOSPITAL

Paula Marincola—Patient Oriented Research

Background Problem
Packed red blood cell (PRBC) transfusion has been associated with increased morbidity and mortality in a variety of perioperative and critical care settings [1-4]. Blood product transfusion is independently associated with increased rates of renal failure, prolonged ventilatory support, serious infection, ischemic cardiac complications, neurologic events, and mortality in the adult critical care setting [4,5]. The association with negative adverse events is dose-dependent with a proportional increase in adverse events for every extra unit of PRBCs transfused [4,5]. Studies in children indicate that more restrictive blood transfusion strategies do not negatively affect outcomes compared to liberal transfusion strategies, as measured by rate of multiple organ dysfunction syndrome, intensive care length of stay, or 28-day mortality [3,7]. In hemodynamically stable, critically ill children without cardiovascular disease, a hemoglobin threshold of 7g/dL for PRBC transfusion has been shown to decrease transfusion requirements without an increase in adverse events [8,9]. PRBC transfusion is an important risk factor for increased duration of mechanical ventilation and mortality in pediatric patients undergoing reparative cardiac surgery [10]. Decision support with Computerized Provider Order Entry (CPOE) has been shown to reduce PRBC utilization in pediatric patients, though prior work excluded patients with congenital cardiac disease [6].

Objectives
- To achieve consensus amongst inpatient groups with the highest rates of PRBC utilization and develop an evidence-based standard for PRBC transfusion. - To improve adherence to evidence-based practice standards for PRBC transfusion in the setting of symptomatic anemia. - To develop and implement a decision support algorithm within the CPOE system which accounts for both a patient’s recent laboratory results and his/her status in specialized patient populations (e.g. cyanotic congenital cardiac patients, preterm neonatal patients). - To significantly reduce PRBC transfusions which do not meet evidence-based practice standards. - To significantly reduce overall PRBC utilization per patient discharged from Monroe Carell Jr. Children’s Hospital at Vanderbilt (MCJCHV).

Materials and Methods
- An evidence-based practice standard was developed by the attending physician faculty within the Pediatric Intensive Care Unit at MCJCHV. This standard was then adapted to incorporate patients cared for by the Hematology-Oncology and Neonatology services. - A decision support system within the CPOE of WizOrder was designed to remind practitioners of evidence-based guidelines for transfusion medicine and was implemented in September 2011. - All patients admitted to MCJCHV during the study period were included within this quality improvement project. - Education sessions for attending physicians, residents and nursing staff within
MCJCHV were provided concurrently with introduction of CPOE-based decision support. Additionally, mousepads highlighting the PRBC transfusion guidelines were introduced in the PICU. Data was collected on the following utilization parameters before and after the modified CPOE algorithm was implemented: (1) Monthly PRBC units transfused per discharge for symptomatic anemia, (2) Monthly PRBC units transfused per discharge for all indications, (3) Determination of adherence with transfusion protocol for each PRBC transfusion ordered based on consensus transfusion algorithm, and (4) Total monthly discharges from MCJCHV.

Conclusions
- Decision support increases adherence to evidence-based PRBC transfusion guidelines in a tertiary care children’s hospital. - PRBC utilization is reduced in pediatric patients using decision support and CPOE. - Future efforts to improve PRBC transfusion practice will focus on the effectiveness of monthly provider feedback regarding transfusion practice, optimization of decision support algorithms and the clinical outcomes associated with reduced PRBC utilization in specific patient sub-populations.

Mentor / Department
Gina Whitney, MD Department of Pediatric Cardiac Anesthesiology, Pediatric Critical Care Medicine Center for Research in Systems Safety
INCIDENCE, RISK FACTORS, AND OUTCOMES FOR HYPOGAMMAGLOBULINEMIA IN PEDIATRIC PATIENTS FOLLOWING STEM CELL TRANSPLANT

Elliot Min - Patient Oriented Research

Background Problem
Hypogammaglobulinemia is a type of primary immune deficiency characterized by insufficient immunoglobulin levels, particularly IgG. Patients with hypogammaglobulinemia are more prone to recurrent infections that can potentially be fatal. In the setting of pediatric stem cell transplant, patients treated for a variety of malignant and non-malignant diseases with both allogeneic and autologous SCT have been shown to have decreased IgG levels following transplant.

