College of Public Health Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#1 Abstract Title: **Drug Overdose Deaths by Industry and Occupation in Kentucky, 2011**

Concentration: Preventive Medicine

Author(s): T.L. Bunn, Kentucky Injury Prevention and Research Center, College of Public Health, U of Kentucky
A.M. Bush, College of Public Health, U of Kentucky
S. Slavova, Kentucky Injury Prevention and Research Center, College of Public Health, U of Kentucky

Abstract: Statement of Purpose: The current study was undertaken to describe the industries and occupations where drug overdose deaths occur to target industry- and occupation- specific employer health and safety programs that focus on drug-free workplaces including random drug testing programs and enhanced substance abuse treatment programs. Methods/Approach: A descriptive analysis of Kentucky electronic death certificates was performed for the year 2011. Results: There were 1,010 drug overdose deaths in the year 2011. The industries where the decedent was employed with the highest numbers of drug overdose deaths were the construction industry (n=74), the food service industry (n=46), and the health/ medical industries (n=44); 120 occurred at home and 70 were disabled. Occupations where the decedent was employed with the highest numbers of drug overdose deaths were the laborer (n=53), construction worker (n=34), and miner, and mechanic occupations (n=23 each); 162 were listed as homemakers, and 129 were listed as disabled. Autopsies were performed on approximately 53% of the deaths. Six hundred fifteen deaths (61%) occurred at home, 133 (21%) occurred in the hospital setting, and 59 (6%) occurred at a friend's house. Only three of the decedents died at work. Most of the deaths were listed as unintentional overdoses (n=899). Conclusions: Workplace drug-free policies should be implemented and enforced in the construction, food service, and healthcare industries. In addition, targeted substance abuse prevention and treatment programs should be provided to those individuals with disabilities. It is recommended that autopsies and toxicology tests be performed on all suspected drug overdose deaths to determine the exact nature of the drug overdose death as well as the specific drugs, drug classes, and drug mixtures that resulted in the deaths. Significance & Contribution to the Field: The results of this study target the specific industries and occupations where random drug testing of employees and employer drug-free workplace policies are warranted. In addition, the disabled population should be targeted for prescription drug lock-in programs and be offered affordable substance abuse prevention and treatment programs.

Supported by: Grant/Cooperative Agreement Number 2U60OH008483-08 from NIOSH.
Primary Presenter / e-mail: A.M. Bush / ambush2@uky.edu
Degree pursuit: DrPH
Mentor or Senior Author / e-mail: T.L. Bunn / tlbunn2@uky.edu

---

#2 Abstract Title: **Smoking Cessation as a Means for Reducing Health Risks: An Evaluation of the Cooper/Clayton Method to Stop Smoking Program (2012)**

Concentration: Health Behavior

Author(s): J.A. Jones, Health Behavior Department, U of Kentucky; D. Armstrong, Kentucky Cancer Program, East; Markey Cancer Center, U of Kentucky; A. Brumley-Shelton, Lexington-Fayette County Health Department; R. R. Clayton, Health Behavior Department, U of Kentucky; C. Hurst, Kentucky Cancer Program, West: U of Louisville
T. M. Cooper, U of Kentucky

Abstract: Introductory Statement: Kentucky has the highest state-specific smoking prevalence rate in the nation with 29.0 % of adults being current smokers (KY BRFSS, 2011). Smoking is a major risk factor for lung disease, cancer, and exacerbates chronic illnesses; it a major public health issue for the state. Conceptualizing smoking cessation as a means of decreasing risk for morbidity and cancer, a diverse group of stakeholders chose to examine the Cooper/Clayton (C/C) Method to Stop Smoking, a smoking cessation program delivered throughout Kentucky. A retrospective study was initially conducted to examine program completion rates and class-level characteristics for classes taught in 2009 and 2010 in order to obtain baseline data, followed by the current evaluation for classes taught in 2012. The C/C Method is a comprehensive program combining an educational and behavioral modification program with nicotine replacement therapy. It is based on best practices of tobacco control programs as well as a long history of anecdotal success and is administered through the Kentucky Cancer Program. In addition, the supportive group atmosphere created by facilitators and other class members is an integral component to the program. Methods: The objectives from this study included: 1). A follow-up evaluation to the baseline data gathered during the 2009-2010 retrospective study in order to allow comparison 2). Report aggregated class-level characteristics for participants who completed the 12 week class series and self-reported to tobacco facilitators to be smoke-free. The research hypothesis included: The estimated abstinence rate after completing the C/C program is greater than 7% (the general proportion of persons who are able to quit smoking without benefit of medicines or behavioral counseling). Data was collected using an online survey emailed to all class leaders who were listed in the C/C tobacco facilitator listserv. Participation was voluntary. Results: Seventy-four facilitators completed surveys regarding: 133 classes; involving 940 participants; in 61 counties throughout Kentucky. The program completion rate for the C/C program was 42.4% based upon 399 participants completing the 12 week program and self-reporting to be non-smoking to tobacco facilitators. Of these non-smokers, two-thirds or 67% were women, more than half (55%) were between the ages of 45-64, and over half had only a high school diploma or GED (53%). In addition, these non-smokers reported having a significant smoking history prior to the class with 27.5% reporting smoking 16-25 years, followed by 26.8% smoking for 26-35 years. Conclusion: The preliminary results from this study provide an optimistic evaluation of the Cooper/Clayton program as being effective in helping smokers quit. It has been reported in the literature that there are immediate health benefits in stopping smoking in addition to lowering the risk for lung cancer and other types of cancers. This study demonstrates a consistent result with the previous, retrospective evaluation and provides an optimistic examination of the C/C program's effectiveness in helping smokers gain control of their addiction to nicotine.

Supported by: Centers for Disease Control & Prevention (CDC)- Comprehensive Cancer Control, 1U58DP003907-01.
Primary Presenter / e-mail: J. A. Jones / jjones@kycancerc.org
Degree pursuit: DrPH
Mentor or Senior Author / e-mail: R.R. Clayton / clayton@email.uky.edu

College of Public Health Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#3 Abstract Title: **Behavior and Attitude Examination of Cigarette Smoking and Marijuana Use**

Concentration: Health Behavior

Author(s): P. A. Capasso, College of Public Health, U of Kentucky

Abstract: Prevalence of cigarette use in the past month has been decreasing over the past decade among Americans 18 to 25 years old. Yet, rate of past month illicit drug use has been increasing, largely stemming from an increase in marijuana use. The purpose of the study is to determine if smoking cigarettes by young adults influences use of marijuana, and if the strength of that relationship is affected by measures of risk perception associated with the use of either substances. The data gathered by the 2011 National Survey on Drug Use and Heath was used and statistical analysis was run to examine the strength of such associations. Significant associations were observed between daily use of cigarettes ever with recent use of marijuana and low risk perception associated with marijuana use, as well as between low risk perception with the use of cigarettes and the use and low risk perception of marijuana. Time order analysis suggest initiation of marijuana use typically follows marijuana use in individuals having used both. Findings are essential to strengthening the understanding of the pathways to marijuana initiation and can provide useful insights as to contributing factors that ought to be addressed in intervention strategies.

Supported by:

Primary Presenter / e-mail: P. A. Capasso / p.capasso@uky.edu

Degree pursuit: MPH

Mentor or Senior Author / e-mail: R. R. Clayton / clayton@uky.edu

#4 Abstract Title: **Determining the association between perceived stigma and HIV testing behavior among Ugandan men and women aged 15-49.**

Concentration: Health Behavior

Author(s): C.T. Okafor, College of Public Health, U of Kentucky

Abstract: Introduction/Background: The United Nations estimates that over two-thirds of the world's population living with the Human Immunodefiency Virus (HIV) resides in Sub-Saharan Africa. With a population of over 33 million people and a decline in HIV prevalence from 29% in 1987 to 6% in 2009, Uganda has often been held up as a model for Africa in HIV/AIDS prevention. However, a recent report by the Joint United Nations Program on HIV/AIDS suggests a rise in HIV prevalence in Uganda from 6% in 2005 to 8% in 2011. Recent studies done in Sub-Saharan Africa have found that HIV stigma is associated with decreased HIV testing. However, few studies have used the cognitive appraisal of knowledge of external stigma as well as personal stigma attitudes in the African context. Method: The 2011 Uganda AIDS Indicator Survey (AIS) is a cross sectional, nationally representative, population-based, HIV serological survey conducted by the Demographic Health Survey program. Analyses were done in three stages, first, separate x2 statistic ($p<.05$) were calculated to examine the relationship between perceived stigma and HIV testing behavior. Additional binary regression was performed for each level of stigma controlling for possible moderators of age, sex, socioeconomic status, marital status and condom use. All analysis was conducted in 2013 using IBM SPSS Statistics for Windows version 21.

Supported by:

Primary Presenter / e-mail: C.T. Okafor / cokafor88@gmail.com

Degree pursuit: MPH

Mentor or Senior Author / e-mail: C.T. Okafor / cokafor88@gmail.com

#5 Abstract Title: **The association between Human papillomavirus (HPV) vaccine awareness and uptake and annual dental visits among young adults in the United States**

Concentration: Health Behavior

Author(s): L. E. Acurio, College of Public Health, U of Kentucky

Abstract: HPV vaccines, Gardasil and Cervarix, are approved for use among females and males aged 9-26 years old to reduce the incidence of cervical cancer. Physician recommendation of this vaccine is a strong predictor for acceptability. Nonetheless, national low rates of vaccine completion remains a Public health concern. Additionally, despite the decrease of smoking prevalence, an estimate of 2,370 new cases of HPV-related head and neck cancers are diagnosed in women and approximately 9,356 are diagnosed in men each year in the United States. Few studies have addressed the role of dentists in discussing risk factors of oral cancer including HPV infection with their patient. Data has showed that HPV vaccine awareness was higher among adolescent who had visit the dentist the prior year. Methods: A cross-sectional analysis of the association between HPV vaccine knowledge and uptake and dental visits was conducted using data from the National Health Survey (NHIS) funded by CDC. Logistic regression models was applied. Results: A total of 4458 participants, ages 18-26, were part of this analysis. Young adults who visited the dentist had 51% chance of having received a shot of HPV vaccine compared to who had not visited the dentist during the past year. Results of a logistic regression model in relation to the vaccine dosage uptake and dental visits are pending.

Supported by:

Primary Presenter / e-mail: L.E. Acurio / leac222@uky.edu

Degree pursuit: MPH

Mentor or Senior Author / e-mail: L.E. Acurio / leac222@uky.edu

College of Public Health Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#6 Abstract Title: **Patterns of and Preferences for Alternative Homeopathic Therapies for Older Adults.**

Concentration: Gernotology

Author(s): P. J. Desin, Department of Gerontology, U of Kentucky

Abstract: Introduction: This study explores alternative and homeopathic options for older adults to assist them with health improvement and maintenance in various types of environments. It presents an overview of some of the strategies available, how they are employed, and outcomes of usage. Methods: The research articles used were reviewed and analyzed based on: if therapies were administered to an individual or group; the occurrence and frequency of therapies used alone or in combination with other types; or alternative therapies used in addition to traditional medical interventions. The extent and nature of positive and negative outcomes were examined. The articles presented diverse techniques for older adults, the probable effectiveness of each method, the impacts that each therapy may have on the participant, and the benefits and risks of the intervention. Personal opinions of practitioners and clients were included in the study. Results: The data are not conclusive, as studies that use a comprehensive design and analysis have not been conducted for each technique on a large scale. There are no studies of validity of the therapies in comparison to standard medical interventions. Review of the literature shows trends of more use of alternative and homeopathic therapies by individuals, or in conjunction with traditional medicine. Practitioners have begun to move toward recommending or providing alternative methods as an adjunct to, or substitute for, standard treatments. Conclusions: There is a need for more research on the efficacy of each therapy, utilizing a rigorous methodology with reliable data collection, and consistent evaluation of the results. A cost-benefit analysis to compare medical and non-medical approaches would possibly substantiate insurance coverage for individuals who prefer non-medical alternatives.

Supported by:

Primary Presenter / e-mail: P. J. Desin / pamela.ruhl@uky.edu

Degree pursuit:

Mentor or Senior Author / e-mail: G. Rowles / growl2@uky.edu

#7 Abstract Title: **Memory Banking: Evaluating A Multi-Session Life Story Intervention**

Concentration: Gernotology

Author(s): A. I. Hoogland, Department of Gerontology, U of Kentucky
B. G. Downer, Department of Gerontology, U of Kentucky
A. Hosier, Department of Family Sciences, U of Kentucky
J. F. Watkins, Department of Gerontology, U of Kentucky
F. Zanjani, Department of Gerontology, U of Kentucky

Abstract: Introduction: Life story interventions lead to a variety of psychological benefits in older adults. Most interventions do not address community-oriented dyadic life story development within the context of aging and caregiving. The Memory Banking (MB) program was designed to reduce caregiver burden through life story development and the use of the Lifeline Interview Method (LIM). MB provides the knowledge and skills for collecting, documenting, sharing, and maintaining life stories. Employing the MB program with 8 groups has successfully led to improvements in mental health and memory. To better understand program strengths and potential areas for improvement, a post-hoc survey was analyzed. Objectives: Determine participants' perceptions of the MB program, including strengths, weaknesses, and areas for improvement. Methods: N=72 older adults (mean age = 71.1) participated and were offered an opportunity to provide feedback via four open-ended questions. Findings: Data indicated that 85% of respondents felt the program met or exceeded expectations. Participants reported primary strengths to be effective memory retrieval, use of the LIM protocol to represent key events in the life course, interactions with other participants, and potential for future benefit for themselves or others. Participants reported primary weaknesses to be the need for more time / additional lessons, periodic confusion regarding lesson instructions, and not enough participant involvement. Conclusions: The MB program is perceived as effective in improving mental health, and offers great promise for lessening caregiving burden provided it does not rush participants, offers greater clarity of instructions, and encourages participant involvement and interaction.

Supported by:

Primary Presenter / e-mail: A. I. Hoogland / aasha.anderson@uky.edu

Degree pursuit: PHD

Mentor or Senior Author / e-mail: F. Zanjani / fzanj2@email.uky.edu

College of Public Health Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#8 Abstract Title: **Body Image in Older Women: How It Reflects with Body Image in Older Men and Younger Women**

Concentration: Gernotology

Author(s): J.C. Anthony, Department of Gerontology, U of Kentucky

Abstract: A study was undertaken to explore poor body image in older women, which remains a serious public health concern. Despite increased public awareness regarding this issue, the majority of older women suffer from poor body image and low body satisfaction. This often leads to risky behavior to lose weight. An in-depth literature review of PsycINFO and PubMed was conducted exploring poor body image in older women, its theoretical foundations, the discrepancy between the eternal self and the aging exterior, how body image differs between older women, older men, and young women, the dangers of poor body image, and mitigating factors. Twenty-nine articles and book chapters were ultimately selected for further detailed analysis. Literature findings were compared to 6 in-depth interviews with an older adult to assess the degree to which a case study reflected what is in the literature. Three themes emerged from the interviews and literature: older women continue to adopt mainstream cultural norms of beauty, this behavior detaches older adults from their body and promotes and maintains harmful behavior, and the eternal spiritual self often does not corroborate with the aging physical exterior. Longitudinal research is needed that follows cohorts of young women of today and in the future to examine how changing gender roles and the media affect the body image of older women.

Supported by:

Primary Presenter / e-mail: J.C. Anthony / Jonathan.C.Anthony@uky.edu

Degree pursuit: PHD

Mentor or Senior Author / e-mail: G.D. Rowles / growl2@email.uky.edu

#9 Abstract Title: **A Two-Step Penalized Regression Method for Family-based Next Generation Sequencing Association Studies**

Concentration: Biostatistics

Author(s): X. Ding, Department of Biostatistics, U of Kentucky
S. Su, Department of Pediatrics, Georgia Health Sciences University
K. Nandakumar, Department of Biostatistics, U of Kentucky
X. Wang, Department of Pediatrics, Georgia Health Sciences University
D. W. Fardo, Department of Biostatistics, U of Kentucky

Abstract: Background: Large-scale genetic studies are often comprised of related participants, and utilizing familial relationships can be cumbersome and computationally challenging. We present an approach to efficiently handle sequencing data from complex pedigrees that incorporates information from rare variants as well as common variants. Method: Whole genome sequencing for a subset of the San Antonio Family Studies participants was conducted through the Type 2 Diabetes Genetic Exploration by Next-generation sequencing in Ethnic Samples (T2D-GENES) Consortium. We examine the 1,215,399 variants on chromosome three that were genotyped on the 955 fully-phenotyped subjects. A two-step polygenic regression adjustment and residual testing approach was adopted to test for both common and rare variants by inclusion of a penalized regression step and applied the method to the SAFS genome sequencing data. Results: MAP4 is consistently discovered using our approach as the variants within MAP4 confer more than 5% heritability for both DBP and SBP. No other gene encompasses that amount of heritability for either trait. The next highest heritability is that of FLNB for SBP (0.28%), and the other genes are correspondingly much less reliably detected. A few genes (e.g., ARHGEF3, FLNB and SCAP) are discovered with at least 10% probability in some models, although it is difficult to infer with confidence any pattern of characteristics for detection when these are so low. It appears that detection probability increases with more weight placed towards the pure lasso penalty. Keywords: complex pedigrees, family-based association, mixed model, penalized regression.

Supported by: The Genetic Analysis Workshop is supported by NIH grant R01 GM031575. This work was supported by NIH grants 8P20GM103436-12 (DWF, KN) and 8P20GM103538-09 (DWF).

Primary Presenter / e-mail: X. Ding / xiuhua.ding@uky.edu

Degree pursuit: PHD

Mentor or Senior Author / e-mail: D. W. Fardo / david.fardo@uky.edu

College of Public Health Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#10 Abstract Title: **Rural Physicians and Spouses in Central Appalachia: Factors that Influence Retention**

Concentration: Health Services Management

Author(s): G. F. Tiu, MPH, College of Public Health, U of Kentucky
J. Ying, PhD, Department of Environmental Health, U of Cincinnati
W. M. Mase, DrPH, MPH, MA, Department of Environmental Health, U of Cincinnati
C. D. Lamberth, MPH, CPH, College of Public Health, U of Kentucky
F. D. Scutchfield, MD, College of Public Health, U of Kentucky

Abstract: Numerous Health Professional Shortage Areas (HPSAs) and Medically Underserved Areas/Populations (MUA/Ps) in rural central Appalachia have faced physician workforce shortages for decades. Physician shortages create challenges to health administrators, physician recruiters, and residents in these communities. Previous studies shed light on the influence of the spouse on recruitment, but there is limited research on the influence of the spouse on rural physician retention. For the scope of our study, we hypothesize the sociocultural integration of the spouse has substantial influence on the physician's decision to remain or leave a rural community. Consequently, the spouse plays a pivotal role in retention rates. We also hypothesize the spouse possesses differing viewpoints on the factors that influence retention. Results from a preliminary study conducted in 2011, using paired t-tests to assess differences between the physician and the spouse, suggested the spouse may view certain factors as more or less influential to retention compared to the physician. A focus group conducted in 2012 supported this supposition. Traditional hard copy questionnaires were distributed to the physicians of Appalachian Regional Healthcare (ARH), a not-for-profit rural hospital system in eastern Kentucky and southern West Virginia located in the central Appalachian region. Surveys were distributed to hospitals in the ARH system. Developing and refining strategies that focus on the needs of the spouses might improve the success of both recruitment and retention rates of the physician workforce to rural areas in central Appalachia.

Supported by: Health Resources and Services Administration Award from the Kentucky and Appalachia Public Health Training Center and UK College of Public Health

Primary Presenter / e-mail: G. F. Tiu / georgianne.tiu@uky.edu
Degree pursuit: DrPH
Mentor or Senior Author / e-mail: F. D. Scutchfield / scutch@uky.edu

---

#11 Abstract Title: **Leader tenure matters: examining the association between leader tenure and financial performance of Local Health Departments (LHD)**

Concentration: Health Services Management

Author(s): E.J. Jadhav, Department of Health Services Management, U of Kentucky
J.W. Holsinger,Department of Health Services Management, U of Kentucky
G.P. Mays, Department of Health Services Management, U of Kentucky

Abstract: Research objectives: Characterize the effect of leader tenure on financial performance of the LHD by comparing leader correlates associated with positively deviant LHD. Classify sociodemographic characteristics of leaders by examining the extent of variation in LHD expenditure levels across communities during the economic downturn period of 2008 – 2010. Data sources and population: The key variables that reflect expenditure, tenure and leader characteristics of LHD executives are available from the cross sectional surveys of the nations local public health agencies conducted by the National Association of County and City Health Officials in 2008 and 2010. Methods/analysis: A longitudinal ecological design was used to analyze variation in leader characteristics and percent change in expenditure for LHDs during the period of 2008 and 2010. Bivariate analysis of LHD financial performance and leader characteristics and logistic regression model to estimate association between expenditure, leader characteristics and LHD characteristics were performed. Analysis: During the recession period only 18.39% of the over 2500 LHDs were positive deviants. Frequency of leader characteristics associated with positively deviant LHDs varied significantly by age, gender, ethnicity, race, education status, full-time employment, leadership experience and tenure. The LHD characteristics roll-over-reserve-fund, governance, reporting-classification and population also appeared to moderate the effect of tenure on financial performance. Conclusion: The prevailing corporate trend of dismissing leaders over existing poor performance as observed during the economic downturn may negatively affect agency performance and put leaders at a disadvantage for improving agency fiscal health. Implications for Public health: The challenge of competing for funds from diverse resources stand out as a required public health leadership competency not explicitly addressed by the public health leadership competency framework. Also to develop educational curricula that includes financial management for training public health workforce leaders to adapt to the changing organizational environment.

Supported by:

Primary Presenter / e-mail: E. D. Jadhav / edja223@uky.edu
Degree pursuit: DrPH
Mentor or Senior Author / e-mail: J.W. Holsinger / jwh@uky.edu

College of Public Health Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#12 Abstract Title: **Evaluating the Association between Occupational Exposures and histology of lung cancer in a cohort of lung cancer patients.**

Concentration: Epidemiology

Author(s): K. O. Diggs, Department of Epidemiology, U of Kentucky

Abstract: Objective: This study was designed to determine if there is an association between certain occupational exposures and the histological subtypes of lung cancer while adjusting for covariates. Methods: Histologically confirmed and surgically resected stage I or II lung cancer cases were recruited from 12 sites in ten counties across Kentucky. A questionnaire was used to collect data on patients' lifetime occupational history, smoking history, and demographic and socioeconomic characteristics. Occupational exposures of the lung cancer cases were grouped into eight categories, and histological types were categorized as adenocarcinoma, squamous cell carcinoma, and other cell types. Odds ratios for developing each type of cancer were estimated using logistic regression, while controlling for smoking, age, gender, Appalachian residence, income, and race. Results: Lung cancer patients who worked five years or more in food service (OR=2.66 [0.48-14.6]) or farming (OR=1.44 [0.56-3.69]) had an increased odds of developing adenocarcinoma, but neither OR was statistically significant. Workers in manufacturing (OR=1.08 [0.23-4.95]), maintenance (OR=1.64 [0.43-6.1]), construction (OR=3.03 [0.96-9.50]), and other jobs (OR=7.43 [0.57-95.8]) were more likely to develop squamous cell carcinoma. Increased odds were observed for other cell types for workers in construction (OR=3.22 [0.77-13.4]), mining (OR= 1.65 [0.36-7.59]) and transportation (OR= 2.51 [0.50-12.5]), but all associations were non-significant. However, adenocarcinoma among construction workers were found to be close to significance (OR=3.03 [0.96-9.50]). Conclusion: Among the participants in this study, there was not a statistically significant increase in risk of developing any particular histological type of lung cancer. Results with regard to construction and squamous cell carcinoma, however, were very nearly significant, which could indicate a need for further study.