Objectives
The objective of this study is to determine which risk factors are linked to post-transplant hypogammaglobulinemia in pediatric patients, as well as the outcomes of these patients.

Materials and Methods
IgG levels are measured every 2 weeks following SCT for the first 100 days and then monthly thereafter. We collected data on 177 pediatric patients receiving allogeneic SCT from September 1999 to March 2011. Hypogammaglobulinemia was defined as IgG<500 mg/dL. Detailed patient and outcome characteristics were recorded.

Conclusions
Hypogammaglobulinemia is a common complication of SCT associated with a number of factors including age, malignant disease, type of SCT, and GVHD. Close monitoring of IgG level should be considered in the patients at highest risk.

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Mentor / Department
Dr. Haydar Frangoul, Pediatric Hematology/Oncology
WHITE MATTER ANISOTROPY AND SENSORY SEEKING IN AUTISM SPECTRUM DISORDER: A DTI STUDY

Abbie Necessary—Patient Oriented Research

Background Problem
Autism Spectrum Disorder is a pervasive developmental disorder defined in DSM-IV by deficiencies in communication, social relatedness, and restricted interests and behaviors. The CDC now estimates its prevalence to be between 1/80 and 1/240, with a 3-4 fold higher rate among boys than girls. Although not included in the diagnostic criteria, children with ASD often exhibit altered sensory behaviors, including hyposensitivity, hypersensitivity, and/or sensation seeking. An underlying mechanism for these abnormal sensory profiles may be the altered integrity of thalamocortical tracts carrying sensory information. An fMRI study by Mizuno et al (2006) showed increased thalamocortical connectivity among children with ASD as compared with age-matched controls. Furthermore, a DTI study by Cheng et al (2010) demonstrated significantly decreased fractional anisotropy in the posterior limb of the internal capsule of ASD patients as compared with controls.

Objectives
The objective of this study was to determine if a correlation exists between sensory seeking behavior and thalamocortical anisotropy in children with Autism Spectrum Disorder, as determined by diffusion tensor imaging.

Materials and Methods
Diffusion Tensor Imaging and T1W MRI was performed on 15 children with ASD between ages 5 and 7. Sensory measures were obtained through Sensory Experiences Questionnaire (SEQ) and consensus-coded Sensory Processing Assessment (SPA) and Tactile Defensiveness and Discrimination Test (TDDT.)

Conclusions
The Mean ADC is an indicator of mean diffusion of water molecules along a fiber tract; thus as ADC increases, integrity of the white matter tracts decreases. The data indicate a pattern such that as sensory seeking behavior increases, the integrity of relevant white matter tracts increases.

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Mentor / Department
Dr. Carissa Cascio, Department of Psychiatry

Vanderbilt University School of Medicine
Emphasis Program-Forum VII-May 2012
FMRI OF REPETITION TASK ASSOCIATED WITH WORD LEARNING IN SKILLED YOUNG ADULT READERS

Rachna Patel, Brittney Pryor, Nicole Roberts - Patient Oriented Research

Background Problem
Repeated reading of words is proposed to approximate the cognitive task of word learning. In order to examine patterns of word learning in adults, we exposed them to repetitions of words and pronounceable pseudo-words. Preliminary data analyzed in the context of neurobiological correlates obtained from fMRI imaging data, are reported.

Objectives
This study utilizes a Word/Pseudo-word repetition task with fMRI imaging to determine whether repeated reading is associated with predictable changes in brain activation in young adult readers. It lays groundwork for testing a hypothesized non-linear pattern of brain activation associated with learning words through repetition.

Materials and Methods
A total of 19 adult (18-24 years) readers (Test of Word Reading Efficiency (TOWRE) SS) completed the repetition task. Ten were Skilled readers with real word accuracy > 63% and nine were Less Skilled readers with real word accuracy < 40%. Stimuli were presented four times each in pseudo-randomized order. Participants pressed a right or left-hand button to indicate whether each stimulus was a Word or Pseudo-word. SPSS analysis assessed reaction time (RT) during the fMRI repetition task to test for repetition (R1, R2, R3, R4) by stimulus type (Words vs. Pseudo-words) by group (Skilled vs. Less Skilled) effects. SPM8 assessed differential fMRI activation between R1 and R4 (Words and Pseudo-words separately) covarying TOWRE.