Supported by:

Primary Presenter / e-mail: K.O. Diggs / kofi.diggs1@uky.edu

Degree pursuit: MPH

Mentor or Senior Author / e-mail: C. M. Hopenhayn / cmhope0@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#13 Abstract Title: **Acute Orofacial Pain Suppression Induced by Viral Vector Gene Delivery**

Author(s):
W.E. Yoder, College of Dentistry, U of Kentucky
R.J. Danaher, College of Dentistry, U of Kentucky
K.N. Westlund, Department of Physiology, U of Kentucky
F. MA, College of Medicine, U of Kentucky
C. Wang, College of Dentistry, U of Kentucky
C.R. Carlson, College of Dentistry and College of Arts & Sciences, U of Kentucky
C.S. Miller, College of Medicine and College of Arts & Sciences, U of Kentucky

Abstract: Objectives: We hypothesized that orofacial inoculation with a herpes simplex virus type-1 (HSV) replication conditional vector that expresses human proenkephalin (Enk) can be effectively delivered to the trigeminal ganglion (TG) for suppression of acute formalin-induced orofacial pain in mice. Methods: Replication conditional vectors expressing Enk (KHPE) or E. coli beta galactosidase (KZ) were topically applied to lightly scarified whisker pads of Balb/C mice. The quantity of vector DNA delivered to the TG was determined in the first group of mice 3 days post inoculation by quantitative real-time PCR (qPCR). Whisker pads were injected with 2.5% formalin ten days after vector delivery in a second group of mice. Nociceptive behaviors were quantified in 3 minute blocks from videotape to determine mean face scratching duration (sec) by an investigator who was blinded to treatment groups. Results: The mean vector DNA copy number detected in the TGs was 182,950 copies/TG. The mean scratch score of animals treated with the KHPE vector (12.8 sec/3min) was significantly lower (53.8%) than that of animals treated with KZ control vector (28.8 sec/3min), during the second phase of the acute formalin response ($p < 0.05$). Conclusion: These findings demonstrated that i) an HSV-based vector encoding Enk (KHPE) can be successfully inoculated in the orofacial region and detected in abundance in the TG, and ii) the pain response is reduced after the delivery of KHPE. To our knowledge this is the first study demonstrating the efficacy of this HSV-based vector for alleviation of acute formalin induced orofacial pain.

Supported by: NIH/NCRR grant 2P20RR020145-06 and Dean's funds

Primary Presenter / e-mail: W.E. Yoder / will.yoder@uky.edu

Mentor or Senior Author / e-mail: C.S. Miller / cmiller@uky.edu

#14 Abstract Title: **Detection & Treatment of a Chronically Covert Pediatric Condylar Head Fracture: Use of a Costochondral Graft**

Author(s):
T. Clifton, Department of Oral & Maxillofacial Surgery, U of Kentucky
A. D. Oliphant, Department of Oral & Maxillofacial Surgery, U of Kentucky
L. L. Cunningham, Department of Oral & Maxillofacial Surgery, U of Kentucky

Abstract: Identification of condylar head fractures in very young pediatric patients can be difficult, and can lead to temporomandibular joint (TMJ) ankylosis. Fracture of the pediatric mandibular condylar head can affect mandibular growth. This case report details a pediatric patient with no known history of facial trauma or mandible fracture who developed TMJ ankylosis and asymmetrical mandibular growth, implicating a chronically covert pediatric condylar head fracture. TMJ reconstruction with a costochondral graft resulted in increased maximal incisal opening and return to a normal diet.

Supported by:

Primary Presenter / e-mail: T. Clifton / trent.clifton@uky.edu

Mentor or Senior Author / e-mail: L. Cunningham / llcunn2@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#15 Abstract Title: **Parental Oral Health Perceptions and Behaviors as a Predicting Factor for Pediatric Oral Health**

Author(s):
A. Grace, Pediatric Dentistry, University of Kentucky
R. Vanderpool, Department of Public Health, University of Kentucky
H. Bush, Department of Biostatistics, University of Kentucky
H-F Li, Department of Biostatistics and Epidemiology, University of Kentucky

Abstract: Purpose: The study's purpose was to determine if a significant relationship exists between parent's dental behaviors and perceptions and their child's examination results. Methods: Parents of children ages 1-5 completed a 24-question survey assessing sociodemographics, oral health knowledge, perceptions, and dental behaviors pertaining to the parent. The Rapid Estimate of Adult Literacy in Dentistry (REALD-30) measured parent's oral health literacy. Pediatric oral health outcomes were assessed using the Basic Screening Survey. Results: A total of 160 dyads participated: 79% were female, 66% over age 30, 64% married, and 74% had dental insurance. At the bivariate level, compared to children with caries, children with no caries were significantly more likely to have parents who were white, married, have higher levels of education, over age 30, and have private health insurance. Caries free children were more likely to have parents who reported the condition of their own teeth as "very good/good", reported less fear of the dentist, and higher literacy scores. Logistic regression suggest the odds of having caries experience for children with non-white parents is 2.86 times that of the children with white parents (95% CI: 1.09, 7.47). Similarly, the odds of having caries is 0.37 times smaller for children with parents with higher education levels than those with lower education levels (i.e., less than 2-year college degree) (95% CI: 0.142-0.944) Conclusions: In this study, expected parental demographic factors (white race, health insurance, married, home/car ownership, higher education) and parental dental perceptions/behaviors (good teeth condition, no dental fears, higher literacy) were associated with children's caries experience. These effects were attenuated by parental race and education, highlighting the importance of outreach to minority and educationally-disadvantaged communities.

Supported by:
Primary Presenter / e-mail: A. Grace / aewurt0@uky.edu
Mentor or Senior Author / e-mail: R. C. Vanderpool / robin@kcr.uky.edu

#16 Abstract Title: **Resection of Ameloblastoma with Fibula Free Flap Reconstruction**

Author(s):
B. Newby, Department of Oral and Maxillofacial Surgery, U of Kentucky
L. Cunningham, Department of Oral and Maxillofacial Surgery, U of Kentucky
D. Oliphant, Department of Oral and Maxillofacial Surgery, U of Kentucky

Abstract: This is a case presentation of a resection of an ameloblastoma with a fibula free flap reconstruction. The patient is a 13 year old African American male that underwent resection of a benign tumor that is locally invasive. The treatment planning was done using a Synthesis Pro Plan model. A team approach to the patient was utilized with UK Oral and Maxillofacial Surgery performing the resection and plastic surgery completing the reconstruction.

Supported by:
Primary Presenter / e-mail: B. Newby / brent.newby@uky.edu
Mentor or Senior Author / e-mail: B. Newby / llcunn2@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#17 Abstract Title: **Reduction of Pain Following Intravenous Infusion of Subanesthetic Ketamine in a Patient with Continuous Neuropathic Pain: A Case Report**

Author(s):
I. Moreno-Hay, Orofacial Pain Center, College of Dentsitry, U of Kentucky
T Weber, Orofacial Pain Center, College of Dentristry, U of Kentucky
J Lindroth, Orofacial Pain Center, College of Dentristry, U of Kentucky

Abstract: Aim of the investigation: We describe a case of chronic continuous neuropathic pain in which relief was obtained following administration of intravenous sedation to which ketamine was added. A 50-year-old female presented in 2006 with a one-year history of constant sharp pain rated 10/10 in the gingiva surrounding teeth #13-15. Multiple systemic medications failed to adequately manage her pain. Limited relief was obtained with a topical compound of lidocaine, amitriptyline and carbamazepine. Daily use of methadone 50 mg decreased her pain level to 4/10. Methods: In July 2012 the patient underwent extraction of tooth #4 for reasons unrelated to her neuropathic pain. This procedure was performed under intravenous sedation using diazepam and fentanyl. A subanesthetic dose of ketamine was added to this intravenous regimen in an attempt to prevent post-operative exacerbation of the patient's neuropathic pain. Results: The patient reported experiencing only nine days of pain during the six months following her IV sedation. During this 6-month period she reduced her daily methadone dose to 20 mg. Pain flare-ups were managed with tizanidine, alprazolam and topical medication. Conclusions: Our experience suggests a possible role for ketamine in obtaining relief from chronic neuropathic pain and reducing opioid tolerance.

Supported by:
Primary Presenter / e-mail: I. Moreno-Hay / imo226@uky.edu
Mentor or Senior Author / e-mail: J. Lindroth / john.lindroth@uky.edu

#18 Abstract Title: **Differential Responses of DCs to Oral Commensal and Pathogenic Bacteria**

Author(s):
Y. Alimova, Center for Oral Health Research, College of Dentistry, U of Kentucky
J. Ebersole, Center for Oral Health Research, College of Dentistry, U of Kentucky
C. Huang, Center for Oral Health Research, College of Dentistry, U of Kentucky

Abstract: DCs are present in the periodontium, respond to the environment at diseased sites, and likely contribute crucial functions to maintaining or re-establishing homeostasis of these oral tissues. The differential induction of host cell responses by oral commensals and pathogens, and the ability of the host to differentiate and respond to trigger adaptive immunity remain unclear. Objectives: While it is clear that DCs can engage a diverse array of microorganisms and present a plethora of antigenic epitopes following intracellular processing, minimal data provide insight into how these cells actually respond to oral commensal and pathogen challenge, how the bacterial triggering alters their maturation and functional properties, and what factors enable them to "sort through" the commensals and pathogens of stimuli within a infection. Methods: THP-1 derived DCs and iDCs were treated with oral commensals and pathogens. Cytokines and gene expression levels were measured. Results: Individual oral bacteria differentially modulate the expression of cytokines and TLR4 in DCs. The results demonstrate high activation of NF-□B as reflected by IL-8 levels, elevated IL-6, L-12, and TNF-α by P. intermedia, F.nucleatum, C.rectus, A.actinomycetemcomitans, S. mutans, S. sanguinis, and S. gordonii all induced some IL-6 and IL-8, as well as IL-10. Pg was somewhat unique by generally inducing only elevated IL-6 and TNF-α. Similar differences were observed with mRNA for selected cytokines and TLR4. Conclusions: The results support that oral bacteria (commensal vs. pathogenic) may differentially stimulate maturation of immune or tolerigenic DCs.

Supported by: P20 GM103538 and the Center for Oral Health Research.
Primary Presenter / e-mail: Y. Alimova / yvalim2@uky.edu
Mentor or Senior Author / e-mail: C.Huang / chuan2@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#19 Abstract Title: **Dental Students' and Pediatric Dentists' Perspectives About Behavior Guidance Techniques**

Author(s): A. Mayes, Department of Pediatric Dentistry, University of Kentucky College of Dentistry
E. Bimstein, Department of Pediatric Dentistry, University of Kentucky College of Dentistry

Abstract: The purpose of this study is to describe and compare the perceptions about pediatric dentistry behavior guidance techniques of pre-doctoral students and graduates from a pediatric dentistry post-doctoral program at the University of Kentucky. A questionnaire, in which the acceptability of 25 different pediatric dentistry behavior guidance techniques and situations was scored using a visual analog scale, was distributed to dental students and to pediatric dentists who completed a post-doctoral pediatric dentistry program. Completed questionnaires were received from 156 dental students and 42 pediatric dentists. Statistical analysis of the differences in scores between the groups was performed using a t-test. The behavior guidance techniques that showed a statistically significant (P<.05) higher acceptability score by the pediatric dentists than the students included: the use of tell-show-do, voice control, hand-over-mouth, nitrous oxide, patient being restrained by a parent or assistant, papoose board, parent being allowed in the clinic, and the use of oral sedation, general anesthesia, and euphemisms when talking to the patient. No statistically significant differences in acceptability scores were noted regarding telling the child that he/she may have pain, explaining the procedure to the patient, encouraging the patient not to be a coward, allowing the patient to stop treatment, and using modeling. This descriptive study highlights the effect of dental education and experience on the perceptions about behavior management techniques.

Supported by:
Primary Presenter / e-mail: A. Mayes / amayes@gmail.com
Mentor or Senior Author / e-mail: E. Bimstein / ebi223@uky.edu

#20 Abstract Title: **Hemifacial Hyperhydrosis Secondary to Penetrating Trauma: Report of a Case**

Author(s): J. Bean, Department of Oral and Maxillofacial Surgery, University of Kentucky

Abstract: Several causes of bilateral or unilateral hyperhydrosis have been suggested in dermatology and nuerology literature. However, very few reports of hyperhydrosis with an etiology of trauma are described. We report a case of a patient with a gunshot wound to the face whose initial presentation included hemifacial hyperhydrosis secondary to penetrating trauma.

Supported by:
Primary Presenter / e-mail: J. Bean / j.bean@uky.edu
Mentor or Senior Author / e-mail: L. L. Cunningham / llcunn2@uky.ed

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#21 Abstract Title: **The Influence of METHYLENE BLUE-Mediated Photodynamic Therapy on Biofilm Bioadhesion to Titanium Substrata**

Author(s):
L. Sharab, Department of Orthodontics, U of Kentucky
T. Mang, Department of Maxillofacial Oral Surgery, SUNY at Buffalo
S. Ciancio, Department of Periodontology, SUNY at Buffalo
R. Baier, Biomaterial Science, SUNY at Buffalo

Abstract: Objectives: Testing the effect of Photodynamic Therapy (PDT) on bioadhesion strength to titanium substrata as a method of cleaning biomaterial surface by examining whether the detachment shear stress would be affected by prior PDT treatment independently from microbial viability. Methods: Biofilms of Streptococcus mutans (ATCC strain 27351) were grown in BHI media with sucrose, initiating the biofilms with bacteria of three different ages (phases). One set of biofilm samples received no PDT (controls); another set received methylene-blue-mediated PDT. A water-jet impingement apparatus was used to determine the adhesive strength of biofilms to the titanium substrata. Scanning electron microscopy (SEM) was performed to obtain images of the samples before and after jet impingement. Replicate biofilms prepared on germanium prisms were characterized by MAIR-infrared spectroscopy. Results: PDT'd microbial biofilms were significantly ($p<0.05$) delaminated and ultimately removed from their substrata biomaterials by the hydrodynamic forces of water-jet impingement. Control (no PDT) biofilms of varying thicknesses required 144-228 dynes/cm² shear stress to delaminate from titanium, while PDT'd biofilms were removed at 90-140 dynes/cm². The thicker areas of biofilms had greater susceptibility to detachment by water–jet impingement. MAIR-IR spectra of replicate biofilms and SEM images of control and PDT'd biofilms confirmed these findings. Colony-forming-unit (CFU) counts routinely correlated well with results from a spectrophotometric Alamar Blue (AB) assay. Conclusion: These results are consistent with proposals that methylene-blue-mediated PDT induces oxidative embrittlement and fragmentation of biofilm matrix biopolymers, allowing easier release by hydrodynamic (rinsing) forces.

Supported by: This work was preformed in, and supported by the State University of NY at Buffalo
Primary Presenter / e-mail: L.Y. Sharab / lina.sharab@uky.edu
Mentor or Senior Author / e-mail: R. Baier / Baier@buffalo.edu

#22 Abstract Title: **Stress and it's Association with Periodontal Disease in Kentucky National Guard Soldiers Serving Overseas**

Author(s):
J. D. Ferrin, Department of Periodontology, U of Kentucky
M. Al-Sabbagh, Department of Periodontology, U of Kentucky

Abstract: Stress, particularity psychological stress has been implicated to be one of the risk factors of developing periodontal disease. The purpose of this study is to evaluate the relation between periodontal health and psychosocial stress. Two groups of soldiers in the Kentucky Army National Guard will be our subjects. Both groups will be deployed but only one group will have a combat specialty. We will develop a correlation between the soldier's occupation specialty, stress levels and periodontal health. This correlation will be determined by Periodontal Screening and Reporting (PSR) and a self-reported stress questionnaire. The stress and periodontal evaluations have both been validated by clinical research. Perceived Stress Questionnaires have been validated as an important tool for psychosomatic researchers. We hypothesize the soldiers in a combat related assignment will have higher stress and more clinical signs of periodontal disease. The soldiers smoking status will be recorded. The goal of this particular study is to determine if combat related stress results in a decrease in periodontal health. We expect to see the soldiers in combat assignments to have higher stress and more severe clinical signs of periodontal disease than their counterparts.

Supported by: COL Jill K. Faris, Deputy Surgeon, Office of the Chief Surgeon, ARNG-CSG
Primary Presenter / e-mail: J. D. Ferrin / perioferrin@gmail.com
Mentor or Senior Author / e-mail: M. Al-Sabbagh / malsa2@email.uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#23 Abstract Title: **Effects of Non-Surgical Periodontal Therapy in Patients with Gestational Diabetes Mellitus**

Author(s): A. Wright, Department of Periodontology, College of Dentistry, U of Kentucky
M.J. Novak, Center for Oral Health Research, College of Dentistry, U of Kentucky
L. Lopez del Valle, Scool of Dental Medicine, University of Puerto Rico
C. Atkins, Delta Dental of Kentucky Clinical Research Center, College of Dentistry, U of Kentucky
J.L. Ebersole, Center for Oral Health Research, College of Dentistry, U of Kentucky

Abstract: Gestational Diabetes Mellitus (GDM) affects 3-5% of women during pregnancy. Moreover, GDM coupled with periodontitis appears to increase the risk of adverse pregnancy outcomes. Objective: This study determined the prevalence of positive clinical responses to non-surgical periodontal therapy in pregnant woman with both GDM and periodontal disease. Methods: A total of 125 women diagnosed with GDM were recruited (UK, UPR) and randomly assigned to a treatment or control group. Benchmarks for health were established as ≤4mm probing depths (PD) and ≤20% bleeding on probing (BOP). The treatment group received non-surgical periodontal therapy (Sc/RP), oral hygiene instructions, and dental products to aid in home care. Up to 5 treatment visits were provided over a period of 4-6 weeks. Results: A total of 47 women completed treatment. Age, ethnicity, baseline blood glucose and baseline BOP did not predict a successful response to Sc/Rp. Baseline PD significantly influenced whether the patient was a responder or non-responder. Patients with baseline mean PD ≤1.5 showed a response rate of 77.78%, while those with baseline mean PD >1.5, had a response rate of only 21.05% (p =0.0025.) Conclusions: These results demonstrated that a subset of expectant women with GDM and periodontitis do not respond to standard non-surgical periodontitis therapy, generally related to their extent of periodontitis early in pregnancy. Women who experience a lower number of sites of PD >4mm are 13 times more likely to reach the benchmarks established for health than women who exhibited a more extensive disease state.

Supported by: NIH/NCRR ARRA award: P20RR020145
Primary Presenter / e-mail: A. Wright / allison.wright@uky.edu
Mentor or Senior Author / e-mail: J.L. Ebersole / jleber2@uky.edu

#24 Abstract Title: **Cathepsin K as a biomarker in the diagnosis of periodontitis and peri-implantitis: A literature review**

Author(s): I. Bhavsar, Department of Periodontology, U of Kentucky
C. Miller, Department of Oral Health Practice, U of Kentucky
M. Al-Sabbagh, Department of Periodontology, U of Kentucky

Abstract: Several studies have shown that development of peri-implantitis results in a marked increase in the rate of implant failure. Different salivary biomarkers have been investigated for the detection of periodontal and peri-implant diseases. Some studies were focused on mammalian proteinases like collagenase and neutrophil elastase. These proteinases cleave the native triple helix region of type 1 collagen fibers. Recently, several reports have detected an increased level of Cathepsin K (CTSK) in saliva and gingival crevicular fluid (GCF) in patients with periodontitis and peri-implantitis as compared to healthy patients. CTSK is a lysosomal cysteine proteinase, predominantly expressed in osteoclasts. CTSK has the unique ability to cleave collagen molecules both in the telopeptide and at multiple sites within the native triple helix. It is closely associated with the osteoclastic function of bone resorption. Previously, the significance of CTSK in bone resorption has been delineated using specific inhibitors. Thus CTSK is a proficient proteinase enzyme that is capable of degrading type I collagen fibers and extracellular matrix component in association with periodontal and peri-implant tissue destruction. A systematic review of the current literature on CTSK levels in GCF and peri-implant sulcular fluid (PISF) in patients with periodontitis and peri-implantitis will be developed. The literature findings indicate higher levels of CTSK with sites that have an increased alveolar bone loss. A marked decrease in CTSK concentration is observed following non-surgical therapy. The volume of CTSK may be gender and site specific. CTSK may be used as a potential biomarker in the detection of periodontitis and peri-implantitis.

Supported by: University of Kentucky College of Dentistry Department of Periodontology
Primary Presenter / e-mail: I. Bhavsar / isbh222@l.uky.edu
Mentor or Senior Author / e-mail: M. Al-Sabbagh / malsa2@email.uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#25 Abstract Title: **Comparison of Oral Health Literacy of Parents Between Areas Serviced by Mobile Dental Clinics versus Non-serviced Areas**

Author(s): J. R. Raleigh, Deparment of Pediatric Dentistry, U of Kentucky
J. F. Yepes, Deparment of Pediatric Dentistry, U of Kentucky

Abstract: Objectives: The purpose of this study is to compare the oral health literacy of parents with children in the public education system serviced by a mobile dental clinic outreach versus parents of children in areas that are not serviced by a mobile dental clinic outreach program. Methods: Surveys were sent out to parents of children in the public school system in kindergarten and first grade in two Appalachian counties. One of the selected counties had mobile dental services while the other county did not. Parents of students who are participants in the mobile dental services received educational materials regarding diet, oral health, sealants, fluoride, and restorative dentistry. The parents completed a 31-question survey evaluating the general oral health knowledge of the parents and determining whether the child has ever received treatment from the mobile dental van. The results of these surveys were then compared. Results: 405 total surveys were distributed. A total of 194 surveys were completed and returned in this study resulting in a 48% response rate. In the county serviced by the mobile dental clinic outreach 33 percent of the parents reported that they did not receive dental mobile services for their child while 65 percent reported that they did receive services. Two percent of the parents reported that they were unsure if their child received care from the mobile dental clinic outreach. The parents of the children who received dental mobile services scored higher on the surveys when compared to parents who did not participate in mobile dental services. Eleven questions targeted the educational materials that the parents received from their child's participation on the dental mobile van. Eight out of the eleven questions were answered correctly at higher percentages by the parents of children participating in the dental mobile van. Conclusions: This study determined that the services of dental mobile vans do help to improve the oral health literacy of parents of young children.

Supported by: University of Kentucky College of Densitry Department of Pediatric Dentistry
Primary Presenter / e-mail: J. R. Raleigh / jrrale0@uky.edu
Mentor or Senior Author / e-mail: J. F. Yepes / jfyepe2@email.uky.edu

#26 Abstract Title: **Analysis of Dental Services in the University of Kentucky Emergency Department**

Author(s): M.L. Harris, Department of Dentistry, Division of Pediatric Dentistry, U of Kentucky
P.S. Stein, Department of Dentistry, U of Kentucky
C.M. Flora, University of Kentucky College of Dentistry

Abstract: Dental services contribute to a large percentage of these non-emergent ED visits. The purpose of this study is to categorize patients visiting the emergency department with a dental related chief complaint, the nature of their dental problems, and compare the trends related to the amount of patients seeking dental treatment in the emergency department at University of Kentucky from 2008-2012. This information was obtained from an original de-identified data set from UK Emergency Department in an Excel document. The statistical analysis was performed by usage of Statistical Package for Social Sciences version 20. During a 4-year period, 6401 patients were admitted to the University of Kentucky Emergency Department due to dental complications. More than 32% of these patients presented to the ED during the weekend while 40% were admitting during the week, after standard business hours. The most frequent chief complaint was tooth pain which represented 68% of all cases. Young adults ages 18-34 represented nearly 60% of the patients. In conclusion, the majority of dental services provided at the University of Kentucky ED are non-emergent. These dental services could be rendered during regular business hours in regular offices.

Supported by:
Primary Presenter / e-mail: M.L. Harris / misee.harris@uky.edu
Mentor or Senior Author / e-mail: P.S. Stein / pam.stein@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#27 Abstract Title: **Resolution of OSA symptoms after Orthognathic Surgery- A Case Report**

Author(s): D. E. Hurtado, Department of Oral and Maxillofacial Surgery, U of Kentucky

Abstract: Obstructive sleep apnea (OSA) has been shown to negatively affect patient's daily living and has multiple etiologies. We report a case of a 16 year old male who presented to UK oral surgery for evaluation and treatment of a skeletal malocclusion. The patients past medical history revealed a diagnosis of obstructive sleep apnea at age 13. After treatment with orthognathic surgery, a resolution his OSA symptoms were reported with a marked increase in daily function.

Supported by:

Primary Presenter / e-mail: D. E. Hurtado / hurtado.de@uky.edu

Mentor or Senior Author / e-mail: L. Sivori / tonysivori@uky.edu

#28 Abstract Title: **Effect of Treatment of Gingivitis on Select Salivary Biomarkers Levels**

Author(s):
B. D. Syndergaard, Department of Periodontology, U of Kentucky
M. Al-Sabbagh, Department of Periodontology, U of Kentucky
C. S. Miller, Department of Oral Health Practice, U of Kentucky
D. R. Dawson, Department of Periodontology, U of Kentucky
J. L. Ebersol, Department of Oral Health Research, U of Kentucky
D. Noll, 4th year Dental Student, U of Kentucky

Abstract: Purpose: The purpose of this study is to determine whether levels of select inflammatory and connective tissue destructive biomarkers (i.e., Iinterleukin-1 β [IL-1 β], IL-6, matrix metalloproteinase-2 [MMP-2], matrix metalloproteinase-8 [MMP-8], macrophage inflammatory protein-1α (MIP-1α), and prostaglandin E2 [PGE2]) in whole saliva distinguish gingivitis before and after treatment. Specific Aims: 1) To identify salivary biomarkers associated with gingivitis. 2) To determine if levels of salivary biomarkers of gingivitis change after standard treatment of gingivitis. 3) To identify salivary biomarkers associated with response to treatment. Subjects: Eighty otherwise healthy adult subjects will be recruited from the University of Kentucky College of Dentistry. Forty subjects who have a minimum of 20 teeth, bleeding on probing (BOP) in less than 20% of sites, probing pocket depths (PD) of ≤4mm in all sites are considered healthy and will be the control group. Forty subjects who have a minimum of 20 teeth, bleeding on probing (BOP) in more than 20% of sites, probing pocket depths (PD) of ≤4mm in all sites are deemed to have gingivitis and will be the test group. Health subjects will expectorate at least ≥5ml whole saliva into sterile tubes at two different times. Gingivitis subjects will expectorate at least ≥5ml whole saliva into sterile tubes twice before dental cleaning and once after the dental cleaning. Research Hypothesis: Select biomarkers of inflammation and connective tissue destruction are present in whole saliva in greater quantities in gingivitis subjects prior to receiving dental prophylaxis treatment compared to post-treatment.

Supported by: University of Kentucky Department of Oral Health Research University of Kentucky Department of Oral Health Practices University of Kentucky Department of Periodontology

Primary Presenter / e-mail: B. D. Syndergaard / bensyndergaard@uky.edu

Mentor or Senior Author / e-mail: M. Al-Sabbagh / malsa2@email.uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#29 Abstract Title: **Effects of aging on osteoclast related genes in non-human primates**

Author(s):
S. Gudhimella , Division of Orthodontics, UK College of Dentistry
S. Huja, Division of Orthodontics, UK College of Dentistry
J. L. Ebersole, Center for Oral Health Research, U of Kentucky
O. A. Gonzalez, Center for Oral Health Research, U of Kentucky
S. Kirakodu, Center for Oral Health Research, U of Kentucky
J. Gonzalez-Martinez, Caribbean Primate Research Center
L. Orraca, School of Dental Medicine, University of Puerto Rico

Abstract: Objective: Osteoclastic activity plays a vital role in bone remodeling during orthodontic treatment. Potential variations in the expression of osteoclastic-related molecules in the oral tissues related with aging remain unclear. The aim of the current study was to determine the age-related changes in osteoclastic gene expression in healthy gingival tissues from non-human primates. Materials and Methods: The study group included 23 healthy non-human primates (M.mulatta). They were grouped as young (<3yrs, n=5), adolescent (3-7 yrs, n=5), adult (12-15 yrs, n=7) and aged (18-22 yrs, n=6). We obtained the unilateral interdental papilla between 2nd premolar and 1st molar from maxilla or mandible and subjected to RNA extraction and further microarray analysis using Gene Chip Rhesus Macaque Genome Array (Affymetrix) and Gene Chip Operating Software 5.0. The expression levels of 22 genes involved in osteoclast formation, attachment and bone resorption were evaluated. For each gene, a simple linear regression model was fit to the scatter plot of expression by age as a continuous variable. A P-value ≤ 0.05 was used to evaluate the significance of correlation. Results: Among the 22 evaluated genes, IL-6 (r= 0.59; p-value=0.003,), IL-17 (r=0.48; p-value 0.020), and M-CSF (r=0.53; p-value 0.009) showed significant positive correlations with age. In contrast, ITGB3 (r= -0.53; p-value=0.009,) had a negative correlation with age. Discussion: Although the up regulation of IL-6, IL-17 and M-CSF could favor the increase in the number of osteoclasts in aging healthy gingiva, the decreased expression of ITGB3 gene could make osteoclasts dysfunctional affecting the magnitude of bone resorption. Conclusion: In conclusion, we identified specific osteoclastic-related genes whose expression change with aging in oral mucosa. In our future studies, we will examine a larger array of osteogenic genes for both bone formation and resorption and continue to focus on specific genes identified by this study analyses.

Supported by: National Institute of General Medical Sciences (NIGMS) grant #-8P20GM103538-09.
Primary Presenter / e-mail: S. Gudhimella / sudhagudhimella@uky.edu
Mentor or Senior Author / e-mail: S. Huja / sarandeep.huja@uky.edu

#30 Abstract Title: **The Role of Autophagy and Aging in Chronic Periodontitis**

Author(s):
E.D. Neuman, Department of Periodontology, U of Kentucky
O. A. Gonzalez, Department of Dental Research and Graduate Studiesm U of Kentucky

Abstract: Introduction: Chronic Periodontitis is a disease marked by the active breakdown of connective tissue and alveolar bone. The breakdown is attributed to the virulence of the periodontal pathogens and the host's inflammatory and immune reactions to these microbes. Recent research seems to place great emphasis on damage caused by the host defenses when inflammatory mediators are responsible for protease and osteoclastic activity. Autophagy is a recently described mechanism by which cytoplasmic material, including soluble macromolecules and organelles, is delivered to lysosomes for degradation2. Emerging evidence indicates that autophagy-deficient cells demonstrate an exaggerated inflammatory response 3, 4, 5. Therefore, a natural assumption would be that chronically inflamed gingival tissues affected by periodontal disease would demonstrate variation in the expression of autophagy-related pathways. Materials and Methods: Ontology analysis of 88 genes related to apoptotic pathways was performed in gingival biopsies of healthy and periodontitis sites from young, adult, and aged non-human primates (Macaca mulatta), using the GeneChip® Rhesus Macaque Genome Array. There were a total of 15 monkeys (11 female, 4 male used in this study. Healthy animals (3 per group) were distributed by age in 3 groups as follows: ≤ 3 yrs (young), 12-15 yrs (adult), and 18-22 yrs (aged). Only adult and aged animals (3 per group) with periodontitis were used, since periodontitis does not occur in young animals1. Results: The results will examine the expression of 24 genes know transcribe proteins involved in the autophagic pathway. The gene expression will be measured in gingival tissue biopsies from young, adult, and aged animals exhibiting both health and periodontal disease. Discussion: The discussion will seek to determine the potential age-related changes in the expression of genes involved in autophagic pathways in healthy and diseased gingival tissue from young, adult, and aged non-human primates (M. mulatta). Considering autophagy has many negative regulatory effects on inflammation, it is hypothesized that the expression of genes involved in autophagy will be negatively correlated with the amount of tissue destruction occurring in tissue affected by periodontal disease and aged individuals.

Supported by: University of Kentucky College of Dentistry Department of Periodontics
Primary Presenter / e-mail: E. D. Neuman / edneum2@uky.edu
Mentor or Senior Author / e-mail: O. Gonzalez / ogonz2@email.uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#31 Abstract Title: **Investigation of a Potential Genetic Link Between Hypodontia and Ovarian Cancer**

Author(s):
M. S. Gilbey, College of Dentistry, U. of Kentucky
A. N. Vu, Private Orthodontic Practice, Johns Creek, GA
K. C. Kirk, College of Dentistry, U. of Kentucky
G. Falcão-Alencar, Center for Oral Health Research, U. of Kentucky
P. E. DiFranco, College of Dentistry, Division of Orthodontics, U. of Kentucky
M. Sakamoto, Private Dental Practice, Tokyo, Japan
D. W. Fardo, College of Public Health, U. of Kentucky
J. K. Hartsfield, College of Dentistry, Division of Orthodontics, U. of Kentucky
L. A. Morford, College of Dentistry, Division of Orthodontics, U. of Kentucky

Abstract: Objective: This case-control study was designed to investigate whether Single Nucleotide Polymorphisms (SNPs) located within five unique Ovarian Cancer Susceptibility Loci (OvCSL) are associated with hypodontia. Method: This study was approved by the UK IRB. Ninety-three unrelated, Caucasian Orthodontic patients have been recruited and classified into two groups: 25 patients with hypodontia and 68 controls. Hypodontia was defined as having 1-to-6 non-3rd molar teeth never form in the adult dentition. The number of partially formed (peg-shaped) teeth were also noted. DNA was isolated from patient saliva and SNPs within five OvCSL (rs2072590, rs2665390, rs3813114, rs6983267 and rs10088218) were genotyped using Taqman®-methodology. A Chi-square analysis was used to access Hardy-Weinberg equilibrium in the control population and to test for association of each SNP with hypodontia (significance at $p<0.05$). Result: Within this population, the teeth most frequently affected by hypodontia or partial formation were the maxillary lateral incisors, followed by mandibular 2nd molars, and maxillary 2nd premolars. While four of the five OvCSL examined showed no association with hypodontia, the OVCSL marker located on chromosome 8q24 (rs10088218) was significantly associated with hypodontia ($p=0.0086$ under a recessive mode-of-inheritance). Conclusion: An overall goal of our research is to determine whether the occurance of hypodontia (and other dental anomalies) could predict the occurrence of other diseases, such as Ovarian Cancer. Our research has demonstrated that a known OvCSL is associated with hypodontia. Future studies are needed to determine whether variation at this loci is uniquely associated with women who concurrently have hypodontia and Ovarian Cancer.

Supported by: Supported in part by a 2012-2013 University of Kentucky College of Dentistry (UKCD) Student Research Fellowship (MSG), the American Association for Women in Dentistry (ANV), the Southern Association of Orthodontics (ANV, PED), and the E. Preston Hicks En

Primary Presenter / e-mail: M. S. Gilbey / msgi223@uky.edu

Mentor or Senior Author / e-mail: L. A. Morford / lorri.morford@uky.edu

#32 Abstract Title: **Differential responses of DCs with polybacterial and monobacterial challenges**

Author(s):
C. Huang, Center for Oral Health Research, College of Dentistry, U of Kentucky
Y Alimova, Center for Oral Health Research, College of Dentistry, U of Kentucky
J. Ebersole, Center for Oral Health Research, College of Dentistry, U of Kentucky

Abstract: Periodontitis is a polymicrobial disease that represents a chronic immunoinflammatory lesion that undermines soft tissue integrity and progresses to alveolar bone resorption. Objectives: How this localized polybacterial stimulus alters DC maturation and functional properties, what factors enable them to “sort through” the composite of stimuli within a polybacterial infection, and the fundamental interactions of iDCs with polybacterial complex resulting in mDCs formation remain unknown. Methods: THP-1 derived DCs and iDCs were treated with various combinations of oral bacteria. Cytokines and gene expression levels by the iDCs related to the functional maturation and ability to interact with T cells were examined. Results: The data suggested that the profiles of cytokines could be modulated by the polybacterial challenge, but not demonstrating a particular pattern of additive, syngeristic, or inhibitory responses that could be predicted from simply evaluating the bacteria individually. Responses to the pathogen (Pg) were modified in combination with various commensal bacteria (Ssa, An). Bacterial binding and uptake by iDCs was also affected by the polybacterial competition. Both Fn and An (at 10-fold excess) appeared to enhance association of Pg with the iDCs, while decreasing uptake by 35-50%. Conclusions: The findings support that investigation of iDC responses to the types of polybacterial consortia that might be encountered in situ in the oral cavity are crucial to fully understand the features of the local innate and adaptive immune responses as they are impacted by specific maturation pathways for the activated iDCs.

Supported by: P20 GM103538 and the Center for Oral Health Research.

Primary Presenter / e-mail: C. Brad Huang / chuan2@uky.edu

Mentor or Senior Author / e-mail: C. Brad Huang / chuan2@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#33 Abstract Title: **Association Analysis of Genetic Markers within the Activin B-A/ Activin B-B Genes and Non-3rd-Molar Naturally Missing Teeth (NMT)**

Author(s):
P.E. DiFranco, Department of Orthodontics, U of Kentucky
L.A. Morford, Department of Orthodontics, U of Kentucky
G.F. Alencar, Dentistry Research, and Graduate Studies, U of Kentucky
M.S. Gilbey, College of Dentistry, U of Kentucky
A. Vu, Department of Orthoodntics, U of Kentucky
K. Kirk, College of Dentistry, U of Kentucky
D. Fardo, Biostatistics, U of Kentucky
J.K. Hartsfield, Department of Orthodontics, U of Kentucky

Abstract: Objective: The aim of this case-control study was to determine the association between genetic variations within or near the Activinb-A (INHBA)/Activin b-B (INHBB) genes and NMT in a population of orthodontic patients. Methods: The study was approved by the UK IRB. Genomic DNA was collected from 97 patients being treated in the UK Orthodontic Clinic (25 with hypodontia, 4 with oligodontia and 68 controls). Genetic markers within the INHBA gene locus (rs6977571, rs3801158 and rs2237436) and INHBB gene locus (rs11890218, rs11902591 and rs7576183) were genotyped using Taqman®-methodology. Hardy-Weinberg-Equilibrium (HWE) testing was employed to assess genotyping quality, and logistic regression for association testing (significance at $p < 0.05$). Results: A total of 47 non-3rd-molar-NMT were observed in subjects with hypodontia. The most common teeth affected by hypodontia were the mandibular-2nd-premolars, maxillary-lateral-incisors, and maxillary-2nd-premolars. Pegged-shaped-teeth were noted in 7 subjects with hypodontia, affecting 13 additional maxillary teeth. A total of 43 non-3rd-molar-NMT were observed in the 4 subjects with oligodontia. All control genotypes maintained HWE. Based on a dominant mode-of-inheritance (MOI), the INHBA marker rs6977571 was associated with general NMT (i.e. hypodontia or oligodontia) compared to controls ($p=0.048$). Under a recessive MOI, the INHBB marker rs7576183 was associated with subjects exhibiting hypodontia (12 GG/13GA/0AA) compared to controls ($p=0.031$). No associations were observed between the other 4 genetic markers tested and NMT. Conclusions: These data suggest that genetic variation within the INBHA and INHBB loci could influence the development of NMT. Further investigation is needed to identify the causative genetic variation(s) within these loci.

Supported by: American Association for Women in Dentistry (ANV), the Southern Association of Orthodontics (PED, ANV) and The UK College of Dentistry E. Preston Hicks Endowed Chair (JKH)

Primary Presenter / e-mail: P.E. DiFranco / pdifra2@gmail.com

Mentor or Senior Author / e-mail: L.A. Morford / lorri.morford@uky.edu

#34 Abstract Title: **Dentists in Appalachia: Regional Net Gain/Loss Analysis of Practicing General Dentists in Kentucky from 2008-2011**

Author(s):
M. Raynor Mullins, Dept of Oral Health Science, U of Kentucky College of Dentistry
J. Ebersole, Center for Oral Health Research, U of Kentucky College of Dentistry
R. Kovarik, Dept of Oral Health Science, U of Kentucky College of Dentistry
J. Aalboe, Dept of Oral Health Science, U of Kentucky College of Dentistry
P. Stein, Department of Oral Health Science, U of Kentucky College of Dentistry

Abstract: The future supply of dentists in Kentucky Appalachian counties (ARC region) is an important health policy consideration for Kentucky. As part of a planning needs assessment for an Appalachian Rural Dental Education Partnership, state dental licensure data for Kentucky were analyzed. Dentists are licensed and re-licensed on a two year cycle in Kentucky. Objective: To determine the relative net gain/loss in the number of dentists in various Kentucky regions. Methods: This study includes data from the most recent available licensure periods (2008-2009/2010-2011). Dental licensure data for the Commonwealth through the Kentucky Board of Dentistry were obtained from the ky.gov database and was divided into four regions: Central Kentucky, ARC, West/West Central and Mississippi Delta. The ARC was subdivided into 5 sub-regions; Big Sandy, Kentucky River, North East, 1-75 and Lake Cumberland. Regional counts of newly licensed dentists and dentists whose licenses expired for any reason (non-renewal, deceased, retired, revoked/suspended) were prepared. Results: From 2008-2011, there was a net gain of 224 general dentists in Kentucky. Most of the gains occurred in the 21 county Central Kentucky region (177/224 dentists). Data showed an 18 dentist net gain in the 54 ARC counties with 2/18 dentists located in the Eastern Kentucky Sub-regions (Big Sandy and Kentucky River). Conclusions: Gains in dentists in Kentucky occurred in the Central Kentucky region with far fewer in the ARC counties, particularly in the Eastern Kentucky sub-region.

Supported by: Appalachian Rural Commission, KY-17066-2011. The content is solely the responsibility of the authors and does not necessarily represent the official views of the ARC.

Primary Presenter / e-mail: P. Stein / pam.stein@uky.edu

Mentor or Senior Author / e-mail: R. Mullins / mraynor@uky.edu

#35 Abstract Title: **Comparison of BMI, AHI and Apolipoprotein E allele e4 (APOE e4) Alleles Among Sleep Apnea Patients with Different Angle Classifications**

Author(s):
J. J. Roedig, Department of Orthodontics, University of Kentucky
G. T. Kluemper, Department of Orthodontics, University of Kentucky
J. Hartsfield, Department of Orthodontics, University of Kentucky
J. Van Sickels, Department of Orthognathic Surgery, University of Kentucky
B. A. Phillips, Department of Sleep Medicine, University of Kentucky
D. Fardo, Department of Biostatistics, University of Kentucky
L. Morford, Department of Orthodontics, University of Kentucky

Abstract: Objective: Obstructive-sleep-apnea-syndrome (OSAS) is characterized by repetitive episodes of complete or partial upper airway obstruction leading to cessation (apnea) or intermittent reduction (hypopnea) of airflow into the lungs during sleep. A variety of phenotypes are associated with OSAS, including obesity and craniofacial-structure discrepancies. A retrognathic (retruded/deficient) mandible is one of the most commonly associated skeletal features of OSAS. Mandibular-deficiency and/or retrusion, especially as it relates to the maxilla, is referred to as a skeletal-class-II-relationship (Class-II), which in turn, is usually associated with a Class II dental relationship. The purpose of this case-control study was to investigate whether genetic variations within the APOE-e4 are associated with OSAS in Class-II patients compared to non-Class-II OSAS patients. Associations between having OSAS, variations in APOE e4 and normal/abnormal body-mass-index (BMI) scores were also examined. Method: OSAS patients with an Apnea-hypopnea-index (AHI) > 15 were recruited and classified into skeletal and dental classification types based on a clinical exam and lateral photographs. Saliva was collected as a source of DNA. APOE-e4 single-nucleotide-polymorphisms (SNPs) rs429358 and rs7412 were genotyped using TaqMan® Methodology. A Chi-square analysis was used to assess Hardy-Weinberg-Equilibrium and for association analysis (significance at $p<0.05$). ANOVA was used to compare BMI and AHI among the skeletal types. Result: Seventy-six Caucasian OSAS patients were recruited to the study, 25 Class II subjects - (8 females/17 males) and 51 non-Class II (3 female/11 male Class III; 13 female/24 male Class I). The average age of the Class-II patients was 57.8, with a mean BMI of 30.7 (obese) and mean AHI of 33.6. The average age of the non-Class-II patients was 55.1, with a mean BMI of 37.4 (obese) and mean AHI of 44.2. Seventy patients were overweight/obese and 6 were normal according to BMI (all 6 were Class-II). Conclusion: There was no association of either genetic marker with OSAS among the skeletal and dental classification types with this size study. Class-II OSAS patients had a significantly lower BMI (30.7) than Class I (37.2) or Class III (37.8) patients ($p<.001$). The AHI was lowest for Class II (33.6), followed by Class III (39.5) and the highest AHI was found in the Class I patients (46.0). Although this trend emerged, the differences between the three groups were not significant. There was however a significant ($p=.05$) difference in AHI between Class II and Class I participants, when only those two groups were compared. Thus, patients who have OSAS and are Class II have a lower average BMI, or are not classified as obese, suggesting that the Class II skeletal relationship is a contributing factor to OSAS in the absence of, or in conjunction with increased BMI.

Supported by: University of Kentucky College of Dentistry Department of Orthodontics
Primary Presenter / e-mail: J. J. Roedig / jroed2@uky.edu
Mentor or Senior Author / e-mail: G. T. Kluemper / gtklue1@email.uky.edu

#36 Abstract Title: **Recent Trends for Newly Licensed General Dentists Practicing in Kentucky and Appalachia**

Author(s):
R. Kovarik, Division of Public Health, College of Dentistry, U of Kentucky
J. Aalboe, Division of Public Health, College of Dentistry, U of Kentucky
P. Stein, Division of Public Health, College of Dentistry, U of Kentucky
M. Mullins, Division of Public Health, College of Dentistry, U of Kentucky

Abstract: Introduction: Forecasting the future supply of dentists for Kentucky and its Appalachian counties involves many considerations. In-migration and two practice location trends of newly licensed general dentists are for planning an Appalachian Rural Dental Education Partnership, trends from 2008-2011 were studied. Objective: Document Kentucky and regional trends for newly licensed general dentists. Methods: Dental licensure data were obtained from the Kentucky Board of Dentistry. Kentucky was divided into 4 regions: ARC, Central Kentucky, Wes/West Central and Mississippi Delta. Annual counts were prepared for newly licensed general dentists, by region. Findings: From 2008-2011, 481 new general dentists were licensed by Kentucky. In 2012, 358 practiced in Kentucky. Significantly 145 of these practicing dentists were educated by out-of-state dental colleges. Most of these new dentists located in Central Kentucky. Conclusions: Total numbers and in-migration of newly licensed general dentists steadily increased from 2008-2011. These trends have important implications for future state and educational planning.