Conclusions
These findings suggest that the repetition task causes more activation in specific regions in the Skilled readers than in the Less Skilled readers. This could be because the Skilled readers are better at recognizing connections between known words and pseudowords. The addition of neuroimaging to the behavioral task may provide more insight into differential performance between Skilled and Less Skilled young adult readers.

Mentor / Department
Sheryl Rimrodt, Kennedy Center and Peabody College
DIAGNOSING POSTURAL TACHYCARDIA SYNDROME: COMPARISON OF TILT TEST VERSUS STANDING HEMODYNAMICS

Walker B Plash—Patient Oriented Research

Background Problem
Postural tachycardia syndrome (POTS) is characterized by increased heart rate (ΔHR) of ≥30 bpm with symptoms related to upright posture. Active stand (STAND) and passive head-up tilt (TILT) produce varying physiologic responses.

Objectives
We hypothesized these different responses would cause variation in the achievement of the POTS HR increase criterion.

Materials and Methods
Patients with POTS (n=15) and healthy controls (n=34) underwent 30 min of TILT and STAND testing. ΔHR values were analyzed at 5 min intervals. Receiver Operating Characteristics analysis was performed to determine optimal cut point values of ΔHR for both TILT and STAND.

Conclusions
Orthostatic tachycardia was similar within 10 min for TILT and STAND, but was greater for TILT (with lower specificity for POTS diagnosis) than STAND at 30 min. The 30 bpm ΔHR criterion is suitable at 10 min, but different ΔHR values are needed if extending the TILT.

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Mentor / Department
Satish Raj, Division of Clinical Pharmacology, Departments of Medicine and Pharmacology
FMRI OF WORD REPETITION TASK BASED ON REACTION TIME

Brittney Pryor, Nicole Roberts, Rachna Patel-Patient Oriented Research

Background Problem
Repeated reading of words is proposed to approximate the cognitive task of word learning (Grill-Spector et al., 2006). Using a computerized Word/Pseudoword repetition task that is associated with behavioral evidence of differential word and pseudoword learning, we examine patterns of brain activation change obtained from fMRI data during the task and investigate correlations with behavioral evidence of word learning in young adult readers.

Objectives
To examine the association between the reaction time performance on a Word/Pseudoword repetition task and changes in brain activation in young adult readers.

Materials and Methods
Participants completed a word/pseudoword differentiation task in an MRI scanner. Data from 28 young adults (ages 18-24 years) who showed >75% accuracy on the fMRI task was assessed. SPSS repeated measures analysis assessed reaction time (RT) by stimulus type (word vs. pseudoword) and SPM8 repeated measures ANOVA assessed fMRI activation (words and pseudowords separately). Reaction times were found to vary most significantly for pseudowords encountered during the first mission. FMRI data during that mission was analyzed to assess the brain regions that showed activation as a factor of reaction time.

Conclusions
Patterns of activation are different for words and pseudowords. Overall, when processing pseudowords, fast responders use more executive function areas instead of posterior reading-related areas (associated with skilled reading).

Mentor / Department
Sheryl Rimrodt, MD, Department of Developmental Medicine
REPETITION TASK AS A PROXY FOR WORD LEARNING IN YOUNG ADULTS

Nicole Roberts - Patient Oriented Research

Background Problem
Repeated word reading is proposed to approximate word learning.

Objectives
1) Confirm that this task approximates word learning
2) Observe the effect of reading ability on performance of this task

Materials and Methods
28 native English speakers (18-24 yr) performed this task with word accuracy >75%. The Test of Word Reading Efficiency (TOWRE) was used to divide participants into Skilled Readers (SR; n=21, SS=92-117) and Less Skilled Readers (LSR; n=7, SS=77-89). Words or pseudowords were presented individually, in a pseudorandomized order, once per repetition for four repetitions (R1-R4). Participants indicated by button press whether the word was real. A Generalized Linear Model (GLM) analysis assessed mean reaction time (MRT) using TOWRE standard score (SS) as a covariate for all participants, then comparing LSR and SR.