Supported by: Appalachian Regional Commission: KY-17066-2011
Primary Presenter / e-mail: R. Kovarik / rekova2@uky.edu
Mentor or Senior Author / e-mail: R. Kovarik / rekova2@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#37 Abstract Title: **Genetic Analysis of Growth-Hormone-Receptor (GHR) SNPs and Pubertal Mandibular Growth**

Author(s):
A. R. Betz, College of Dentistry, University of Kentucky
K.E. George, College of Dentistry, University of Kentucky
L.A. Morford, Center for Oral Health Research, University of Kentucky
G. Falcao-Alencar, Collehe of Dentistry, University of Kentucky
J.V. Macri, Indiana University, Indiana, IN
J.K. Hartsfield, Oral Health Science, University of Kentucky

Abstract: The aim of this study was to determine whether single-nucleotide-polymorphisms (SNPs) in the Growth-Hormone-Receptor (GHR) gene influence Caucasian mandibular ramus growth during the pubertal growth spurt. Previous studies using Asian populations have demonstrated a correlation between three neighboring non-synonymous SNPs near the 3'-end of the GHR gene (rs6180, and rs6182 rs6184) and adult mandibular ramus height. Unfortunately, rs6182 and rs6184 occur at extremely low frequency in Caucasians and could not be utilized. Instead, we examined rs4130114 and rs2972408 which occur in two separate Caucasian linkage-disequilibrium-blocks upstream of the rs6180 marker in the GHR gene. Caucasian subjects (28 females and 20 males) were chosen for the study based on their cervical-vertebral maturation-stage (CVMS). Lateral cephalometric radiographs were analyzed using Dolphin Cephalometric Software for S-Go, Co-Go, and Ar-Go. DNA from each subject was genotyped at three SNP loci within the GHR gene (rs6180, rs4130114 and rs2972408) utilizing Taqman®- Methodology. For each SNP and Cephalometric measurement examined, annualized growth measurements were first grouped based on each subjects' SNP-genotype and then were analyzed by ANOVA for differences in growth (significance at $p<0.05$). One-way analysis-of-variance showed that the annualized S-Go growth in females with SNP rs4130114 was borderline statistically significant ($p=0.056$), with heterozygous females displaying the largest growth increases. No other comparisons of GHR genotype and Cephalometric measurement were significant in Caucasian males or females. While this study does suggest that rs4130114 could be an indicator of ramus growth in Caucasian females, the findings of previous studies which showed an increased ramus height in Chinese rs6180-C carriers were not reproduced in this Caucasian population.

Supported by: College of Dentistry Student Research Fellowship (AB), A Southern Association of Orthodontists Grant(KEG), The Indiana University Bixler Fund for Research in Genetics (JKH),and E. Preston Hicks Endowed Chair (JKH)

Primary Presenter / e-mail: A.R. Betz / ashley.betz@uky.edu

Mentor or Senior Author / e-mail: J.K. Hartsfield / james.hartsfield@uky.edu

#38 Abstract Title: **Future Dental Services Supply: Aging Distribution and Characteristics of Practicing Dentists and Dental Specialists in Kentucky and the Appalachian Region**

Author(s):
Aalboe, J., Division of Public Health, College of Dentistry, University of Kentucky
Mullins, R., Division of Public Health, College of Dentistry, University of Kentucky
Kovarik, R., Division of Public Health, College of Dentistry, University of Kentucky
Stein, P., Division of Public Health, College of Dentistry, University of Kentucky

Abstract: The future supply of dentists for rural Kentucky and the ARC region is an important health policy consideration for Kentucky. As part of a planning needs assessment for an Appalachian Rural Dental Education Partnership, state dental licensure data for Kentucky were analyzed. Objective: Determine age and distribution patterns in Kentucky and the ARC region of practicing dentists. Methods: Workforce assessments were calculated as frequency distributions for dentists and dental specialists by age and geographic location. Results: The results demonstrate that nearly 50% of the 2063 practicing general dentists and 53% of the 448 dental specialists in Kentucky were over the age of 50 in 2012. In the ARC region (54 counties), 52% of the 395 practicing general dentists and 45% of the 58 specialists are aged 50 and older. With two ARC Sub-regions, Big Sandy and North East each reporting 60% of their practicing general dentists as age 50 and older. Regional distributions indicate that of the 120 counties in Kentucky, the Central Triangle (23 counties) has the greatest concentration of dentists (60%, n=1215) and dental specialists (64%, n=288) compared to the ARC regions 19% (395) of general dentist and 13% (58) of specialists. Conclusion: Replacement of the aging dentist population in Appalachia, a region with fewer dentists, is likely to be very challenging. Private practice dentist are faced with demographic and economic changes as well as changes in Medicaid, managed care, private dental insurance and corporate competition. Secondary analyses determined that newly licensed dentists are choosing practice locations in the Central Triangle region, intensifying the problem.

Supported by: Appalachian Regional Commission

Primary Presenter / e-mail: J.A. Aalboe / joanna.aalboe@uky.edu

Mentor or Senior Author / e-mail: J.A. Aalboe / joanna.aalboe@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#39 Abstract Title: **Oral Health Status and Biomarkers of Myocardial Infarction**

Author(s): J. Kolasa, University of Kentucky
J. Ebersole, University of Kentucky
R. Kryscio, University of Kentucky
C. Campbell, University of Kentucky
D. Kinane, Departments of Pathology and Periodontics, University of Pennsylvania, Philadelphia, PA
J. McDevitt, Chemistry/Bioengineering, Rice University, Houston, TX
N. Christodoulides, Rice University, Houston, TX
P. Floriano, Rice University, Houston, TX
C. Miller, University of Kentucky

Abstract: Objective: To determine whether oral health status confounds biomarker levels used in the assessment of myocardial infarction (MI). Methods: A cross-sectional clinical study was implemented where oral health status was determined and serum and unstimulated whole saliva (UWS) were obtained from 92 MI patients (<48 hours of chest pain onset) and 111 age- and gender-matched non-AMI controls. Serum and UWS were assayed for 21 proteins relevant to cardiovascular disease using Beadlyte technology (Luminex®) and enzyme immunoassays. Data were analyzed by t-tests, chi-square, ANOVA and receiver operator characteristics (ROC) using PC-SAS version 9.3. Results: Serum levels of brain natriuretic peptide (BNP), troponin I, creatine kinase-MB, myoglobin and C-reactive protein (CRP) were significantly elevated in the MI patients (5-30 fold, $P<0.001$), with poorer oral health and fewer teeth being associated with lower BNP and CRP levels. Salivary levels of the cardiac panel biomarkers were less discriminatory of MI than serum levels and showed greater influence by oral health status. Whereas saliva CRP levels were significantly elevated in MI patients ($P<0.0004$) compared to the mean of the controls regardless of oral health or number of teeth in the groups, CRP levels were elevated at greatest concentration in MI patients with the most teeth and poor overall oral health. In the ROC analyses, serum had better discriminatory capacity for MI than saliva, with minimum affect by oral health. In contrast, in saliva only CRP discriminated the two groups when oral health was good or at least 20 teeth were present. Conclusions: These results indicate that select biomarkers for MI were directly reflective of the cardiac event in both serum and saliva, although salivary levels of the biomarkers were generally less discriminatory. Overall, oral health had minimal impact on the validity of the cardiac panel biomarkers in serum and salivary CRP.

Supported by: National Institute of Health P20 RR020145, U01 DE017793 and M01-RR02602, the University of Kentucky General Clinical Research Core and partially supported by the Clinical and Translational Science Award UL1RR033173 to the University of Kentucky.

Primary Presenter / e-mail: J. Kolasa / jrkola2@uky.edu

Mentor or Senior Author / e-mail: J. Ebersole / jeffrey.ebersole@uky.edu

#40 Abstract Title: **Successes of Seven Years of Prevention-Focused Dental Outreach in Rural Appalachia**

Author(s): N. Stone, Dentistry, U of Kentucky
J. Ebersole, Dentistry, U of Kentucky
R. Kovarik, Dentistry, U of Kentucky
M. R. Mullins, Dentistry, U of Kentucky
S. Turner, Dentistry, U of Kentucky

Abstract: In 2006, a mobile dental outreach program began operating full-time at the UK North Fork Valley Community Health Center in Hazard, Kentucky, a federally-qualified health center administered by the University of Kentucky. This program continues to provide preventive dental care to children aged 0-18 at forty different elementary schools and Head Start centers in a four county area in southeastern Kentucky, in the heart of rural Appalachia. The program serves approximately 2,000 children each school year. Baseline data from the 2006/2007 school year indicated that this population had the second highest rates of untreated tooth decay in the nation, as well as urgent dental needs much higher than the previously reported state rates. The successes of this consistent, prevention-focused mobile dental outreach program will be presented in this poster presentation. Since baseline data was reported at the conclusion of the 2006/2007 school year, the subsequent seven years of the program have revealed a continual decrease in untreated tooth decay rates, 14% lower in the elementary school and 16% lower in the Head Start populations, as well as urgent dental need rates that have been cut in half from 20% to 9%. Another significant success is a four-way partnership between the UK dental outreach team, the Head Start program, a regional pediatric dentist, and the local hospital which has resulted in improved treatment completion from a baseline of only 8% to nearly 70%.

Supported by: HRSA D59HP04084, Kentucky-Consortium for Applied Oral Health Research, National Center for Research Resources/NIH (D1ARH05653-01-00) , HRSA-07-102, Health Center Cluster 2008-2011 HRSA, Designated Health Projects: Kentucky Oral Health Network Scope 2008

Primary Presenter / e-mail: N. Stone / daria.stone@uky.edu

Mentor or Senior Author / e-mail: M. R. Mullins / mraynor@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#41 Abstract Title: **Non-interference of Pacemaker and ICD Activity by Electrical Dental Devices in Humans**

Author(s):
J.L. Meeks, Dental Student, College of Dentistry, U of Kentucky
C.S. Miller, Department of Oral Medicine, U of Kentucky
S.C. Elayi, Department of Cardiology, Gill Heart Institute, U of Kentucky
G.X. Morales, Department of Cardiology, Gill Heart Institute, U of Kentucky
S.D. Lusher, Department of Cardiology, Gill Heart Institute, U of Kentucky

Abstract: Objectives: To determine if electrical dental devices interfere with the pacing function of common implanted cardiac pacemakers or implantable cardioverter-defibrillators (ICDs) in humans. Methods: Twenty-six consecutive asymptomatic nonpacemaker-dependent patients were subjected to commonly used types of electrical dental equipment (i.e., battery operated curing light, ultrasonic bath, ultrasonic scaler, electric pulp tester, and electric toothbrush) in the outpatient Cardiology Clinic. Dental devices were operated at all power levels for 60 seconds at various distances, ranging from directly over the device to 18 inches away to simulate routine use in the dental office. Telemetry associated electrocardiogram recordings were obtained using standard chest leads and interpreted in real-time by a cardiologist who noted any interferences. Ten pacemakers (4 St. Jude®, 3 Medtronic®, 1 Boston Scientific®, 1 Cylos®, and 1 Biotronik®) and sixteen ICDs (8 St. Jude®, 3 Medtronic®, and 5 Boston Scientific®) were tested. During testing, the atrial lead was made the most sensitive to help discriminate interference in telemetry vs. pacing. Results: To date, twenty-six patients have been enrolled and studied. Interference in sensing and pacing was not detected in any case nor were adverse effects detected. Interference was noted, however, in communication between the wand and the telemetry program upon use of the ultrasonic scaler in all cases. Conclusion: These data, which represent the largest cohort study to date using a variety of dental devices, suggest that these electrical devices commonly used in dental practices do not interfere with the pacing of cardiac patients' pacemakers or ICDs. However, they do interfere with the telemetry. Our findings contrast with previous in-vitro studies published in the literature and should help in the development of clinical guidelines regarding dental management of patients with pacemakers or ICDs.

Supported by:

Primary Presenter / e-mail: J.L. Meeks / jillianm05@gmail.com

Mentor or Senior Author / e-mail: C.S. Miller / cmiller@uky.edu

#42 Abstract Title: **Drink Smart with Cal the Cow!**

Author(s):
L. Hancock Jones, Department of Public Health Dentistry, UK College of Dentistry
J. Knight, West Area Health Education Center
B. Crook, Hopkins County Health Department
N. Stone, Dentistry Oral Health Science, UK College of Medicine

Abstract: Drink behaviors for children are a contributing factor in Early Childhood Caries. The Western Kentucky Regional Dental Coalition (WKRDC) partners applied for funding, in partnership with United Way of the Coalfield,toaddress drink behaviors in a social marketing campaign targeting the first grade students of Hopkins County , KY. Using “The New Drink Pyramid” slogan created by Dr. Nikki Stone, the WKRDC hopes to reinforce contemporary dietary guidelines for children which include consuming 2 or more servings of dairy foods daily, limit intake of 100% juice to 4 to 6 oz daily, and restrict other sugared beverages to occasional useper the American Academy of Pediatrics. The Drink Smart campaign hopes to investigate the current drinking habits of local children, to educate the students as to the importance of making good drink choices, and how proper dental care includes proper nutrition.

Supported by:

Primary Presenter / e-mail: L.B. Hancock Jones / lha225@uky.edu

Mentor or Senior Author / e-mail: L.B. Hancock Jones / Lha225@uky.edu

College of Dentistry Research Day

Poster Presentation Abstracts

8th Annual CCTS Spring Conference

April 8, 2013

#43 Abstract Title: **The Economic Impact of Dentist's Offices in Appalachia**

Author(s):
A. Stewart, Center for Business and Economic Research, Gatton College, U of Kentucky
M.T. Childress, Center for Business and Economic Research, Gatton College, U of Kentucky
M. Mullins, Division of Dental Public Health, College of Dentistry, U of Kentucky
P. Stein, Division of Dental Public Health, College of Dentistry, U of Kentucky
R. Kovarik, Division of Dental Public Health, College of Dentistry, U of Kentucky
L.J. Brown, Division of Dental Public Health, College of Dentistry, U of Kentucky

Abstract: Introduction: The local impact of dental practice revenue in Appalachia is important. To help assess need for an Appalachian Rural Dental Education Partnership (ARDEP), the county level economic impact of dental offices in the ARC region was studied. Objective: Determine multipliers and the economic impact of a typical new dentist's office in the ARC region and Kentucky. Methods: Kentucky was divided into major regions: ARC, Central Kentucky and Western Kentucky. The IMPLAN model (Minnesota IMPLAN Group) was used to develop multipliers and prepare county estimates. National Economic Census (2007) revenue data for Kentucky dentist offices was used and adjusted for 2012 dollars. Numbers of dentists were obtained from the Kentucky Dental Licensure database, Kentucky Board of Dentistry. Findings: Economic multipliers for ARC counties ranged from 1.37 to 1.57. County impact for a new dental office ranged from $563,843 to $1,313,380. Fifty five percent of ARC counties in the census sample counties fell below average gross revenue of $600,000 Central Kentucky counties were 77% above $600,000 with multipliers from 1.34 to 1.9. Western Kentucky Counties were 55 % above $ 600,000 with multipliers from 1.34 to 1.9. Conclusions: The economic impact of dental practice revenue multiplied across Kentucky and for the ARC region is substantial, including county impacts. The value of improvements in oral health on child development, education and general health were not estimated. Given the burden of disease in Appalachia, such improvements would likely add substantial economic value to these estimates.

Supported by: Appalachian Regional Commission Ky-17066-2011

Primary Presenter / e-mail: A. Stewart / alstew01@uky.edu

Mentor or Senior Author / e-mail: M.T. Childress / mtch224@uky.edu

#44 Abstract Title: **Insurance Contributions to Gross Revenue of General Dentists in Kentucky and Appalachia**

Author(s):
M.R. Mullins, Division of Dental Public Heath, College of Dentistry, University of Kentucky
L.J. Brown, Division of Dental Public Health, College of Dentistry, University of Kentucky
R. Kovarik, Division of Dental Public Heath, College of Dentistry, University of Kentucky
P. Stein, Division of Dental Public Heath, College of Dentistry, University of Kentucky
J.L. Ebersole, Center for Oral Health Research, College of Dentistry, University of Kentucky

Abstract: Introduction: As the Affordable Care Act is implemented and increases in Medicaid enrollment occur, increased dentist participation in the Kentucky Medicaid Program will become very important. To help assess need for an Appalachian Rural Dental Education Partnership (ARDEP), regional levels of Medicaid participation and the relative contribution of government programs to dental gross revenue are being studied. Study Objective: Estimate percent contribution to annual gross receipts of general dentists, by insurance type and for out-of-pocket direct payment by patients. Method: The American Dental Association (ADA) conducts annual surveys of Dental Practice. A Kentucky Report of historical self-responses by practicing dentists to these surveys was developed. Kentucky was sub-divided into major regions: Appalachia, Central Kentucky and Western Kentucky. Responses were tabulated separately for incorporated practitioners, unincorporated practitioners and for sole proprietors. Findings: The contributions of government programs (Medicaid and KCHIP) to gross revenue for general dentists varied greatly with the highest percentages reported for the Appalachian Region: Incorporated (8.2%), Unincorporated (21.5%) and sole proprietors (17.8%). Government program contributions to gross revenue by practice were very low in Central Kentucky (3.2% to 4%) and Western Kentucky (8.4% to 9.4%). For all regions, private dental insurance (43% to 53%) and direct patient payment (29% to 40%) were the major contributors to gross revenues. Conclusions: General dentists in all regions of Kentucky are heavily dependent on collections from private insurance and direct patient payments .The small relative contributions of government programs to gross revenue has important implications for future Medicaid policy and dentist participation.

Supported by: Appalachian Regional Commission: KY-17066-2011

Primary Presenter / e-mail: M.R. Mullins / mraynor@uky.edu

Mentor or Senior Author / e-mail: M.R. Mullins / mraynor@uky.edu

#45 Abstract Title: **The action of stimulating adenylyl cyclase within motor nerve terminals in the regulation of synaptic vesicles.**

Category: Undergraduate

Author(s): Y. Zhu, Dept. of Biology, U of Kentucky
W.-H. Wu, Dept. of Biology, U of Kentucky
R.L. Cooper, Dept of Biology, U of Kentucky

Abstract: Past studies using the crayfish neuromuscular junction (NMJ) have shown that serotonin (5-HT) can enhance synaptic transmission even after synaptic depression is induced and that this is partially due to activation of the IP3 signaling. Recently it was shown that blocking PLC (which decreases in IP3 formation) dampens the 5-HT induced response; however, there was still a substantial action that was induced by 5-HT. cAMP has been suggested to be involved in 5-HT action in invertebrate neurons. To test the idea that 5-HT might stimulate cAMP to account for some of the enhanced responses forskolin (an adenylyl cyclase activator) was added to non-depressed and synaptically depressed NMJs. To examine for a commonality in altering synaptic transmission, NMJs of the larval Drosophila were also examined. What is interesting about the larval NMJs is that they are insensitive to application of 5-HT. The novel aspect in this study compared to previous studies is in examining if the reserve pool (RP) of vesicles can be recruited following depression of the readily releasable pool (RRP) of synaptic vesicles through activation of adenylyl cyclase.

Supported by:
Primary Presenter / e-mail: Y. Zhu / yan.zhu@uky.edu
Mentor or Senior Author / e-mail: R.L. Cooper / RLCOOP1@email.uky.edu

#46 Abstract Title: **The effects of K+ on skeletal muscle, synaptic transmission and the relationship with deep tissue injury of muscle.**

Category: Undergraduate

Author(s): E. C. Burns, Center of Muscle Biology & Dept. of Biology, U of Kentucky
E. E. Dupont-Versteegden, Center of Muscle Biology & Div. of Physical Therapy, Dept. Rehabilitation Sci., College Health Sciences, U of Kentucky
R. L. Cooper, Center of Muscle Biology & Dept. of Biology, U of Kentucky

Abstract: Currently, deep tissue injuries (DTI) of skeletal muscle and skin are being treated similarly to Stage III or IV pressure ulcers. Presently, this is the only accepted standard of treatment for DTI. The primary skeletal muscle damage can produce secondary effects which can increase the spread of the damage zone. This can come about by the additive effects of intracellular contents, particularly the ion K+, released from crushed muscle cells in the spreading of DTI. Since the 1930's it has been known that fluid from damaged skin tissue would cause sensory neurons to stop responding (Feng, 1933). Also, it is well known that increasing the [K+]o in a saline Ringer solution 10 times the normal will result in cell (i.e., muscle) death. However, the consideration in the exposure time and effects of restoring normal [K+]o on the health of skeletal muscle has not been fully addressed. We are examining the effects of rapid rises of [K+]o over various periods of time before returning back to normal levels on the health of the muscle and the effects on synaptic properties at the neuromuscular junction. At present we are conducting investigations on the crayfish opener muscle as a model. We plan to gather information on treatment and assessment of DTIs in urgent care centers as well as establish rodent models for experimentation.

Supported by: Gertrude Ribble Biology Fellowship
Primary Presenter / e-mail: E. C. Burns / ecbu223@uky.edu
Mentor or Senior Author / e-mail: R. L. Cooper / rlcoop1@uky.edu

#47 Abstract Title: **Characterization of 5-HT receptor subtype in sensory-CNS-motor circuit in Drosophila larvae**

Category: Undergraduate

Author(s): A. Bankemper, Dept. of Biology, U of Kentucky
Z. Majeed, Dept. of Biology, U of Kentucky
R. L. Cooper, Dept. of Biology, U of Kentucky

Abstract: It is known that serotonin (5-hydroxytryptamine, 5-HT) can modulate the sensory-CNS-motor activity in Drosophila larvae. But the 5-HT receptor subtypes underlying the circuit activity have yet to be investigated. We hypothesize that activation of 5-HT2 and/or 5-HT7 increases the circuit activity in Drosophila third instar larvae. It has been revealed that Drosophila genome encodes four 5HT receptor subtypes, 5-HT1ADro, 5-HT1BDro, 5-HT2Dro, and 5-HT7Dro. 5-HT receptors in Drosophila are G-protein coupled receptors (GPCR). 5-HT1A and 5-HT1B are coupled with Gα inhibitory (Gαi). 5-HT2 is coupled with Gαq heterotrimeric G-protein and 5-HT7 is coupled with Gα stimulatory (Gαs). To test the action of pharmacological agents on the 5-HT receptors, the segmental nerves leading to the CNS were stimulated at 40Hz, 10 pulses while the body wall muscle fibers on the contralateral side were monitored. The evoked EPSPs in muscles 6 or 7 were counted before and after adding various pharmacological agents. In this study, various 5-HT agonists (5-HT1A agonist: 8-Hydroxy-DPAT hydrobromide; 5-HT1B agonist: CP 93129 HCl; 5-HT2 agonist: DOI hydrochloride; and 5-HT7agonist: AS 19) were used. We are now using a UAS-GAL4 system with specific UAS-RNAi-5-HT lines to knockdown specific 5-HT receptors in respective 5-HT receptor expressing neurons. Preliminary pharmacological results suggest 5-HT2 receptors heighten the activity within this circuit. In completing these studies we will be able to conclude which specific 5-HT receptor subtypes impact a sensory-CNS-motor circuit.

Supported by: Cooper -personal funds
Primary Presenter / e-mail: A. Bankemper / abankemper@uky.edu
Mentor or Senior Author / e-mail: R.L. Cooper / RLCOOP1@email.uky.edu

#48 Abstract Title: **The influence of serotonin alteration on behavior and development in Drosophila**

Category: Undergraduate

Author(s): Z. Majeed, Dept. of Biology, U of Kentucky
R. Swoveland, Dept. of Biology, U of Kentucky, Dunbar High School
R. Cooper, Dept. of Biology, U of Kentucky

Abstract: Serotonin (5-HT) is an essential molecule that acts as a neurotransmitter and a neuromodulator. Moreover, it has been shown that 5-HT acts as a signaling molecule during development. In this study, we investigated the consequences of the 5-HT alteration on behavior, such as, locomotor and feeding behaviors, and development of the organism. The embryos were collected after laying by the females on the apple-juice agar. Then 15 embryos were put inside the fly food that contained various concentrations of 5-HT, 5-HTP (precursor of 5-HT) or PCPA (inhibitor of tryptophan hydroxylase, TRH). Third instar larvae were employed for the behavioral assays. The results have shown that 5-HT (100mM) significantly decreased the body wall contractions (BWCs), as an indicator of locomotor behavior, and also decreased the mouthhook movements (MHMs), as an indicator of feeding behavior. Furthermore, 5-HT feeding affected on the development of larvae since these larvae were very small in size in comparison to control larvae. 5-HTP at 5mM and 25mM markedly decreased body wall contractions; however, it did not have dramatic effect on feeding behavior (MHMs). PCPA administration from first-instar to third-instar larvae stages negatively affected on locomotor (BWCs) and feeding behaviors (MHMs). Also, we used UAS-GAL4 system to misexpress TRH, the rate-limiting enzyme of 5-HT biosynthesis, in serotonergic neurons. The results have shown that TRH misexpression did not have a noticeable effect on the locomotor and feeding behaviors. We concluded that the disturbance of 5-HT homeostasis negatively influence the locomotor and feeding behavior and development of the organism.

Supported by: Cooper-personal funds.
Primary Presenter / e-mail: Z. Majeed / zana.majeed@uky.edu
Mentor or Senior Author / e-mail: R. L. Cooper / RLCOOP1@email.uky.edu

#49 Abstract Title: **A laboratory exercise in quantifying synaptic transmission: Quantal measures and analysis**

Category: Undergraduate

Author(s): S. Kenney, Dept. of Biology, U of Kentucky
R.L. Cooper, Dept. of Biology, U of Kentucky

Abstract: The purpose of the presented laboratory exercise is for students to observe and measure quantal synaptic vesicular release of neurotransmitter. This exercise utilizes crayfish neuromuscular junctions (NMJs) because of the ease in dissection and viability of the preparation. Students electrically stimulate a crayfish motor nerve in order to measure evoked and spontaneous vesicular events through direct counts, amplitude measurements, and charge measurements to quantify synaptic transmission. The crayfish abdominal extensor muscles are in groups with some being tonic (slow) and others phasic (fast) in their synaptic phenotypes. The NMJs of the abdominal extensors are used to investigate quantal properties in synaptic transmission. Also, one can examine the influence of neuromodulators, pharmacological agents and various concentrations of Ca2+ in the extracellular fluid on synaptic transmission in these preparations. With a loose patch electrode (focal macropatch) place over NMJs one can record spontaneous and evoked quantal events. The methods taught in this lab procedure are direct counting of evoked quantal events, measuring the amplitude and area under the curve of both evoked and spontaneous responses and estimate a mean quantal content. Overall, using the three methods to index quantal transmission allows for comparison among the different approaches in order to determine which are the most useful for the type of synaptic properties. Discussions on the variation in the shapes of single quantal events, pre- and post-synaptic contributions to the quantal responses as well as effects on the mean quantal content measurements are tackled.

Supported by: Dept. of Biology, Univ of KY and personal funds (RLC)
Primary Presenter / e-mail: S. Kenney / sarah.kenney@uky.edu
Mentor or Senior Author / e-mail: R.L. Cooper / RLCOOP1@email.uky.edu

#50 Abstract Title: **Dopamine's influence on nervous system anatomy during juvenile development**

Category: Undergraduate

Author(s): D. Potts, Dept of Biology, U of KY
J. S. Titlow, Dept of Biology, U of KY
R.L. Cooper, Dept of Biology, U of KY

Abstract: Changes in dopaminergic activity during embryogenesis have been shown to affect dendrite morphology in the peripheral nervous system of Drosophila melanogaster and in the mammalian striatum. Morphological differences then lead to abnormal behavior so we are curious about the role of dopamine homeostasis in maintaining synaptic connections. And because one of the most common insults to dopamine homeostasis in humans is prescription stimulant treatment for ADHD we are focused on the effects of methylphenidate (Ritalin®, dopamine transport blocker) on CNS structure during juvenile stages of development. To investigate this we have used the GAL-4/UAS system in D. melanogaster to drive expression of green fluorescent protein (GFP) to the cell membrane of specific neurons. These transgenic fly lines were then treated with methylphenidate (1mg/mL in standard fly food) for 24hr during the third instar larva stage, a treatment that has been shown to cause a slight reduction in mouth hook and body wall movements. The goal then has been to compare neural anatomy in these flies to their drug naive siblings. Fixed whole mount sections of the larval brains were visualized using confocal microscopy and GFP fluorescence was observed either in a subset of sensory neurons (sensory-GAL-4) or in dopaminergic neurons (ple-GAL-4). As expected there were no gross anatomical defects (e.g. cell death or abnormal wiring) in the treated flies from either line. But what we expected to see was differences in subcellular structures, e.g. numbers of synaptic boutons or secondary/tertiary branches. These details were not possible to discern in the sensory-GAL-4 line because of the density of cells expressing GFP in sensory neuropils and longitudinal tracts in the ventral nerve cord. This was also true of higher order branching in the ple-GAL-4 line but we were able to quantify synaptic boutons on identifiable dopaminergic neurons. We are in the process of analyzing these data and implementing a recombination strategy to label smaller subsets of neurons. These findings will reveal how the cell membrane dopamine transporter is involved in the maintenance of synaptic connections, which has functional implications for plasticity in brain regions receiving dopaminergic input.

Supported by: Dept. of Biology, Univ of KY and personal funds (RLC)
Primary Presenter / e-mail: D. Potts / douglas.potts@uky.edu
Mentor or Senior Author / e-mail: R.L. Cooper / RLCOOP1@email.uky.edu

#51 Abstract Title: **What fruit fly behavior teaches us about dopamine homeostasis, and vice versa**

Category: Undergraduate

Author(s): J. Browne, Dept of Biology, U. of KY
J.S. Titlow, Dept of Biology, U. of KY
R.L. Cooper, Dept of Biology, U. of KY

Abstract: Dopamine functions as a neuromodulator to mediate state-dependent plasticity in neural circuits. In many animals the neural circuits modulated by dopamine are involved in motor behavior or in feeding behavior. Aberrations in dopamine homeostasis are associated with abnormal CNS function, as in Parkinson's disease, hyperactivity, and possibly addiction. This conserved role for dopaminergic modulation has made us interested in how the nervous system adapts to changes in dopamine levels. Fruit flies are an ideal organism to study this because they exhibit reiterative stereotyped behaviors in response to various stimuli that are influenced by pharmacological and genetic manipulations in dopamine signaling. Negative geotaxis is a highly stereotypical behavior exhibited by adult flies and it was previously shown that pharmacological inhibition of dopamine synthesis attenuates this response. By supplementing fly food with dopamine and assaying this behavior we show that a systemic increase in dopamine also attenuates the response. Another sensory-motor behavior exhibited by adult flies is a robust response to sucrose when it is applied to sensory receptors on their labella, i.e. a proboscis extension reflex (PER) is activated by stimulation of gustatory neurons. Dopamine's role in this circuitry has been well-characterized and we were able to extend previous results showing that this reflex is potentiated by an increase in endogenous dopamine. Next we will test to see if systemic depletion of dopamine levels also potentiates the PER. This would support the theory that dopamine signaling functions within a homeostatic range, the implication being that dopamine acts like a binary switch on these circuits. When dopamine levels deviate from this range the modulatory effect doesn't become less on, or more on, it is just on or off. This property probably emerges from the dynamic distribution of dopamine receptors on the cell membrane.

Supported by: Dept. of Biology, Univ of Ky. and personal funds (RLC)
Primary Presenter / e-mail: J. Browne / Jessica.Browne@uky.edu
Mentor or Senior Author / e-mail: R.L. Cooper / RLCOOP1@email.uky.edu

---

#52 Abstract Title: **Effects of Ethanol Exposure and Hypoxia Combination on Behavioral Deficits in a Rodent Model**

Category: Undergraduate

Author(s): R. Gupta, Department of Psychology, U of Kentucky
M. Carter, Department of Psychology, U of Kentucky
S. Barron, Department of Psychology, U of Kentucky

Abstract: Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorders (FASDs) are characterized by a variety of cognitive and behavioral deficits resulting from alcohol consumption during pregnancy. We know that there is variability in the possible outcome following prenatal ethanol (ETOH) exposure although we do not understand all of the factors that contribute to this variability. One hypothesis is that a history of prenatal ETOH exposure may reduce the ability of the fetus to respond to subsequent fetal or perinatal challenges that occur. During labor and delivery, brief periods of reduced oxygen levels (hypoxia) are fairly common and the healthy fetus has a variety of compensatory mechanisms that usually protect the developing brain. We hypothesized that prenatal ETOH exposure would exacerbate the effects of a brief hypoxic challenge on behavioral outcome. This hypothesis was examined using a rodent model to assess the effects of ETOH and/or hypoxia on locomotor activity and spatial learning. On postnatal days (PND) 1-7, a time period that overlaps the 3rd trimester brain growth spurt of human pregnancy, Sprague Dawley rat pups were placed in three treatment groups: the ethanol exposed group (4.5 g/kg/day), an intubated control group, and a non-treated control group. On PND 8, ½ of the rats experienced an 8.5 min hypoxic challenge. On PND 20-21, activity was recorded in a circular open field chamber for 30 minutes daily. The hypoxia/ETOH exposed offspring were hyperactive and spent more time in the center of the open field, compared to all other treatment groups. Adolescent offspring (PND 40 – 41) were then tested in a water maze to measure acquisition and 24 hr. retention of the spatial task. Males exposed to hypoxia/ETOH took longer to learn the task relative to all other groups. There were no differences in hypoxia /ETOH females and all groups showed normal 24 hr. retention. These results suggest that a previous history of neonatal ETOH exposure increased the adverse consequences of a brief hypoxic challenge. Further work is ongoing to understand the underlying mechanisms and ways to reduce these effects as well as possible sex differences in sensitivity.

Supported by: This work was supported in part by NIAAA grant # AA17956 to SB and NIDA T32-DA16176.
Primary Presenter / e-mail: R. Gupta / rekha.gupta@uky.edu
Mentor or Senior Author / e-mail: S. Barron / sbarron@uky.edu

Poster Presentation Abstracts

#53 Abstract Title: **Understanding the Effects of Hypoxiain Combination with Ethanol Withdrawal in Vitro**

Category: Undergraduate

Author(s):
A. Manuel, Department of Psychology, U of Kentucky
M. Carter, Department of Psychology, U of Kentucky
B. Lewis, Department of Psychology, U of Kentucky
K.A. Wellmann, Department of Psychology, U of Kentucky
S. Barron, Department of Psychology, U of Kentucky

Abstract: Exposure to ethanol (ETOH) and oxygen deprivation during development can result in a variety of adverse outcomes for a fetus. Our lab has previously shown that hypoxia related cell death is enhanced in hippocampal slices that have been exposed to ETOH. The multiplicative damage observed following ethanol withdrawal (EWD) in combination hypoxia may be a result of the similar excitotoxic mechanisms that underlie these two insults. To better understand the characteristics of the cellular damage, two experiments were run using a hippocampal slice culture model. The first experiment investigated the time course of damage over 24 hours following EWD and hypoxia (oxygen glucose deprivation (OGD)) and the 2nd experiment investigated the effects of these insults on neuronal survival using immunohistochemistry. Slices were exposed to 100mM ETOH or control culture media for 10 days. Slices then received OGD treatment or control (air) for 30 min. In Exp 1, propidium iodide (PI) uptake (a non-specific marker of cell damage) was analyzed every 4 hours for 24 hours following OGD treatment. In Exp 2, the neuronal nuclear protein (NeuN) was used to assess neuronal viability. EWD/OGD exposed slices showed a steady increase in PI uptake, relative to controls and EWD or OGD alone slices, from the 4 to 16 hour time points following treatment in the CA1 region. There was no interactive effect in the CA3; however, there was an increase in damage from the 4 to 20 hour time point in OGD treated slices. OGD slices had greater PI uptake compared to controls in the DG, but this effect did not change over time. Unlike damage observed with PI, NeuN staining revealed only a main effect of EWD such that slices exposed to ETOH had a decrease in neuronal content in the CA1, CA3, and DG regions compared to non-ETOH treated slices. Exposure to OGD during EWD did not reduce neuronal content beyond that of EWD alone. These results show that EWD/OGD related damage increases well after the initial insult, suggesting an importance in the timing and duration of possible protective interventions. The results also indicate that the interactive damage is not specific to neurons but may involve other cell types such as glia. Taken together, these findings highlight the need to further investigate the damaging mechanisms underlying ETOH and hypoxia exposure in order to discover effective treatments.

Supported by: This work was supported in part by NIAAA grant # AA17956 to S. Barron and NIDA T32-DA16176 to M. Carter.

Primary Presenter / e-mail: A. C. Manuel / acma229@g.uky.edu

Mentor or Senior Author / e-mail: M. Carter / megancarter84@gmail.com

#54 Abstract Title: **Optimizing methods to quantify CYP1A enzyme activity in mouse brain with and without PCB exposure**

Category: Undergraduate

Author(s):
A.A. Ashworth, Department of Biological Sciences, Northern Kentucky U
U C.P. Curran, Department of Biological Sciences, Northern Kentucky U

Abstract: Polychlorinated biphenyls (PCBs) are widespread toxicants banned from production after neurological damage developed in children exposed during gestation and lactation. Genetic differences can influence how these chemicals are metabolized, so we use a mouse model in an effort to identify genes which affect human susceptibility to developmental PCB exposure. Coplanar PCBs activate the aryl hydrocarbon receptor (AhR) in high-affinity Ahrb mice and increase cytochrome P450 (CYP1) expression, including CYP1A2 protein which can sequester PCBs in the liver. Our work and the work of others have shown that this sequestration is protective. However, our previous research also found an increase in CYP1A1 mRNA in the brains of our most susceptible mouse line with the AhrbCyp1a2(-/-) genotype. Other researchers have reported differential expression and regulation of CYP1 enzymes in the brain. So, we are now assessing CYP1A protein levels and activity in various brain regions. We used the EROD assay as a test for CYP1A1 activity and the MROD assay for CYP1A2 activity. Liver from AhrbCyp1a2(+/+) was used as a positive control whereas Cyp1a1(-/-) and Cyp1a2 (-/-) knockout mice served as the respective negative controls. The optimum range of protein is 0.5 – 1.0g of tissue and there was enough in the cortex, cerebellum, and hypothalamus to conduct the assays. We found that 100mM potassium phosphate is an optimal buffer to homogenize the tissue, compared with 50mM Tris buffer. Including 2mM EDTA lowered enzymatic activity three-fold in our pilot study. Enzyme activity was highest in PCB-treated mice with a high-affinity Ahrb allele.

Supported by: NIEHS R15ES020053-01A1 and Kentucky Biomedical Research Infrastructure Network (KBRIN) Faculty Fellowship (P20 GM103436-12)

Primary Presenter / e-mail: A.A. Ashworth / ashwortha1@nku.edu

Mentor or Senior Author / e-mail: C.P. Curran / curranc1@nku.edu

Poster Presentation Abstracts

#55 Abstract Title: **Assessing anxiety in wild type, heterozygous and double knockout Cyp1a1_1a2(-/-) mice**

Category: Undergraduate

Author(s): B.T. Hays, Department of Biological Sciences, Northern Kentucky U
U C.P. Curran, Department of Biological Sciences, Northern Kentucky U

Abstract: Previous work in our lab uncovered motor deficits in Cyp1a2(-/-) mice and in a related strain of double knockout Cyp1a1_1a2(-/-) mice. We generated heterozygous Cyp1a1_1a2(+/-) mice to determine if there is a gene-dose effect, and we have expanded our behavior tests to more completely characterize the effect of gene loss on brain function. We are conducting tests on the offspring of heterozygous parents which include wild type (+/+) mice, heterozygous (+/-) mice and knockout (-/-) mice. To explore differences in behavior, we compared marble-burying behavior which is a commonly used measure of anxiety. Mice were placed into a shoebox cage for 20 min. with 3cm of bedding and 15 marbles. The number of marbles buried at least 2/3 was scored. Preliminary results will be reported for male and female mice of all three genotypes.

Supported by: NIEHS R15ES020053-01A1 and Kentucky Biomedical Research Infrastructure Network (KBRIN) Faculty Fellowship (P20 GM103436-12)

Primary Presenter / e-mail: B.T. Hays / breannh@gmail.com

Mentor or Senior Author / e-mail: C.P. Curran / curranc1@nku.edu

#56 Abstract Title: **Comparison of Cognitive Function in Two Strains of C57BL/6 Mice**

Category: Undergraduate

Author(s): J.W. Branham, Department of Biological Sciences, Northern Kentucky U
A.A. Ashworth, Department of Biological Sciences, Northern Kentucky U
H.F. Garber, Department of Biological Sciences, Northern Kentucky U
C.P. Curran, Department of Biological Sciences, Northern Kentucky U

Abstract: The most common strain of mice used in animal research is C57BL/6 or B6. Although this strain of mouse is inbred, random mutations and separation of B6 mice in geographically distinct facilities resulted in an accumulation of genetic differences. Recently, single nucleotide polymorphisms (SNPs) have been identified in multiple substrains of the B6 line. To determine if these differences could affect results in common behavioral tests, we compared motor and cognitive function in two of the most commonly used substrains: C57BL/6J, originating from Jackson laboratory, and C57BL/6N, originating from the National Institutes of Health. We used Morris water maze to assess spatial learning and memory and novel object recognition to assess non-spatial learning and memory. In the water maze, C57BL/6J mice outperformed the C57BL/6N mice on the first day of Cued Platform testing. However, C57BL/6N mice had significantly shorter latencies and shorter path lengths during the third (Shift) phase of Hidden Platform testing ($P<0.05$). This is the most difficult phase with the platform reduced in size and shifted to a new location. There were no significant differences in novel object recognition. Our findings suggest the choice of substrain as a control or background strain might influence the interpretation of results from classic neurobehavioral tests.

Supported by: NIEHS R15ES020053-01A1 and Kentucky Biomedical Research Infrastructure Network (KBRIN) Faculty Fellowship (P20 GM103436-12)

Primary Presenter / e-mail: J.W. Branham / jbranham34@yahoo.com

Mentor or Senior Author / e-mail: C.P. Curran / curranc1@nku.edu

Poster Presentation Abstracts

#57 Abstract Title: **Spontaneous alternation behavior in offspring of heterozygous Cyp1a1_1a2(+/-) mice**

Category: Undergraduate

Author(s): J.M. Brown, Department of Biological Sciences, Northern Kentucky U
C.P. Curran, Department of Biological Sciences, Northern Kentucky U

Abstract: Previous work in our lab uncovered motor deficits in Cyp1a2(-/-) mice lacking the metabolic enzyme CYP1A2 and in a related strain of double knockout Cyp1a1_1a2(-/-) mice. We generated heterozygous Cyp1a1_1a2(+/-) mice to determine if there is a gene-dose effect. We are conducting a behavioral battery of tests on the offspring of heterozygous parents which include wild type (+/+) mice, heterozygous (+/-) mice and knockout (-/-) mice. Here, we will present data on spatial working memory. We used the The Y-Maze test of spontaneous alternation behavior and allowed mice to freely explore a three-armed maze for 5 min., calculating the percent of actual v. possible alternations from one arm to the next.

Supported by: NIEHS R15ES020053-01A1 and Kentucky Biomedical Research Infrastructure Network (KBRIN) Faculty Fellowship (P20 GM103436-12)

Primary Presenter / e-mail: J.M. Brown / brownj16@mymail.nku.edu

Mentor or Senior Author / e-mail: C.P. Curran / curranc1@nku.edu

#58 Abstract Title: **Role of 4-Hydroxynonenal (4-HNE) in Pain Following Spinal Cord Injury**

Category: Undergraduate

Author(s): A. R.Veldhi, Department of Neurology, School of Medicine, University of Louisville
E. D. Emberton, Department of Neurology, School of Medicine, University of Louisville
S. A. Myers, Department of Neurosurgery, School of Medicine University of Louisville
J. Petruska, Department of Neurosurgery, School of Medicine, University of Louisville
D. S.K. Magnuson, Department of Neurosurgery, School of Medicine, University of Louisville
A. S. Siu, Department of Neurosurgery, School of Medicine, University of Louisville
M. S. Evans, Department of Neurology, School of Medicine, University of Louisville
R. A. Vaishnav, Department of Neurology, School of Medicine, University of Louisville

Abstract: The reactive aldehyde 4-hydroxynonenal (4-HNE) is a lipid peroxidation byproduct and biomarker of oxidative stress in spinal cord injury (SCI), whose levels peak at 24 hours post injury (Carrico, Vaishnav et al 2009). 4-HNE can activate transient receptor potential ankyrin 1 (TRPA1) channels of pain sensing neurons in vitro and may cause pain (Trevisani, Siemens et al. 2007). The overall goal of this project is to determine if 4-HNE can directly contribute to pain in SCI. Here we report an initial characterization of the distribution of 4-HNE using fluorescent immunohistochemistry in sham and injured rat spinal cord tissue at 24 hours post injury. We performed image analysis on the tissue that we also counterstained with neuronal and nuclear markers to determine the localization of 4-HNE. We also assessed whether 4-HNE co-localized with TRPA1. When compared to shams, there appeared to be much more intense staining of 4-HNE at the epicenter in the injured spinal cord tissue, as expected. 4-HNE and TRPA1 co-localized in both the injured and sham spinal cord tissue. In the sham spinal cords, 4-HNE and TRPA1 co-localized primarily in the dorsal horn; however, at the epicenter of the injured tissue, the general anatomy of the cord was disrupted. Co-localization of 4-HNE and TRPA1 was mainly detected in what appeared to be swellings of axons in the white matter. From these results we conclude that 4-HNE does co-localize with TRPA1 in the spinal cord. To determine direct binding and activation of TRPA1 by 4-HNE and any role of 4-HNE in post-injury pain, further studies are necessary.

Supported by: Summer Research Scholar Program, University of Louisville School of Medicine (EDE) and research funding from the Department of Neurology (RAV, MSE) and the UofL KSCIRC P30 cores.

Primary Presenter / e-mail: A.R. Veldhi / sasafras27@hotmail.com

Mentor or Senior Author / e-mail: R.A. Vaishnav / radhika.vaishnav@louisville.edu

29th Annual Spring Neuroscience Research Day (BGSFN)

Poster Presentation Abstracts

8th Annual CCTS Spring Conference
April 8, 2013

#59 Abstract Title: **Pain hypersensitivity following peripheral nerve injury is associated with increased glutamate-evoked [Ca2+]i mobilization in dorsal horn neurons**

Category: Technical Staff

Author(s):
S. Doolen, Department of Physiology, U of Kentucky
C.B. Blake, Department of Physiology, U of Kentucky
B.N. Smith, Department of Physiology, U of Kentucky
B.K. Taylor, Department of Physiology, U of Kentucky

Abstract: Central sensitization in the spinal cord requires glutamate receptor activation and intracellular Ca2+ mobilization. We used Fura-2AM bulk loading of mouse slices together with wide-field Ca2+ imaging to measure glutamate-evoked increases in extracellular Ca2+ in spinal cord dorsal horn. The aims of this study were to: 1. Evaluate the contribution of glutamate receptor subtypes to glutamate-evoked Ca2+ transients spinal cord slices; 2. Correlate the magnitude of glutamate-evoked Ca2+ responses with neuropathic pain-like behaviors; and 3. Confirm findings using exogenous glutamate-evoked Ca2+ responses with more physiological stimulus; electrically-evoked neurotransmitter release from peripheral inputs. Results: Bath-applied glutamate robustly increased [Ca2+]i in 14.4 ± 2.6 cells per dorsal horn within a 440 x 330 um field-of-view, with an average time-to-peak of 27 s and decay of 112 s. Repeated application produced sequential responses of similar magnitude, indicating the absence of sensitization, desensitization or tachyphylaxis. Ca2+ transients were glutamate concentration-dependent with a Kd = 0.64 mM. Ca2+ responses predominantly occurred on neurons since: 1) Over 95% of glutamate-responsive cells did not label with the astrocyte marker, SR-101; 2) 62% of fura-2 AM loaded cells exhibited spontaneous action potentials; 3) 75% of cells that responded to locally-applied glutamate with a rise in [Ca2+]i also showed a significant increase in AP frequency upon a subsequent glutamate exposure; 4) In experiments using simultaneous on-cell recordings and Ca2+ imaging, glutamate elicited a Ca2+ response and an increase in AP frequency. AMPA/kainate (CNQX)- and AMPA (GYKI 52466)-selective receptor antagonists significantly attenuated glutamate-evoked increases in [Ca2+]i, while NMDA (AP-5), kainate (UBP-301) and class I mGluRs (AIDA) did not. Compared to sham controls, peripheral nerve injury significantly decreased mechanical paw withdrawal threshold and increased glutamate-evoked Ca2+ signals. Conclusions: Bulk-loading fura-2AM into spinal cord slices is a successful means for determining glutamate-evoked Ca2+ mobilization in naïve adult dorsal horn neurons. AMPA receptors mediate the majority of these responses. Peripheral neuropathic injury potentiates Ca2+ signaling in dorsal horn.