Conclusions
The significant MRT decreases overall and for pseudowords suggest that this task approximates word learning. Pseudowords were intended to minimize the effects of word familiarity; the increased MRT for pseudowords over words and the more significant pseudoword MRT decrease imply success. For pseudowords, the similar pattern of MRT decrease for both groups suggests a similar pattern of word learning, however, the SR had faster MRTs, implying that reading ability was important for performance. This task has been used in fMRI to assess brain activation changes associated with word learning.

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Mentor / Department
Sheryl L Rimrodt, Department of Pediatrics, Kennedy Center, Peabody College
VISUALLY EVOKED POTENTIAL DETECTION OF AMBLYOPIA IN THE CLINIC

Sina Salehi Omran - Patient Oriented Research

Background Problem
Amblyopia, a neurological visual deficit in one eye, is a common condition in the pediatric ophthalmology setting. Preverbal children with amblyopia risk factors can be challenging to manage, as they may have a fixation preference but may or may not have amblyopia.

Objectives
We developed a user- and patient-friendly test using visually evoked potentials to aide in the diagnosis of amblyopia in such children.

Materials and Methods
We tested 33 normal children and 43 amblyopic children (age 3-12 years) using the Diopsys NOVA-TR system. A checkerboard pattern reversal visual evoked response was produced at 2 Hz for each of 5 spatial frequencies. Stimuli were presented for 10 seconds (20 reversals) and the entire test typically took less than five minutes. The relative diminution of P100 amplitude between the eyes, and the absolute prolongation of P100 latency were compared for each spatial frequency.

Conclusions
A pattern-reversal visual evoked response at 5 spatial frequencies can be used to correctly identify children with amblyopia, without misclassifying many non-amblyopic individuals. This is important since fixation preference testing can be unreliable in detecting amblyopia in preverbal children. The development of a clinically useful evoked potential test will help pediatric ophthalmologists diagnose and manage amblyopia in children of this age group.

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DISORDERS OF SENSORY PERCEPTION IN PRETERM INFANTS CORRELATE WITH LOWER GESTATIONAL AGE AT BIRTH AND AVERSELY AFFECT NEURODEVELOPMENT IN INFANTS

Jessica Solomon - Patient Oriented Research

Background Problem
Preterm infants experience multiple disruptions to brain development. Abnormal sensory inputs in the neonatal intensive care unit (NICU) could affect sensory perception and learning in these infants, which is known to result in altered neurodevelopment in term infants.

Objectives
We hypothesized that we could characterize the frequency and type of sensory perception disorders in preterm infants, and that deficits would correlate with neurodevelopment during the first year of life.

Materials and Methods
Prospective study of 100 infants 6-18 months, with birth weight <1500g (median gestational age at birth (GA) 28 weeks, range 23-34) without blindness or deafness followed in Vanderbilt's NICU follow-up clinic. Examiners blinded to the subject's NICU course and GA assessed all infants using the Test of Sensory Function in Infants (TSFI). Clinic personnel performed the Developmental Assessment of Young Children (DAYC) and parents completed the Infant Toddler Sensory Profile (ITSP).

Conclusions
Preterm infants have a high prevalence of sensory perception deficits, which adversely affect their motor and cognitive development in infancy. Therefore, it is essential to identify and further analyze the factors associated with the NICU experience that affect sensory function and may contribute to poor neurodevelopmental outcomes.

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Mentor / Department
Nathalie Maitre, MD, PhD, Department of Neonatology
FACTORS ASSOCIATED WITH LIMITED TRANSTHORACIC ECHOCARDIOGRAPHY IN TRAUMA PATIENTS

Ariana Tabing—Patient Oriented Research

Background Problem
Injured patients frequently have significant hemodynamic derangements requiring invasive monitoring to assess volume status and optimize resuscitation. While echocardiography is increasingly utilized for hemodynamic assessment, the success rate is frequently limited in trauma patients.

Objectives
We hypothesized that identification of patient-specific risk factors is predictive of unsuccessful TTE in trauma patients.