Supported by: Supported by R01NS45954 (BKT), R01DK080901 (BNS), and the Applied Statistics Lab and the Center for Clinical and Translational Science (CCTS) at the University of Kentucky. The CCTS is supported by NCRR UL1RR033173.

Primary Presenter / e-mail: S. Doolen / suzanne.doolen@uky.edu

Mentor or Senior Author / e-mail: B.K. Taylor / brad.taylor@uky.edu

#60 Abstract Title: **Does Age Influence the Inflamatory Response to Spinal Cord Injury**

Category: Technical Staff

Author(s):
W. M. Bailey, SCoBIRC, U of Kentucky
J. C. Gensel, Physiology, U of Kentucky

Abstract: Macrophages, derived from resident microglia and blood monocytes, persist indefinitely at sites of spinal cord injury (SCI) and contribute to both pathological and reparative processes. More specifically, the classically activated macrophage phenotype (M1) is associated with cell loss and pathology whereas the alternatively activated phenotype (M2) is believed to promote cell protection, regeneration, and plasticity, in the response to injury. Age is a key regulator in determining macrophage phenotype; exaggerated inflammatory responses, consisting primarily of M1 macrophages occur in the central nervous system of aged vs. younger animals. Therefore, we hypothesize that the inflammatory response to SCI differs with age. To address this hypothesis we compared the inflammatory response in young (3-4 month old) and aged (14-16 month old) mice after laminectomy receiving either a sham or a moderate contusion SCI (75 K dyne Infinite Horizons). After confirming function deficits at 1,3 and 7 dpi, we collected and isolated mRNA from 5mm of spinal cord centered on the injury site and used a custom inflammatory panel Taqman Array plate to compare relative gene expression between groups. We detected a significally dampened M2 response to SCI in aged vs. young animals with decreased expression of Arg1 and Retnla. Further, aged animals had significantly higher expression of the M1 markers Fcgr1 and TNF-alpha. Additional studies are being conducted to examine the effects of age on recovery and lesion pathology. Collectively these data demonstrate age-related differences in inflammatory response to SCI. The incidence of spinal cord injury (SCI) among older individuals has increased in recent years; however, little basic science research is being conducted examining the effects of age on endogenous repair processes. Based upon the data of the current study, we postulate that basic science models of SCI underrepresent the spectrum of the human SCI population and that age at time of SCI should be considered as a factor when testing basic and clinical therapies.

Supported by: University of Kentucky New Investigator Start-up

Primary Presenter / e-mail: W. M. Bailey / willybailey@gmail.com

Mentor or Senior Author / e-mail: J. C. Gensel / gensel1@uky.edu

#61 Abstract Title: **Calcium-dependent Cellular Mechanism of Aging and Diabetes: Focus on Insulin**

Category: Technical Staff

Author(s):
K. L. Anderson, Department of Molecular and Biomedical Pharmacology, U of Kentucky
C. DeMoll, Department of Molecular and Biomedical Pharmacology, U of Kentucky
R. Griggs, Department of Physiology, U of Kentucky
B. K. Taylor, Department of Physiology, U of Kentucky
N. M. Porter, Department of Molecular and Biomedical Pharmacology, U of Kentucky
O. Thibault, Department of Molecular and Biomedical Pharmacology, U of Kentucky

Abstract: The prevalence of obesity and T2DM increases with age. While widely recognized in the periphery, insulin resistance also exists in the brain, where decreased insulin sensitivity appears associated with cognitive decline. Here we present results from studies on the impact of glucose and insulin levels on cognitive and Ca2+-dependent electrophysiological markers of brain aging. Intranasal and acute insulin treatments were evaluated for their impact on learning and memory processes. Hippocampal slices from Zucker diabetic fatty (ZDF) rats also were monitored for Ca2+ dysregulation. Four groups of 10 aged F344 rats received daily intranasal doses of long-acting insulin Levimir® (0.143, 0.286 or 0.571 IU/ Kg/ day), 10 received the insulin-analog Humalog® (0.143 IU/ Kg/ day) and twenty received saline. Ten young F344 received saline. Treatment lasted for 11-18 days with MWM training starting on the fifth day. Animals receiving the low and the high dose of Levimir® showed a trend for improved performance on the 24 hr recall task compared to the middle dose. In ZDF rats, compared to controls, no difference was noted in the AHP, the Ca2+ attained during synaptic stimulation or resting Ca2+ levels. Extracellular field potentials revealed no significant genotype difference. In acute ex-vivo insulin experiments, the AHP was significantly reduced by insulin. Together these studies indicate that long-term insulin treatment, or a combination of aging with brain insulin therapy, may be necessary to reveal hormone-mediated changes in the brain. A prolonged diabetes period may be necessary to reveal brain effects in ZDF rats.

Supported by: NIA award: R01 AG0033649
Primary Presenter / e-mail: K. L. Anderson / Katie.Anderson2@uky.edu
Mentor or Senior Author / e-mail: O. Thibault / othibau@uky.edu

#62 Abstract Title: **Creation of a Model of Retinitis Pigmentosa in Zebrafish**

Category: Technical Staff

Author(s):
S. N. Perkins, Department of Biology, U of Kentucky
M. A. Forbes-Osborne, Department of Biology, U of Kentucky
M. R. Stone, Department of Biology, U of Kentucky
A. C. Morris, Department of Biology, U of Kentucky

Abstract: Retinitis Pigmentosa (RP) is a progressive retinal degenerative disease characterized by primary loss of rod photoreceptor cells (PRCs) presenting with night blindness followed by secondary loss of cone PRCs, which can result in total blindness. RP is caused by a heterogeneous group of variably penetrant mutations. While mutations in over 40 genetic loci have been causally linked to RP, a quarter of all cases result from mutations in rhodopsin (RHO), the light-capturing photopigment found in PRCs. These alleles display variable age of onset and disease severity and information about how PRC death occurs is sporadic or absent. For many mutations no animal model exists. Currently, there is no effective treatment and no cure for RP. The large number of genes and their disparate mechanisms by which they cause vision loss are a major road block in developing pharmacologic treatment. Unlike humans, zebrafish regenerate retinal cells lost to disease or injury. Transgenic models of constitutive PRC-specific cell death exist but do not accurately reflect RP disease conditions. Treatment of transgenic fish with a progestin agonist will result in the activation of a transactivator controlling expression of one of several dominant human RHO to selectively ablate rod PRCs. Following degeneration, the expression can be quenched and regeneration observed in real time. We have demonstrated that transgenic embryos express RHO after induction, and have identified germline transgenic zebrafish carrying either one of several inducible RHO mutations or the transactivation construct. Double transgenic lines have been created for one mutation and validation of RHO expression is underway.

Supported by: The Pew Scholars Program in Biomedical Sciences
Primary Presenter / e-mail: S. N. Perkins / snperk2@uky.edu
Mentor or Senior Author / e-mail: A. C. Morris / ann.morris@uky.edu

Poster Presentation Abstracts

#63 Abstract Title: **The p38α MAPK regulates microglial responsiveness to diffuse traumatic brain injury**

Category: Technical Staff

Author(s):
D. Goulding, Sanders-Brown Center on Aging, U. of Kentucky
A.D. Bachstetter, Sanders-Brown Center on Aging, U. of Kentucky
R.K. Rowe, Spinal cord & Brain Injury Research Center, U. of Kentucky
M. Kaneko, Sanders-Brown Center on Aging, U. of Kentucky
J. Lifshitz, , Spinal Cord & Brain Injury Research Center, U. of Kentucky; Barrow Neurological Institute at Phoenix Children's Hospital
L.J. Van Eldik, Sanders-Brown Center on Aging, and Dept of Anatomy and Neurobiology, U of Kentucky

Abstract: Neuropathology following traumatic brain injury (TBI) is the result of both the immediate impact injury and secondary injury mechanisms. Unresolved post-traumatic glial activation is a secondary injury mechanism that contributes to a chronic state of neuroinflammation in both animal models of TBI and human head injury patients. We recently demonstrated, using in vitro models, that p38α MAPK signaling in microglia is a key event in promoting cytokine production in response to diverse disease-relevant stressors and subsequent inflammatory neuronal dysfunction. From these findings, we hypothesized that the p38α signaling pathway in microglia could be contributing to the secondary neuropathologic sequelae following a diffuse TBI. Mice where microglia were p38α deficient (p38α KO) were protected against TBI induced motor deficits and synaptic protein loss. In wild type (WT) mice, diffuse TBI produced microglia morphological activation that lasted for at least 7 days; however, p38α KO mice failed to activate this response. Unexpectedly, we found that the peak of the early, acute phase cytokine and chemokine levels was increased in injured p38α KO mice compared to injured WT mice. The increased cytokine levels in the p38α KO mice could not be accounted for by more infiltration of macrophages or neutrophils, or increased astrogliosis. By 7 days after injury, the cytokine and chemokine levels remained elevated in injured WT mice but not in p38α KO mice. Together, these data suggest that p38α balances the inflammatory response to acutely attenuate the early proinflammatory cytokine surge, while perpetuating the chronic microglia activation after TBI.

Supported by: Alzheimer's Association Zenith Award ZEN-09-134506 (LVE) and NIH grants F32 AG037280 (ADB), R01 NS065052 (JL), R21 NS072611 (JL), and R01 NS064247 (LVE).

Primary Presenter / e-mail: D. Goulding / dsgoul2@uky.edu

Mentor or Senior Author / e-mail: L.J. Van Eldik / linda.vaneldik@uky.edu

#64 Abstract Title: **Novel in vivo probes for CNS serine-threonine protein kinases: attenuation of synaptic dysfunction**

Category: Technical Staff

Author(s):
E. Dimayuga, Sanders-Brown Center on Aging, U. of Kentucky
A.D. Bachstetter, Sanders-Brown Center on Aging, U. of Kentucky
B. Xing, Sanders-Brown Center on Aging, U. of Kentucky
S.M Roy, Dept of Molecular Pharmacology and Biological Chemistry, Northwestern U
V. Tokars, Dept of Molecular Pharmacology and Biological Chemistry, Northwestern U
D.M. Watterson, Dept of Molecular Pharmacology and Biological Chemistry, Northwestern U
O. Arancio, Columbia U
L.J. Van Eldik, Sanders-Brown Center on Aging, and Dept of Anatomy and Neurobiology, U of Kentucky

Abstract: Serine-threonine protein kinases are more numerous than tyrosine kinases and are critical to CNS function, yet there is a dearth of selective, CNS-active kinase inhibitors for in vivo investigations. Prevailing assumptions raise concerns about whether single kinase inhibitors can show in vivo efficacy for CNS pathologies, and debates over viable approaches to the development of safe and efficacious kinase inhibitors are unsettled. To address the unmet needs and challenges, we targeted the stress related p38αMAPK. This kinase is implicated in neuroinflammation and synaptic dysfunction and is present in both glia and neurons, thereby offering the unusual potential to generate enhanced responses through targeting a single kinase in two distinct cell types involved in pathology progression. We report a novel, isoform-selective p38αMAPK inhibitor (MW108) and its validation by cellular target engagement and mechanism of action. Efficacy in vivo demonstrates utility, and insights from co-crystallography may facilitate future kinase inhibitor design.

Supported by: Alzheimer's Association ZEN-09-134506 (LVE), Thome Memorial Foundation (LVE), and NIH grants R01 NS064246 (LVE), R01 AG031311 (DMW), R01 NS056051 (DMW), U01 AG043415 (DMW), and F32 AG037280 (ADB).

Primary Presenter / e-mail: E. Dimayuga / Edgardo.Dimayuga@uky.edu

Mentor or Senior Author / e-mail: L.J. Van Eldik / linda.vaneldik@uky.edu

Poster Presentation Abstracts

#65 Abstract Title: **Involvement of TRPC4 in Mustard Oil Induced Visceral Hyperalgesia in Rat**

Category: Professional Staff

Author(s): L. P. Zhang, Department of Physiology, U of Kentucky
F. Ma, Department of Physiology, U of Kentucky
K. N. Westlund, Department of Physiology, U of Kentucky

Abstract: The transient receptor potential (TRP) cation channel superfamily members are noted for their ability to activate nociceptive nerve endings specialized for transmission of signals perceived as pain. Characterization of the TRP family receptors is ongoing based on sequence homology and functional similarities. Several TRP channel family members remain less well characterized, including the TRP canonical channel isoform 4 (TRPC4). Transient receptor potential canonical (TRPC) proteins constitute a family of seven (TRPC1-7) nonselective cation channels are expressed in vascular smooth muscle cells from human vessels of all calibers and in smooth muscle from organs such as the uterus and the gastrointestinal tract. TRPC channels have recently emerged as important players in the control of smooth muscle function. In this study, we investigated the role of TRPC4 in colonic infusion of mustard oil induced visceral hyperalgesia. TRPC4 deficient rats and their matched Fisher 344 wild type rats were used. Intracolonic infusion of mustard oil induced a severe visceral hyperalgesia and a secondary allodynia in wild type rats, but not in TRPC4 deficient rats. The visceral hyperalgesia and secondary allodynia were assessed by monitoring spontaneous pain related behaviors (including lower abdomen stretching and licking) and mechanical threshold testing in the hand paws. In addition, either i.p. injection or oral feeding a potent TRPC4 channel inhibitor, 4-methyl-2-(piperidin-1-yl)quinoline (ML204) effectively blocked mustard oil induced visceral pain related behaviors in wild type rats. The results implicate that TRPC4 is involved in visceral pain transmission.

Supported by: NIH award: NS039041 (KNW).
Primary Presenter / e-mail: L. P. Zhang / lzhanh@uky.edu
Mentor or Senior Author / e-mail: K. N. Westlund / kwhigh2@uky.edu

#66 Abstract Title: **Infraorbital nerve trauma induces chronic orofacial allodynia in mice**

Category: Professional Staff

Author(s): F. Ma, Department of Physiology, U of Kentucky
L. Zhang, Department of Physiology, U of Kentucky
K.N. Westlund, Department of Physiology, U of Kentucky

Abstract: Chronic trigeminal neuropathic pain attacks can be excruciating for patients during chewing, talking, and even light touch. A mouse trigeminal infraorbital nerve trauma model is introduced here that successfully promotes hypersensitivity in the vibrissal whisker pad persisting over 10 weeks. The chronic orofacial pain model is induced by chromic gut suture laid adjacent to the infraorbital nerve (ION) in this small experimental animal rather than tied around the nerve. Slight compression and chemical effects on the infraorbital nerve by the chromic gut suture cause partial nerve bundle trauma and inflammation. At the end of the experiment, chromic gut suture was found remaining along the infraorbital nerve. Nerve edema as well as inflammatory infiltration was observed. Mechanical threshold of the affected whisker pad was significantly decreased on day 3 after chromic gut suture placement. The expression of neuronal injury marker activating transcription factor 3 (ATF3) is slightly increased in trigeminal ganglion neurons indicating that the chromic gut suture causes mild neuronal injury. Microphage infiltration was also detected in the affected infraorbital nerve bundle. In the spinal trigeminal nucleus, immunoreactivity for activated microglia marker OX42 was increased on postoperative day 70. A 10 week duration for mechanical allodynia has not been reported by other studies in mouse orofacial neuropathic pain models. Our results provide support for a simpler, more effective operative mouse model which better mimics chronic orofacial pain functionally by causing peripheral nerve trauma and mechanical allodynia persisting over 10 weeks.

Supported by: University of Kentucky President's Research Fund (KNW) start-up funds from the Dean of the College of Medicine (KNW)
Primary Presenter / e-mail: F. Ma / fei.ma@uky.edu
Mentor or Senior Author / e-mail: K.N. Westlund / kwhigh2@uky.edu

#67 Abstract Title: **The PPARγ Agonist, Pioglitazone, Reverses Painful Diabetic Neuropathy in the Zucker Diabetic Fatty Rat and DB/DB Mouse**

Category: Professional Staff

Author(s): R. R. Donahue, Department of Physiology, U of Kentucky
T. Iannitti, Department of Physiology, U of Kentucky
B.K. Taylor, Department of Physiology, U of Kentucky

Abstract: The thiazolinedione PPARγ agonist, pioglitazone, is FDA-approved for the treatment of Type II Diabetes. Our laboratory has found that acute systemic administration of pioglitazone (10-100mg/kg) reversed pain-like behaviors after peripheral nerve injury, an effect that could be blocked with the PPARγ antagonist, GW9662. Therefore, we tested the hypothesis that pioglitazone also reduces behavioral signs of Type II Painful Diabetic Neuropathy (PDN). To do this, we evaluated behavioral responses to noxious mechanical (paw pressure), noxious heat, and non-noxious cool (6ºC cold plate) stimuli in obese Zucker Diabetic Fatty (ZDFfa/fa) and their lean controls. We also evaluated behavioral responses to noxious heat (52.5ºC hot-plate test) and non-noxious mechanical stimuli in db/db mice and normoglycemic controls. Non-fasting blood glucose levels were monitored weekly in both species. Rats or mice arrived at 12 or 7 wk of age, and were tested once a week for 12 or 10 wk, respectively. ZDFfa/fa arrived hyperglycemic; compared to lean controls, they exhibited lower thresholds (hypersensitivity) to noxious pressure. At approximately 15 wk of age, ZDFfa/fa developed cold and heat hypersensitivity while db/db mice developed heat hypersensitivity at 8 wk. Cold and/or heat hypersensitivity, but not glucose levels, was dose-dependently reduced by a single intraperitoneal injection of pioglitazone in ZDFfa/fa (10-100mg/kg) and db/db (100-300 mg/kg). These results indicate that pioglitazone rapidly reduces behavioral signs of PDN via a mechanism that is independent of their anti-diabetic properties and is likely non-genomic. Supported by NS62306, DA18732, and DA19656 to BKT.

Supported by: Supported by NS62306, DA18732, and DA19656 to BKT.
Primary Presenter / e-mail: R.R. Donahue / rrdo222@uky.edu
Mentor or Senior Author / e-mail: B.K. Taylor / brad.taylor@uky.edu

#68 Abstract Title: **Nociceptin and APDC (group II mGluR agonist) attenuate mechanical and heat hypersensitivity in chronic pancreatitis induced by high fat and alcohol diet in rats**

Category: Professional Staff

Author(s): S. L. McIlwrath, Department of Physiology, U of Kentucky
K. N. Westlund High, Department of Physiology, U of Kentucky

Abstract: Diets rich in alcohol, plant and animal fats are contributing factors to the development of pancreatitis which can be severely painful. After inducing a dietary model of chronic pancreatic inflammation in Fischer rats, we studied the ability of several compounds to reduce pancreatitis-induced mechanical and heat hypersensitivity to identify the different signaling pathways involved in maintenance of the hypersensitivity. Adult male Fischer 344 rats were fed a liquid diet containing 6% ethanol and 30% vegetable oil as well as 8 g of lard daily. Before and during this time primary and secondary hypersensitivity to mechanical and heat stimulation was determined. Secondary mechanical hypersensitivity was characterized by probing the abdomen 10 times each with 4 different von Frey filaments eliciting 0.4, 1.2, 5.5, 15 g bending force in an ascending order. The number of times the animal withdrew its abdomen was recorded. On the footpads, mechanical thresholds were determined by usign the up-down method. Secondary heat hypersensitivity was measured by determining the response latency to radiant heat applied to the abdomen. Latencies of responses in the hotplate test (50°C) were also used to describe heat sensitivity. Nociceptin, an opioid-related peptide (20, 60, 200 nMol/kg), tricyclic antidepressant amitriptylin (3, 10 mg/kg), and (2R,4R)-APDC, a group II mGluR agonist (3mg/kg), were tested for their ability to attenuate pancreatitis induced hypersensitivity. Baseline mechanical and thermal thresholds/latencies did not change over time in naïve animals that received normal low soy rat chow. Within 4 weeks Fischer rats receiving the high-fat and alcohol diet developed mechanical and thermal hypersensitivity. Abdominal stimulation with the 1.2 g von Frey filament resulted in a doubling of responses. Latencies on the hotplate were decreased by 56% from 21.3 to 9.8 sec. All three compounds tested attenuated mechanical and thermal hypersensitivity using a single dose. Effects were maximal within 1 hr of administration and abolished within 24 hrs. Unlike the other two compounds, amitriptyline caused agitation at the higher dose. Both APDC and nociceptin appeared to have no negative side effects and future experiments will determine if animals become sensitized to these compounds with repeated daily dosing.

Supported by: Supported by NIH R01 NS039041-14 (KNW)
Primary Presenter / e-mail: S. L. McIlwrath / sabrina.mcilwrath@uky.edu
Mentor or Senior Author / e-mail: K. N. Westlund High / kwhigh2@uky.edu

#69 Abstract Title: **The p38β MAPK isoform is not required for lipopolysaccharide-induced proinflammatory cytokine production and neurotoxicity in the brain**

Category: Postdoctoral Fellow

Author(s): B. Xing, Sanders-Brown Center on Aging, U of Kentucky
A.D. Bachstetter, Sanders-Brown Center on Aging, U of Kentucky
L.J. Van Eldik, Sanders-Brown Center on Aging, and Dept of Anatomy and Neurobiology, U of Kentucky

Abstract: The p38 MAPK pathway plays a key role in regulating the production of proinflammatory cytokines, such as TNFα and IL-1β, in peripheral inflammatory disorders. There are four major isoforms of p38 MAPK (p38α, β, δ, γ), with p38α and p38β the targets of most p38 MAPK inhibitor drugs. Our previous studies demonstrated that the p38α MAPK isoform is an important contributor to stressor-induced proinflammatory cytokine up-regulation and neurotoxicity in the brain. However, the potential role of the p38β MAPK isoform in CNS proinflammatory cytokine overproduction and neurotoxicity is poorly understood. In the current studies, we used primary microglia from wild type (WT) and p38β knockout (KO) mice in co-culture with WT neurons, and measured proinflammatory cytokines and neuron death after LPS insult. We also measured neuroinflammatory responses in WT and p38β KO mice after administration of LPS by intraperitoneal or intracerebroventricular injection. WT and p38β KO microglia/neuron co-cultures showed similar levels of TNFα and IL-1β production in response to LPS treatment, and no differences in LPS-induced neurotoxicity. The in vitro results were confirmed in vivo, where levels of TNFα and IL-1β in the CNS were not significantly different between WT or p38β KO mice after LPS insult. Our results suggest that, similar to peripheral inflammation, p38α is critical but p38β MAPK is dispensable in the brain in regards to proinflammatory cytokine production and neurotoxicity induced by LPS inflammatory insult.