Materials and Methods
Retrospective review of all TTE performed in trauma patients in the ICU from 2006-2011 by credentialed cardiac sonographers at an academic level-one trauma center. Success of TTE was judged by reported image quality (good/adequate, fair, and difficult/limited). Patient risk factors assessed were gender, BMI, intubation status, tube thoracostomy status, and abbreviated injury score specific to chest and abdomen. Descriptive statistics, univariate tests, and a proportional odds regression model. Multivariate analysis included BMI, intubation status, and thoracostomy status. Primary endpoint was reported TTE quality; suboptimal was defined as “fair” or “difficult/limited”.

Conclusions
TTE is of limited success in obese trauma patients and those whose thoracic injuries require placement of thoracostomy. While echocardiography may be useful in hemodynamic assessment of ICU patients, the success of TTE is marginal in this population. This represents a potential case of need for alternative methods of echocardiographic hemodynamic assessment in trauma patients.

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none

Mentor / Department
Dr. Oliver Gunter
CLINICAL CHARACTERISTICS OF NRAS MUTANT MELANOMA

Charles Terry - Patient Oriented Research

Background Problem
‘Driver mutations’ in the NRAS oncogene reportedly define a subset of melanomas and may represent a novel therapeutic target in this disease.

Objectives
We examined clinical characteristics of patients with melanoma harboring NRAS mutations.

Materials and Methods
We reviewed data from patients with melanoma seen at the Vanderbilt Ingram Cancer Center (VICC) whose tumors underwent mutational profiling for 43 recurrent mutations in 6 genes using the SNaPShot melanoma panel. We collected patient characteristics including age, gender, location of primary tumor, tumor stage at diagnosis, sites of metastatic disease, histologic features of the tumor, and treatment history.

Conclusions
Mutant NRAS defines a clinically relevant molecular subset of melanoma which occurs more commonly in CSD and non-CSD primary sites. Our on-going analyses will focus on determining progression free and overall survival in patients with metastatic disease treated with various chemo-, immuno-, and/or targeted therapies.

Mentor / Department
William Pao, Department of Medicine
RISK FACTORS ASSOCIATED WITH SICKLE CELL RETINOPATHY.

Uzoamaka Ugochukwu - Patient Oriented Research

Background Problem
Sickle cell retinopathy (SCR) is a major sight-threatening complication of sickle cell disease (SCD), an autosomal recessive hemoglobin disorder. Incidence of retinopathy differs among the SCD variants, as high as 70% in SC-disease, despite a mild clinical course. The more common and severe genotype, SS has a lower prevalence of SCR. Recently, SCD has been classified into distinct sub-phenotypes. A vasculopathy sub-phenotype, linked to intensity of hemolysis, comprising pulmonary hypertension, leg ulceration and stroke and a viscosity-vaso-occlusive sub-phenotype involving acute painful episode, acute chest syndrome and osteonecrosis. The exact mechanism underlying for the varied ocular manifestations in SCD is unknown. Baseline hemoglobin (Hgb), high MCV in males and low fetal hemoglobin (HgbF) have been associated with proliferative sickle cell retinopathy.

Objectives
The objective of the study is to investigate risk factors associated with sickle cell retinopathy based on the selected clinical variables that reflect sub-phenotypes and known markers.

Materials and Methods
A retrospective analysis was performed on records of 161 patients from Vanderbilt Pediatric and Adult SCD clinics. Patients with ocular exams at the Vanderbilt Eye Institute were selected. The genotypes of patients included in the study are SS (72% of the patients), SC (14%), S beta+ thalassemia (7%) and S beta0 thalassemia (7%). Data extracted included demographics, type of retinopathy, treatment, hemoglobin evaluations, and other laboratory variable. Descriptive statistics was performed to analyze data.

Conclusions
Further studies are needed to better understand underlying pathobiologic mechanism of ocular manifestations of SCD is required.

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Mentor / Department
Adetola Kassim, MD, Hematology/Oncology
THE EFFECT OF ORGAN PRESERVATION SOLUTION ON DONOR LIVER PROTEIN EXPRESSION

Prakash Vempati - Patient Oriented Research

Background Problem
The shortage of available donor livers has led to extending the donor criteria (ECD) and improved preservation protocols. There are no biomarkers of metabolic function defining the extended criteria liver or the effect of organ preservation solution. Characterization of post-translationally modified proteins may help to better define the ECD and understand the biochemical requirements of organ preservation.