Supported by: NIH R01 NS064247; NIH F32 AG037280; Alzheimer's Association ZEN-09-134506.
Primary Presenter / e-mail: B. Xing / bxing2010@uky.edu
Mentor or Senior Author / e-mail: L.J. Van Eldik / linda.vaneldik@uky.edu

---

#70 Abstract Title: **Comprehensive behavioral characterization of an APP/PS-1 double knock-in mouse model of Alzheimer's disease**

Category: Postdoctoral Fellow

Author(s): S.J. Webster, Sanders-Brown Center on Aging, U. of Kentucky
A.D. Bachstetter, Sanders-Brown Center on Aging, U. of Kentucky
L.J. Van Eldik, Sanders-Brown Center on Aging, and Dept of Anatomy and Neurobiology, U of Kentucky

Abstract: Despite the extensive mechanistic and pathological characterization of the APP/PS1 knock-in mouse model of Alzheimer's disease (AD), very little is known about the AD-relevant behavioral deficits in this model. Characterization of the baseline behavioral performance in a variety of functional tasks and identification of the temporal onset of behavioral impairments are important to provide a foundation for future preclinical testing of AD therapeutics. Here we perform a comprehensive behavioral characterization of this model, discuss how the observed behavior correlates with the mechanistic and pathological observations of others, and compare this model to other commonly used AD mouse models. Four different groups of mice ranging across the lifespan of this model (test groups: 7, 11, 15, and 24 months old) were run in a behavioral test battery consisting of tasks to assess motor function (grip strength, rotor-rod, beam walk, open field ambulatory movement), anxiety-related behavior (open field time spent in peripheral zone vs. center zone and elevated plus maze), and cognitive function (novel object recognition, radial arm water maze). We observed no differences in motor function or anxiety-related behavior between APP/PS-1 knock-in mice and wild type counterpart mice for any age group. Cognitive deficits in both recognition memory (novel object recognition) and spatial working memory (radial arm water maze) became apparent for the knock-in animals as the disease progressed. This is the first reported comprehensive behavioral analysis of the APP/PS1 knock-in mouse model of AD. The lack of motor/coordination deficits or abnormal anxiety levels, coupled with the age/disease related cognitive decline and high physiological relevance of this model, make it well suited for utilization in preclinical testing of AD-relevant therapeutics.

Supported by: NIH grants R01 NS064247 (LVE), P01 AG005119 (LVE), F32 AG037280 (ADB), and by the Edward N. & Della L. Thome Memorial Foundation Awards Program in Alzheimer's Disease Drug Discovery Research (LVE).
Primary Presenter / e-mail: S.J. Webster / scott.webster@uky.edu
Mentor or Senior Author / e-mail: L.J. Van Eldik / linda.vaneldik@uky.edu

#71 Abstract Title: **Effect of Combined Subthalamic (STN) and Nigral (SNr) Stimulation on Gait and Postural stability in Parkinson's disease (PD)**

Category: Postdoctoral Fellow

Author(s): F.Zaheer, Department of Neurology, U of Kentucky
C.G. van Horne, Department of Neurosurgery, U of Kentucky

Abstract: Objective: To objectively determine effects of combined STN and SNr stimulation on postural stability and gait in PD patients. Background: PD is the second most common neurodegenerative disorder characterized by rigidity, resting tremor, bradykinesia, gait and postural difficulties. Levodopa, deep brain stimulation of STN or Globus Pallidus internus help in improving motor symptoms but improvement in gait and posture is suboptimal, causing falls and impaired quality if life. SNr has been shown to have role in automatic control of locomotion. Study design: 8 PD patients, appropriately selected for DBS will be recruited. They will have significant gait and posture difficulties according to Unified Parkinsons disease rating scale (UPDRS). DBS electrodes will be placed in routine fashion with distal contact in SNr. Patients will be tested with stimulation off and STN on-stimulation at base line and then STN will be programmed to best results during first 4 months. At 4 months, testing will be done with on- STN and combined STN /SNr (via interleaving). Combined stimulation will be tried to best results for next 4 months. From 8-12 months, programming will be done using best setting. Standardized clinical testing for PD and gait including UPDRS, Timed sit, stand and walk test, Freezing of gait questionnaire, and Tinetti Performance oriented mobility assessment will be done during testing sessions to determine effect of different stimulation parameters. Conclusion: We hypothesize that significant improvement in gait dysfunction and postural stability will be observed with combined STN and SNr stimulation as compared to STN stimulation alone.

Supported by: Submitted for CCTS pilot award
Primary Presenter / e-mail: F. Zaheer / fariha.zaheer@uky.edu
Mentor or Senior Author / e-mail: C. G. van Horne / craigvanhorne@uky.edu

#72 Abstract Title: **Calpain in the Brain: Alzheimer's disease alters expression**

Category: Postdoctoral Fellow

Author(s): C. B. Rogers, Spinal Cord and Brain Injury Research Center, U of Kentucky
S. Ghoshal, Spinal Cord and Brain Injury Research Center, U of Kentucky
J. W. Geddes, Spinal Cord and Brain Injury Research Center, U of Kentucky

Abstract: Increases in intracellular calcium are thought to contribute to the two hallmark pathologic features of Alzheimer's disease (AD): neurofibrillary tangles (NFTs) composed of aggregated tau protein; and senile plaques composed primarily of β-amyloid (Aβ) protein. Calpains are calcium-activated proteases shown to contribute to NFT and plaque formation making them a potential target for AD prevention and treatment. Currently, seven calpain isoforms (Calpain 1, 2, 5, 7, 10, 12 and 15) have been identified in the central nervous system (CNS). Previous studies in a mouse AD model revealed increased expression of calpains 10 and 12, whereas in humans, AD causes increased expression and activation of calpain 2 (m-calpain) in the hippocampus. However, the expression levels of other calpain isoforms have not been examined in the brain of patients with mild cognitive impairment (MCI) or AD and were the focus of this study. mRNA from gray matter was isolated from the cerebellum, pre-frontal cortex and posterior cingulate from age-matched controls (n=10), MCI (n=10) and AD (n=10) post-mortem human brain samples. mRNA expression of calpains 1, 2, 5, 7, 10, 12 and 15 were evaluated by qPCR. In AD, but not MCI, calpain 2 and 10 mRNA levels significantly increased in the posterior cingulate and calpain 10 also increased in the pre-frontal cortex. Calpain 1 mRNA levels were significantly decreased with AD in the posterior cingulate. In summary, significant elevations in calpain 2 and 10 expression were observed in the posterior cingulate cortex obtained post-mortem from individuals with AD, but were not altered in MCI. This suggests that the progression of MCI to AD may involve changes in calpain expression and altered activation.

Supported by: NIA pilot grant 5P30AG028383-07 and UK Aging Training Grant T32AG000242-18
Primary Presenter / e-mail: C. B. Rogers / colin.rogers@uky.edu
Mentor or Senior Author / e-mail: J. W. Geddes / jgeddes@uky.edu

#73 Abstract Title: **Characterizing a GFAP-specific conditional β-catenin knockout mouse: Implications for cell proliferation after trauma**

Category: Postdoctoral Fellow

Author(s): D.M. Sama, Physiology, Spinal Cord and Brain Injury Research Center, U of Kentucky
S.K. Madathil, Physiology, Spinal Cord and Brain Injury Research Center, U of Kentucky
J. Chen, Neurological Surgery and Stark Neurosciences Research Institute, Indiana U
K.E. Saatman, Physiology and Spinal Cord and Brain Injury Research Center, U of Kentucky

Abstract: β-catenin, known for its role in canonical Wnt signaling, can also influence proliferation of astrocytes and neural progenitor cells (NPCs), two cell populations greatly affected by traumatic brain injury (TBI). Brain injury induced by the widely used lateral controlled cortical impact (CCI) model causes initial loss of immature neurons and delayed proliferation of NPCs and astrocytes in the hippocampus ipsilateral to impact. We hypothesize that β-catenin is critical for post-injury proliferation of astrocytes and NPCs, both of which express glial fibrillary acidic protein (GFAP). Our studies utilize a novel transgenic mouse (cat-cKO) in which β-catenin is conditionally knocked out in GFAP-expressing cells using the Cre-lox system. Mice were injected with bromodeoxyuridine (BrdU) 4h prior to euthanasia at 72h after CCI brain injury, to label dividing cells at a time of peak GFAP+ cell proliferation. Dual immunofluorescent labeling for BrdU and GFAP confirmed increased GFAP+ cell proliferation in the ipsilateral hippocampus of wild-type (WT) mice (n=4-5), while cat-cKO mice (n=4-6) showed significantly less GFAP+ cell proliferation. Numbers of immature neurons identified using doublecortin (DCx) were reduced in cat-cKO compared to WT mice in the ipsilateral and, unexpectedly, the contralateral hippocampus. We postulated that the pool of NPCs was diminished before injury due to withdrawal of doxycycline (Dox), and hence β-catenin deletion, for many weeks prior to injury. However, reducing Dox removal time (4wk, 2wk, 7d, or 3d prior to injury) did not affect reductions in DCx+ neurons or proliferating astrocytes in brain-injured cat-cKO mice. Studies to elucidate the cause of bilateral modulation of immature neuron survival in cat-cKO mice are ongoing. Future studies will explore downstream effects of β-catenin-dependent GFAP+ cell proliferation on functional outcomes following trauma.

Supported by: NIH R01 NS072302, Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT) 7-20, NIH R21 NS072631

Primary Presenter / e-mail: D.M. Sama / diana.mathis@uky.edu

Mentor or Senior Author / e-mail: K.E. Saatman / k.saatman@uky.edu

#74 Abstract Title: **The Effects Of Environmental Enrichment On Methamphetamine-Induced Conditioned Place Preference**

Category: Postdoctoral Fellow

Author(s): C. E. Wilmouth, Department of Psychology, College of Arts and Sciences, U of Kentucky
M. T. Bardo, Department of Psychology, College of Arts and Sciences, U of Kentucky

Abstract: Methamphetamine (METH) is a highly addictive stimulant, which in recent years has reached nearly epidemic levels of use worldwide. Environmental enrichment produces protective effects against the rewarding properties of a number of addictive drugs such as cocaine and heroin. Recent findings however, suggest that enriched rearing does not alter sensitivity to METH reinforcement in a self-administration paradigm. The present experiment examined whether environmental enrichment alters sensitivity to METH-induced conditioned place preference (CPP). Male Sprague-Dawley rats were reared in either enriched or isolated conditions from postnatal day 21 to 65 and then were tested for METH-induced CPP with 3 doses of METH (0.0, 0.3 or 1.0 mg/kg). Consistent with the self-administration findings, enrichment did not alter the reinforcing properties of METH in the CPP paradigm. These findings suggest that while enrichment may have protective effects against the rewarding properties of many other abused drugs, these effects do not extend to METH.

Supported by: NIH Funding: R01 DA12964 and T32 DA01617

Primary Presenter / e-mail: C. E. Wilmouth / carrie.wilmouth@uky.edu

Mentor or Senior Author / e-mail: M.T. Bardo / mbardo@email.uky.edu

#75 Abstract Title: **Chronic Intermittent Ehtanol Exposure Produces Loss of Mature Neurons in Hippocampal Slice Cultures**

Category: Graduate Student

Author(s):
A.Reynolds, Depts of Psychology and Spinal Cord and Brain Injury Research Center, U of Kentucky
J.Berry, Depts of Psychology and Spinal Cord and Brain Injury Research Center, U of Kentucky
L.Sharrett-Field, Depts of Psychology and Spinal Cord and Brain Injury Research Center, U of Kentucky
M.A. Prendergast, Depts of Psychology and Spinal Cord and Brain Injury Research Center, U of Kentucky

Abstract: Chronic intermittent ethanol exposure (CIE) is implicated in neurodegeneration of the hippocampus produced by exposure to binge-like concentrations of EtOH and multiple periods of EWD. The present studies examined the loss of mature neurons after 1, 2, or 3 cycles of 5 days EtOH exposure (50 mM), followed by a 24-hour period of EWD, or continuous EtOH exposure. NeuN IR (Fox-3), a marker of mature neuron density, was significantly decreased in each hippocampal subregion with 2 or 3 cycles of CIE, but not 1 cycle. Thionine staining of cultures following 3 cycles CIE confirmed significant cellular losses within each hippocampal subregion, confirming NeuN IR. Continuous exposure to EtOH for 18 consecutive days did produce deficits in NeuN IR or thionine staining. These studies demonstrate the loss of mature neurons and neuronal degradation in the pyramidal cell layers of the CA1 and CA3, and granule cell layer of the dentate gyrus after 3 cycles of 5 days EtOH exposure (50 mM), followed by a 24-hour period of EWD. Additional cultures exposed to 3 cycles of CIE and APV (40 μM) during EWD demonstrate significant increases in NeuN IR compared to cultures exposed to 3 cycles of CIE in the CA1 and dentate gyrus. These data suggest that neuronal injury associated with CIE reflects over activity of NMDAR.

Supported by: Supported by NIAAA # AA013388
Primary Presenter / e-mail: A.R. Reynolds / anna.reynolds7@gmail.com
Mentor or Senior Author / e-mail: M.A. Prendergast / prender@uky.edu

---

#76 Abstract Title: **Impulsivity in a Rat Model of ADHD: Effects of Age and Methylphenidate Treatment**

Category: Graduate Student

Author(s):
S. S. Somkuwar, Department of Pharmaceutical Sciences, U of Kentucky
M. T. Bardo, Department of Psychology, U of Kentucky
K. K. Kantak, Department of Psychology, Boston U, Boston, MA
L. P. Dwoskin, Department of Pharmaceutical Sciences, U of Kentucky

Abstract: Impulsivity is a hallmark of attention deficit hyperactivity disorder (ADHD) and a predictor of cocaine abuse vulnerability. Spontaneously hypertensive rats (SHR) are a well accepted animal model of ADHD. Treatment of adolescent SHR with a therapeutically-relevant dose of methylphenidate (MPH) resulted in increased cocaine self-administration during adulthood, compared to MPH-treated Wistar-Kyoto (WKY; inbred) and Wistar (WIS; outbred) rats. Therefore, the current study tested the hypothesis that MPH treatment during adolescence increases impulsivity in adult SHR, compared to control WKY and WIS. Further, the effects of chronic MPH treatment on impulsivity during adolescence and adulthood were investigated. Adolescent SHR, WKY and WIS were administered MPH (1.5 mg/kg) or vehicle from postnatal day 28 to 55 (P28-55). Beginning P77, these rats were trained on differential reinforcement of low rates 30 sec (DRL30) schedules to assess impulsivity. Inter-response time (IRT) distribution parameters were compared between strains. Further, separate cohorts of adolescent rats (P28-55) and adult rats (P77-120) were administered chronic MPH or vehicle and concurrently evaluated on DRL30. MPH treatment during adolescence increased proportion of short IRTs ($p<0.001$) compared to vehicle control in adult SHR, but not in WKY or WIS, indicating enhanced impulsivity in SHR, thus supporting the current hypothesis. Further, MPH-treated adolescent SHR, but not adult SHR, produced greater proportion of short IRTs ($p=0.052$) compared to vehicle control, indicating that MPH increases impulsivity during adolescence. In conclusion, MPH treatment produces a lasting increase in impulsivity in an age- and strain-specific manner, which may underlie the enhanced cocaine self-administration in MPH-treated SHR.

Supported by: NIDA Grant DA011716 and a Kentucky Opportunity Fellowship (SSS).
Primary Presenter / e-mail: S. S. Somkuwar / sucharita.sen@uky.edu
Mentor or Senior Author / e-mail: L. P. Dwoskin / ldwoskin@email.uky.edu

#77 Abstract Title: **Sleep Architecture, Maze Performance and Synaptic Properties after Acute Stress in Young and Aged Rats**

Category: Graduate Student

Author(s):
H.M. Buechel,Department of Pharmacology, U of Kentucky
J. Popovic, Department of Pharmacology, U of Kentucky
K. Anderson, Department of Pharmacology, U of Kentucky
O. Thibault, Department of Pharmacology, U of Kentucky
E.M. Blalock Department of Pharmacology, U of Kentucky

Abstract: In healthy young subjects, acute stress influences cognition and sleep architecture, and synaptic behavior in the hippocampus. However, little work has investigated acute stress' influence on aged subjects, who often suffer from impaired cognition and dysregulated sleep. To address this, we implanted young and aged subjects with wireless telemetry and monitored sleep architecture. Subjects were trained in the Morris water maze for 3 days, and then restrained for 3 hours prior to a water maze probe trial (n = 7-9/group). After the probe trial, rats were returned to their housing room and post-stress EEG and EMG data were collected. The following morning, hippocampi were prepared for electrophysiologic measures of synaptic activity. Aged animals showed significant deficits in water maze performance, decreases in deep sleep, and weakened synaptic communication compared to young. Interestingly, acute stress exposure made young animal measures more aging-like, while making aged measures more young-like (e.g., younger animals showed slower maze performance, reduced deep sleep and weakened synaptic behavior, while aged animals showed the reverse). Results here suggest that acute stress may have age-selective beneficial (hormesis-like) influence on cognition, sleep architecture and underlying synaptic behavior.

Supported by: RO1-AG037868
Primary Presenter / e-mail: H.M. Buechel / hmbuec2@uky.edu
Mentor or Senior Author / e-mail: E.M. Blalock / eric.blalock@uky.edu

#78 Abstract Title: **Teaching with Leeches- An Undergraduate Neuroscience Module**

Category: Graduate Student

Author(s):
J. Titlow, Dept. of Biology, U of Kentucky
Z. R. Majeed, Dept. of Biology, U of Kentucky & Dept. of Biology, Col. of Sci, Univ. of Salahaddin, Erbil, Iraq
J.G. Nicholls, Dept. of Neurobiol. & Cognitive Neurosci., SISSA, Trieste, Italy
R. L. Cooper, Dept. of Biology, U of Kentucky

Abstract: The freshwater leech has aided in the discovery of many basic neuroscience principles, especially in the fields of neurophysiology, ethology, and developmental biology. We have adapted four leech experimental protocols into a teaching module for upper level biology courses. Concepts demonstrated in these exercises include: action potentials and threshold, neural circuitry, synaptogenesis, muscle innervation, and sensory field mapping. The preparation is ideal for training because the neurons are large enough to be seen with inexpensive optics (40x magnification is sufficient), adult CNS tissue maintains activity in saline for several hours, and there are 21 relatively simple ganglia that permit trial and error and give multiple students an opportunity to collect intracellular recordings. With a single specimen students can 1) record from identified neurons in the ganglion, 2) dissect a patch of innervated skin and trace sensory receptors back to their respective cell bodies within the CNS, 3) isolate individual cells and culture them together to study synaptogenesis, and 4) inject dyes to visualize neural anatomy. Within the first lab session our students were able to inject current into sensory cells and observe the various action potential waveforms. At this poster we will be happy to discuss the laboratory setup and current research in leech neurobiology.

Supported by: Dept of Biology and Personal funds (RLC).
Primary Presenter / e-mail: J. Titlow / joshtitlow@uky.edu
Mentor or Senior Author / e-mail: R.L. Cooper / RLCOOP1@email.uky.edu

#79 Abstract Title: **AD-associated SNPs in ABCA7: Translating a Mechanism into a Potential Therapeutic Target**

Category: Graduate Student

Author(s): J.B. Vasquez, Department of Phsyology, U of Kentucky

Abstract: Genome wide association studies (GWAS) have recently identified genes with single nucleotide polymorphisms (SNPs) associated with Alzheimer's disease (AD), including ABCA7, a lipid transporter within the brain. Here, we hypothesize that the AD-associated SNPs alter ABCA7 expression. To evaluate this hypothesis, we genotyped two AD associated SNPs, rs3764560 and rs3752246, and used qPCR to quantify ABCA7 expression in 60 human brain RNA samples. We found that the minor allele of rs3764650 was associated with decreased ABCA7 expression and increased AD risk. Agents that increase ABCA7 expression would be predicted to reduce AD risk. Currently, we are using next generation sequencing to assess allele expression imbalance (AEI) to substantiate our qPCR findings. For this work, we genotyped two exonic SNPs, rs4147914 and rs4147930, and are sequencing cDNA from heterozygous individuals to assess whether one allele is expressed at higher levels than the other allele. To translate these results into a possible therapy, we have found that valproic acid induces ABCA7 in vitro. Hence, we propose that valproic acid may act more robustly than the AD SNP, and thereby provide more robust protection from AD. To begin to assess this possibility, we are comparing ABCA7 expression in lymphocytes from humans, before and after treatment with valproic acid in vivo. Overall, these studies will identify the mechanism of action of an AD-associated SNP and translate this mechanism into a potential therapy. Specific Aims: 1 – Elucidate the mechanisms by which rs3764650 modulates ABCA7 mRNA expression in vitro to test the hypothesis that the function of rs376460 is dependent on cis-acting factors. This will include qPCR and next generation sequencing studies, as well as in vitro cell-line based mechanistic studies. 2 – Evaluate the ability of valproic acid to induce ABCA7 in vitro and in vivo as a potential AD-protective mechanism.

Supported by: PPG 3048106839

Primary Presenter / e-mail: J. B. Vasquez / Jared.Vasquez@uky.edu

Mentor or Senior Author / e-mail: S.G. Estus / steve.estus@uky.edu

---

#80 Abstract Title: **Stop the TIC: Alleviating Trigeminal Neuropathic Pain using PPAR-gamma Agonists**

Category: Graduate Student

Author(s): D. Lyons, Department of Physiology, U of Kentucky
L.P. Zhang, Department of Physiology, U of Kentucky
K.N. Westlund High, Department of Physiology, U of Kentucky

Abstract: This study examined the diabetes drug, pioglitazone, for decreasing oxidative stress as a contributory mechanism in trigeminal neuropathic pain. Pioglitazone provides protection through activation of nuclear receptor Peroxisome Proliferator-Activated Receptor gamma (PPAR-gamma), known to attenuate mitochondrial dysfunction, a primary source of cellular oxidative stress. The PPAR-gamma agonist has been shown to be effective in suppressing inflammation and inhibiting other types of neuropathic pain but has never been explored in studies of trigeminal orofacial pain. Trigeminal neuropathic pain is an orofacial pain condition characterized by chronic aching and burning sensation or even sharp, electric-like shooting pain caused by trigeminal nerve damage. Compressive injury of the trigeminal nerve, believed to be initiated by arteriole pulsation in clinical cases, can initiate pain that cannot be adequately treated with available pharmaceutical drugs. The studies examined effects of PPAR-gamma agonist administration in a novel chronic neuropathic pain model producing trigeminal inflammatory compression (TIC) injury developed for mice in our laboratory. This model has a symptomatology correlating extremely well with the clinical aspects of trigeminal neuropathic pain. TIC is produced by placing chromic gut suture adjacent to the infraorbital nerve to induce mechanical and thermal hypersensitivity in mouse whisker pad. The studies found PPAR-gamma effective with both systemic and oral pioglitazone administration for reversal of pain related hypersensitivity and in inhibition of reactive oxygen species (ROS). PPAR-gamma isoform specificity was determined in comparisons of Pioglitazone with PPAR-beta/delta agonists. These studies are determining a new use for PPAR-gamma agonists to block trigeminal neuropathic pain in mice.

Supported by: This project described was supported by Dr. Karin Westlund High's start funding and her University Professorship.

Primary Presenter / e-mail: D. Lyons / dnlyon2@uky.edu

Mentor or Senior Author / e-mail: K.N. Westlund High / kwhigh2@email.uky.edu

Poster Presentation Abstracts

#81 Abstract Title: **Loss of Microglia in the Hippocampus following Binge Ethanol Exposure**

Category: Graduate Student

Author(s): S.A. Marshall, Department of Pharmaceutical Sciences, U of Kentucky
J.A. McClain, Department of Pharmaceutical Sciences, U of Kentucky
K. Nixon, Department of Pharmaceutical Sciences, U of Kentucky

Abstract: Excessive alcohol intake results in hippocampal neurodegeneration that has been linked to a variety of cognitive deficits. As neuroinflammation may contribute to alcohol-induced neurodegeneration, this study examined microglia, a key component of neuroinflammatory responses. We have shown previously that microglia are partially activated following binge alcohol exposure, including an increase in the 18 kDa translocator protein and complement receptor 3 after exposure. However, it was not clear if this increase in receptors was due to an increase in the number of microglia. Therefore, we examined microglia number and morphology immediately following binge ethanol exposure. Sprague-Dawley rats received ethanol 3x a day for 4d with an initial dose of 5g/kg and later doses based on intoxication. The number of Iba-1+ cells in the hippocampus was estimated by stereology and cell morphology was assessed as resting or activated. Microglial number in ethanol treated animals was decreased by at least 33%. Morphological analysis of Iba-1 immunoreactivity showed more activation in the CA2/3 region of ethanol exposed animals compared to controls but not in the CA1 or DG. Interestingly, a subset of microglia observed in ethanol exposed rats exhibited characteristics that did not match morphological criteria for activation. These microglia displayed processes that ranged from a slight beaded appearance to complete fragmentation, resembling characteristics of dystrophic microglia described in other neurodegenerative diseases. The presence of dystrophic microglia could be indicative of dying microglia or at the least, dysfunctional microglia, which is consistent with the observed loss in microglia number. A loss in normally functioning microglia would impact their endogenous neuroprotective mechanisms which could be disruptive to the neuronal environment.