Objectives
To identify differential protein expression in donor livers preserved with HTK vs UW solutions and its relationship to patient outcomes following liver transplantation.

Materials and Methods
Clinical information was collated for 89 adult donor-recipient pairs between 2008-2010. Donors were stratified into HTK (N=46) and UW (N=43) preserved donor liver tissue groups. Quantitative protein profiling was performed with MUDPIT using HPLC-ESI-MS/MS, and Normalized Spectral Abundance Factor (NSAF) differences in protein expression patterns were analyzed using Wilcoxon rank sum tests. The False Discover Rate method accounted for multiple class comparisons.

Conclusions
Numerous proteins show significant expression differences between livers perfused with UW and HTK preservation solutions. Proteomic profiling may be an effective method to simultaneously assess numerous aspects of liver metabolism.

Mentor / Department
Dr. Burnett S. Kelly, Surgery
SORT-1 IS A NOVEL GENETIC PREDICTOR OF ATORVASTATIN POTENCY (ED50)


**Patient Oriented Research**

**Background Problem**
Despite their efficacy, more than 50% of patients using HMG-CoA-reductase inhibitors (statins) still experience cardiovascular events. Many of these residual events can be attributed to variability in LDL-cholesterol (LDL-C) response to statin therapy. Genetic variability among individuals contributes to this variability.

**Objectives**
While there is great interest in defining the genetic architecture underlying statin response, large multicenter trials have failed to yield genetic determinants of LDL-C lowering by statins. We used a more rigorous phenotyping approach and conducted a genotype-phenotype association study using two large clinical practice-based cohorts. Our approach reduces misclassification bias encountered in large single-dose trials, and uses “real world” clinical data to determine the genetic contributors to LDL-C lowering by atorvastatin and simvastatin, the most frequently prescribed statins in the US.

**Materials and Methods**
Natural Language Processing (NLP) was used to extract accurate drug exposure histories from comprehensive electronic medical records for patients exposed to multiple statin doses during routine care. Drug exposure was linked to clinical lipid data, and nonlinear mixed effects modeling was used to construct dose response curves and derive potency (ED50) and maximal lipid lowering efficacy (Emax) for atorvastatin and simvastatin. Candidate gene loci (144 variants) from the Global Lipids Consortium were genotyped using a bead array, and each variant was tested for association with statin dose response.

**Conclusions**
SORT1 is a novel predictor of statin potency.

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**Mentor / Department**
Russell A. Wilke, MD, PhD., F.A.C.P. Department of Medicine Division of Clinical Pharmacology
CHANGES OVER TIME IN THE RECRUITMENT OF ADDITIONAL BRAIN REGIONS TO ACCOMPLISH SIMPLE MOTOR TASKS IN CHRONIC ALCOHOL-DEPENDENT PATIENTS

Jonathan Wolfe - Patient Oriented Research

Background Problem
Patients with chronic alcohol dependence exhibit neurocognitive impairments attributed to alcohol induced damage to frontocerebellar tracts. Deficits are typically found in complex task performance, whereas simple task performance is preserved due to various compensatory changes. Such changes involve recruiting additional brain regions during performance of motor tasks. Recruitment of the right parietal postcentral gyrus in alcoholics has been previously demonstrated during maximal self-paced finger tapping tasks.

Objectives
We were interested in determining how brain activation changes in alcoholic patients after cessation of alcohol abuse.

Materials and Methods
We compared brain activation patterns in the right parietal postcentral gyrus during a maximal self-paced finger tapping task in 10 pairs of right-hand dominant, age and gender matched, severe, uncomplicated alcoholics and normal controls at three time periods. The time periods were approximately three days, three weeks, and three months after cessation of alcohol consumption.

Conclusions
Activation in the right postcentral gyrus is representative of the dysfunctional activation seen in alcoholics during completion of simple motor tasks. The decrease in the activation of this region between each time point can be used as a proxy for the restoration normal brain activation patterns in alcoholics after cessation from alcohol abuse. The general trend of decreased activation between three days and three weeks paired with a definitive trend of decreased activation between three weeks and three months suggests that the timeline for recovery is around the order of three months.

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