Supported by: Funded by NIAAA R01AA016959 & NIDA T32DA016176
Primary Presenter / e-mail: S.A. Marshall / simon.alexm@uky.edu
Mentor or Senior Author / e-mail: K. Nixon / kim-nixon@uky.edu

---

#82 Abstract Title: **Region-Specific Alterations in Nicotinic Acetylcholine Receptor Expression Following Adolescent Binge Alcohol Exposure**

Category: Graduate Student

Author(s): K.Y. Chen, Pharmaceutical Sciences Department, U of Kentucky
D.M. Hopkins, Pharmaceutical Sciences Department, U of Kentucky
J.R. Pauly, Pharmaceutical Sciences Department, U of Kentucky
K. Nixon, Pharmaceutical Sciences Department, U of Kentucky

Abstract: Adolescence is a period where neuronal development is not yet complete, as such the brain is susceptible to insult. Alcohol and nicotine use is often initiated at this time, and the adolescent hippocampus is more sensitive to alcohol's damaging effects. One shared pharmacological target of both drugs is the brain's cholinergic system. Nicotine use during adolescence has been shown to produce permanent changes in the receptor densities of nicotinic acetylcholine receptors (nAChR); however, the effect of adolescent alcohol exposure on nAChR expression is not well understood. Therefore, we examined the effect of adolescent binge alcohol exposure on the expression of nicotinic cholinergic receptor subtypes at several time points. Adolescent male Sprague-Dawley rats were administered 25% (w/v) alcohol or isocaloric dextrose in a nutritionally complete diet via gastric intubation every 8 hours for 4 days according to the Majchrowicz model. Animals were sacrificed at 0, 2, 7, 30 days following alcohol exposure and nAChR subtype expression in several hippocampal, limbic, and cortical regions were analyzed using microdensitometry. Receptor expression was determined using autoradiography with [125I] α-bungarotoxin (α7), [125I] epibatidine(α4β2), and cytisine blocked [125I] epibatidine (α3β4). Increases in both α7 and α4β2 containing nAChR expression were observed in alcohol treated rats in the CA regions of the hippocampus compared to controls. In contrast, α4β2 containing nAChR expression is increased while α7 nAChR expression is decreased in the dentate gyrus of alcohol treated rats when compared to controls. These data suggest that alcohol exposure during adolescence produces unique effects dependent on the specific nAChR subtype and brain region examined.

Supported by: NIH Award: R01AA016959, R01HD061996
Primary Presenter / e-mail: K.Y. Chen / kevin.chen@uky.edu
Mentor or Senior Author / e-mail: K. Nixon / kim-nixon@uky.edu

#83 Abstract Title: **Oral pioglitazone attenuates painful diabetic neuropathy in the Zucker Diabetic Fatty rat model of type 2 diabetes**

Category: Graduate Student

Author(s):
R.B. Griggs, Department of Physiology, U of Kentucky
S. Doolen, Department of Physiology, U of Kentucky
K. Anderson, Department of Molecular and Biomedical Pharmacology, U of Kentucky
C. DeMoll, Department of Molecular and Biomedical Pharmacology, U of Kentucky
R. R. Donahue, Department of Physiology, U of Kentucky
O. Thibault, Department of Molecular and Biomedical Pharmacology, U of Kentucky
B.K. Taylor, Department of Physiology, U of Kentucky

Abstract: Therapies for painful diabetic neuropathy (PDN), which occurs in up to 50% of type 2 diabetics, are only moderately effective in a subset of patients. To determine the efficacy of pioglitazone, an FDA approved therapy for type 2 diabetes, we tested the hypothesis that pioglitazone reduces pain-like behavior and neuronal sensitization while simultaneously preventing diabetes progression. Treatment began during pre-diabetes, when blood glucose and HbA1c are slightly elevated but below clinical cutoffs, in Zucker Diabetic Fatty (ZDF) rats – a genetic model of type 2 diabetes. We measured pain-like behavior, blood glucose, weight, and HbA1c levels weekly during a longitudinal study with Control and Diabetic rats aged 11-19 weeks. Animals were then sacrificed for post-mortem imaging analyses. We used a repeated measures ANOVA design with diabetes and drug as our independent variables and four groups of n=10. Pioglitazone (Actos®) was incorporated into chow and fed to Control and Diabetic rats for 7 weeks (13-19 weeks of age) at a dose of 30 mg pioglitazone / kg body weight / day. Un-modified chow was fed to additional Control and Diabetic animals as a control. Pioglitazone significantly delayed the onset of heat hypersensitivity and completely attenuated hypersensitivity to mechanical pressure. Pioglitazone reduced activation of extracellular signal-regulated kinase evoked by hindpaw mechanical stimulation. As expected, pioglitazone mitigated hyperglycemia and diabetes-induced elevations in HbA1c. We conclude that pioglitazone reduces hyperalgesia and neuronal sensitization in the dorsal horn of the spinal cord. Pioglitazone may be particularly useful in the subset of diabetic patients with PDN.

Supported by: Supported by National Institute of Neurological Disorders and Stroke 1T32NS077889 to R.B. Griggs and 5R01NS062306 to B.K. Taylor.

Primary Presenter / e-mail: R.B. Griggs / ryan.griggs@uky.edu

Mentor or Senior Author / e-mail: B.K. Taylor / brad.taylor@uky.edu

---

#84 Abstract Title: **Calpain5: Highly expressed in the CNS, Localizes to mitochondria and nucleus, Carries a NLS and Associates with PML bodies.**

Category: Graduate Student

Author(s):
R. Singh, Anatomy and Neurobiology; Spinal Cord and Brain Injury Research Center (SCoBIRC), U of Kentucky
C. Mashburn, Spinal Cord and Brain Injury Research Center (SCoBIRC), U of Kentucky
V. Bondada, Spinal Cord and Brain Injury Research Center (SCoBIRC), U of Kentucky
S. Ghoshal, Spinal Cord and Brain Injury Research Center (SCoBIRC), U of Kentucky
D. Lou, Spinal Cord and Brain Injury Research Center (SCoBIRC), U of Kentucky
J. Geddes, Anatomy and Neurobiology; Spinal Cord and Brain Injury Research Center (SCoBIRC), U of Kentucky

Abstract: Calpain5 (CAPN5) is an atypical member of the calpain family. It lacks the EF hand motif characteristic of classical calpains (CAPN1 & 2) but retains catalytic and Ca2+binding domains. Tra-3, an ortholog of CAPN5, has been shown to be involved in necrotic cell death in C.elegans; although CAPN5 has not been investigated in the mammalian CNS. We compared relative mRNA levels of calpains in rat CNS, revealing CAPN5 as the second most highly expressed calpain. Examining relative levels of CAPN5 from late embryonic day 18 to postnatal day 90, indicated lower mRNA but higher protein levels during CNS development. Using X –gal staining in Capn5 +/- mice, immunostaining of rat brain sections and SH-SY5Y cells, and subcellular fractionation of rat brain cortex, we found that CAPN5 is a non-cytoplasmic calpain, localized in nucleus and enriched in synaptic mitochondria. Proteinase K treatment of mitochondria and mitoplasts from B35 rat neuroblastoma cells and rat synaptic mitochondria, revealed CAPN5 to be localized on the inner mitochondrial membrane, and released from mitochondria on membrane permeabilization with alamethicin. By utilizing immunolabelling, confocal imaging, nuclear subfractionation and transient transfections, we evaluated the subnuclear localization of CAPN5. CAPN5 was detected in punctate domains, binds to nucleic acid and associates with PML protein, a tumor suppressor protein. We further demonstrate that CAPN5 carries a nonconventional bipartite nuclear localization signal. Together, these findings demonstrate that CAPN5 is a non-cytosolic calpain, abundant in the CNS, and localized to the mitochondria inner membrane and nuclear PML bodies.

Supported by: Kentucky Spinal Cord and Head Injury Research Trust and NIH P01NS058484

Primary Presenter / e-mail: R.Singh / rranj2@uky.edu

Mentor or Senior Author / e-mail: J.Geddes / jgeddes@uky.edu

Poster Presentation Abstracts

#85 Abstract Title: **Markov Modeling of Sleep-Wake Dynamics for Application in Neurotherapy**

Category: Graduate Student

Author(s):
F. Yaghouby, Center for Biomedical Engineering, University of Kentucky
T. Zhang, Department of Biology, University of Kentucky
M. Striz, Department of Biology, University of Kentucky
K. Donohue, Department of Electrical and Computer Engineering, University of Kentucky
B. O'Hara, Department of Biology, University of Kentucky
S. Sunderam, Center for Biomedical Engineering, University of Kentucky

Abstract: Understanding the consequences of genetics and neural disorders on behavior involves extensive behavioral analysis of animal models. Here, the utility of hidden Markov models (HMMs) estimated from invasive (EEG, EMG) and noninvasive (motion) physiological measurements in mice for characterizing progressive sleep-wake dynamics is investigated. Adult mice were implanted with EEG/EMG preamplifiers and placed in cages equipped with a piezoelectric sensor on the floor. The "piezo" motion signal tracks EMG and discriminates sleep from wakefulness. The sensor also responds to respiratory thoracic movement, which is less regular in REM than non-REM sleep. HMMs were used to sequence EEG/EMG time series in 4s windows into REM, non-REM, and Wake states. HMMs were found to track instantaneous sleep-wake state with over 90% accuracy from EEG/EMG measurements. Classification using HMMs estimated from noninvasive piezo signal features was comparable to HMMs based on EEG/EMG features, except that REM can be overestimated. Trends in HMM properties were also inspected to track progressive changes in behavior such as circadian variation and recovery from surgery. The trace Tn of the HMM's state transition matrix was used as a measure of the relative probability that an ongoing state will persist uninterrupted. Tn patterns were stable in baseline recordings (reflecting normal sleep-wake cycles), but fell dramatically following surgery and recovered over time. HMMs estimated from physiological measurements could provide quantitative markers of behavior and recovery from brain injury. We propose to use this approach as the basis for modeling the effect of interventions on mouse sleep regulation and dynamics.

Supported by: This work was supported in part by National Institutes of Health grant NS065451 and a grant from the Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT) 10-5A.

Primary Presenter / e-mail: F. Yaghouby / f.yaghouby@uky.edu

Mentor or Senior Author / e-mail: S. Sunderam / ssu223@uky.edu

#86 Abstract Title: **Insulinoma-Associated 1a (Insm1a) is Required for Photoreceptor Differentiation and Cell Cycle Progression in the Developing Zebrafish Retina**

Category: Graduate Student

Author(s):
M.A. Forbes-Osborne, Department of Biology, U of Kentucky
S.G. Wilson, Department of Biology, U of Kentucky
A.C. Morris, Department of Biology, U of Kentucky

Abstract: Proper development of the vertebrate eye requires a complex series of carefully coordinated gene expression events, regulated in part through the expression of multiple cascades of transcription factors. Insulinoma-associated 1 (Insm1) is an evolutionarily conserved zinc-finger transcription factor expressed throughout the developing nervous and neuroendocrine systems, including in the developing retina. Insm1 is upregulated in response to chronic rod photoreceptor degeneration and in cancers. While Insm1 has known functions in neuroendocrine development, its role in retinal development is less clear. Few direct targets of Insm1 have been identified, and little is known about the mechanism of Insm1 transcriptional regulation. In this study, we examined the function of insm1a during zebrafish retinal development. Morpholino mediated knockdown of insm1a was combined with light microscopy, immunohistochemistry, in situ hybridization and in vitro reporter gene experiments to determine the effect of insm1a on retinal neurogenesis. Knockdown of insm1a caused a significant and specific decrease in eye area at 2 days post fertilization (dpf). Further analysis revealed a significant decrease in differentiated rod and cone photoreceptors at 3 dpf, with rod photoreceptors remaining reduced at 4 dpf. Other retinal cell types showed either no change or slight reduction in number, coupled with immature cellular morphology. Cell cycle changes were also observed. Our data show that reduced insm1a results in a rod photoreceptor deficiency in the developing retina, accompanied by reduced neuronal maturity, and changes in cell cycle kinetics. Taken together, these results suggest a requirement for insm1a in rod photoreceptor differentiation as well as cell cycle progression.

Supported by: NIH award: R01EY021769, The Pew Biomedical Scholars Program, Fight for Sight Foundation, and The Gertrude Flora Ribble Graduate Fellowship, Department of Biology, University of Kentucky

Primary Presenter / e-mail: M.A. Forbes-Osborne / maforb2@uky.edu

Mentor or Senior Author / e-mail: A.C. Morris / ann.morris@uky.edu

Poster Presentation Abstracts

#87 Abstract Title: **Sox4 Regulates Ocular Morphogenesis in Zebrafish**

Category: Graduate Student

Author(s): W. Wen, Department of Biology, U of Kentucky
L. S. Pillai-Kastoori, Department of Biology, U of Kentucky
A. C. Morris, Department of Biology, U of Kentucky

Abstract: Sox4 is a member of the group C family of SRY-box containing transcription factors. Sox4 promotes differentiation of multiple cell lineages during development. Zebrafish have two co-orthologs of the mammalian sox4 gene: sox4a and sox4b, though their functions during zebrafish ocular development are not clear. This project studies the role of sox4 during eye development in zebrafish. Sox4 expression was detected by reverse transcript PCR (RT-PCR) in the developing zebrafish from 24 hours post fertilization (hpf) through 2 months of age. Whole mount in-situ hybridization (WISH) showed sox4a was expressed in the developing zebrafish retina from 24 hpf to 5 days post fertilization (dpf). As retinal development progressed, the expression of sox4a was gradually restricted to the persistently neurogenic ciliary marginal zone (CMZ). Morpholino-mediated sox4 knockdown resulted in microphthalmia , rod photoreceptor reduction, coloboma and variable ventral retinal defects. Midline secreted Sonic Hedgehog induces the expression of optic stalk marker pax2, which was expanded in sox4 morphants, indicating that sox4 knockdown resulted in increased Hedgehog (Hh) signaling. Treatment with the Hh signaling inhibitor cyclopamine rescued the coloboma phenotype in sox4 morphants . Overexpression (OE) of sox4 in zebrafish embryos prevented proper segregation of the early eye field, resulting in cyclopia. Interestingly, retinal neurogenesis in the cyclopic retinas was not significantly affected by overexpression of sox4. In conclusion, the rescue of the coloboma phenotype in sox4 morphants by cyclopamine and the cyclopia phenotype in sox4 OE embryos suggests that Sox4 protein is required to maintain proper levels of Hh signaling during ocular morphogenesis.

Supported by: NIH Grant R01EY021769; The Pew Scholars Program in Biomedical Science; Knights Templar Eye Foundation.

Primary Presenter / e-mail: W. Wen / wen.wen@uky.edu

Mentor or Senior Author / e-mail: A. C. Morris / ann.morris@uky.edu

---

#88 Abstract Title: **Exposure to Corticosterone During Ethanol Exposure and Withdrawal Augments the Loss of Synaptophysin Immunoreactivity in a NR2B-dependent Manner**

Category: Graduate Student

Author(s): J. N. Berry, Department of Psychology, U of Kentucky
L. J. Sharrett-Field, Department of Psychology, U of Kentucky
A. R. Reynolds, Department of Psychology, U of Kentucky
M.A. Prendergast, Psychology and Spinal Cord and Brain Injury Research Center, U of Kentucky

Abstract: High levels of stress, marked by elevations in corticosterone (CORT), often precede and accompany alcohol abuse, with ethanol withdrawal (EWD) producing even further increases in CORT. Both elevations of CORT and chronic ethanol (EtOH) are known to produce increases in the expression and/or function of the glutamatergic N-methyl-D-aspartate (NMDA) receptor, while the polyamine sensitive NR2B subunit is particularly affected. Using the organotypic hippocampal slice culture model, the current studies examined the effect of 11 days of exposure to CORT (100-500 nM) in the presence or absence of 50 mM EtOH for 10 days followed by a subsequent 24 hour EWD on changes in synaptophysin immunoreactivity, as well as the role of the NR2B subunit in the loss of synaptophysin observed. CORT exposure for 11 days in EtOH-naïve cultures resulted in no significant loss of synaptophysin immunoreactivity in the pyramidal cell layer of the CA1 region of the hippocampus. Similarly, no significant loss of synaptophysin immunoreactivity was found following 10 days of EtOH exposure or 10 days of EtOH exposure and a subsequent 24 hour EWD. However, co-exposure to CORT during EtOH exposure and subsequent withdrawal resulted in a significant loss of synaptophysin immunoreactivity. Further, co-exposure to the NR2B antagonist ifenprodil for 24 hours during EWD attenuated the loss of synaptophysin immunoreactivity produced by co-exposure to CORT and EtOH/EWD. These results suggest that co-exposure to CORT during EtOH exposure and subsequent withdrawal may result in reduced synaptic viability in a NR2B-dependent manner.

Supported by: NIAAA R01AA013388 (MAP) and NIDA T32DA016176 (JNB)

Primary Presenter / e-mail: J. N. Berry / jnberry@uky.edu

Mentor or Senior Author / e-mail: M.A. Prendergast / prender@uky.edu

#89 Abstract Title: **Sox11 Drives Ocular Morphogenesis by Regulating Levels of Hedgehog Signaling**

Category: Graduate Student

Author(s):
L. Pillai-Kastoori, Department of Biology, U of Kentucky
W. Wen, Department of Biology, U of Kentucky
S. G. Wilson, Department of Biology, U of Kentucky
E. Strachan, Ophthalmology and Medical Genetics, U of Alberta, Edmonton, Canada
O. Lehmann, Ophthalmology and Medical Genetics, U of Alberta, Edmonton, Canada
A. C. Morris, Department of Biology, U of Kentucky

Abstract: PURPOSE: The SRY-Box transcription factor Sox11 functions as a regulator of cell fate, survival, and differentiation in both embryonic and adult nervous system. Previously, we have shown that reduced levels of sox11 in zebrafish result in in microphthalmia, coloboma, and specific reduction in rod photoreceptor cells. The goal of this study is to determine the mechanism of action of Sox11 during ocular development in zebrafish and characterize the functional activity of human SOX11 sequence variants. METHODS: Translation blocking morpholinos were injected into 1-cell stage zebrafish embryos. The embryos were collected at different time points and processed for whole-mount in situ hybridization and immunohistochemical examination. Embryos were treated with 2 µm cyclopamine between 5.5-13 hours post fertilization. DNA samples from probands with MAC (microphthalmia, anophthalmia, and/or colobomata) were screened by sequencing the SOX11 coding sequence. In vitro transcribed sox11 mRNA was co-injected with sox11 morpholinos into zebrafish embryos. RESULTS: Knockdown of sox11 resulted in coloboma, accompanied by expanded expression of the optic vesicle marker pax2.1. The morphant ocular phenotypes, including the rod photoreceptor deficit, could be rescued by pharmacological inhibition of the Hedgehog pathway. Two MAC patients with heterozygous sequence variations (p.G145C and p.351S-S354dup.) in SOX11 were identified. In contrast to wild type human SOX11 mRNA, mRNA containing either mutation could not rescue the abnormal eye phenotypes in the zebrafish sox11 morphants. CONCLUSIONS: Our results reveal that Sox11 regulates early ocular and photoreceptor development in part by maintaining proper levels of Hedgehog signaling. Studies are ongoing to determine the effects of mutations in SOX11 on the function of SOX11 protein.

Supported by: Grant from the Knights Templar Eye Foundation, The Pew Scholars Program in the Biomedical Sciences, Lyman T. Johnson Graduate Fellowship, U of Kentucky

Primary Presenter / e-mail: L. Pillai-Kastoori / lakshmi.pillai@uky.edu

Mentor or Senior Author / e-mail: A.C.Morris / ann.morris@uky.edu

#90 Abstract Title: **Effects of Ionotropic Glutamate Receptor Blockade in Delay and Probability Discounting**

Category: Graduate Student

Author(s):
J. R. Yates, Psychology and Center for Drug Abuse Research Translation, U of Kentucky
J. S. Beckmann, Psychology Center for Drug Abuse Research Translation, U of Kentucky
M. T. Bardo, Psychology and Center for Drug Abuse Research Translation, U of Kentucky

Abstract: Discounting refers to the decrease in subjective value of a reinforcer as a function of the delay to or odds against its delivery. Although the glutamate NMDA and AMPA receptors are critical in learning and memory formation, little is known about the role of ionotropic glutamate receptors in discounting behavior. The goal of the present study was to determine if ionotropic glutamate receptors differentially mediate delay and probability discounting. Twenty-four male, Sprague Dawley rats received training in either a delay or probability discounting task. During the discounting tasks, a response on one lever always resulted in immediate delivery of one sucrose pellet. A response on the other lever resulted in delayed or uncertain delivery of 4 pellets. The delay to or odds against obtaining the larger reinforcer increased across blocks of trials. Upon reaching stability, rats were treated with different doses of the NMDA receptor antagonist MK-801 (0, 0.01, or 0.03 mg/kg, s.c.). A subset of rats (n=6 each task) also were tested to determine the possible role of AMPA receptors in discounting behavior. Rats were treated with the AMPA receptor antagonist CNQX (0, 1, or 3 mg/kg, s.c.). MK-801 (0.03 mg/kg) decreased sensitivity to delayed and probabilistic reinforcement, whereas CNQX did not alter discounting behavior in either task. These results show that NMDA glutamate receptors, but not AMPA receptors, mediate discounting in response to delayed and probabilistic reinforcement. Future work needs to address the potential neuroanatomical substrates involved in glutamate's effects in discounting behavior.

Supported by: NIH grants P50 DA05312 and T32 DA016176

Primary Presenter / e-mail: J. R. Yates / justin.yates@uky.edu

Mentor or Senior Author / e-mail: M.T. Bardo / mbardo@email.uky.edu

Poster Presentation Abstracts

#91 Abstract Title: **Dependence of Volume of Distribution on Gel Strength for Convection Enhanced Delivery of Drugs to the Brain.**

Category: Graduate Student

Author(s):
K. Sunthankar, Anatomy & Neurobiology, U of Kentucky
C. A. Brown, Anatomy & Neurobiology, U of Kentucky
A. Fountain, Anatomy & Neurobiology, U of Kentucky
P. A. Hardy, Anatomy & Neurobiology, U of Kentucky
L. H. Bradley, Anatomy & Neurobiology, and Molecular & Cellular Biochemistry, U of Kentucky

Abstract: Convection Enhanced Delivery (CED) is emerging as an effective clinical method for delivering therapeutic agents directly to the brain to treat neurological diseases, including Parkinson's disease. While this method has had varying success in clinical trials, standardized CED in vitro models are needed to develop CED techniques which improve the reliable distribution of therapeutic compounds. Many groups, including ours, have conducted model studies using agarose gel mimics, which simulate the isotropic, porous environment of grey matter structures, such as the putamen. However, the composition of the gels is not defined in the literature. To gain insight into the dependence of the infusion pressure required, and the volume of distribution of compounds as a function of varying agarose gel strength, we infused safranin O dye into 0.6% agarose gels of tensile strengths of 500, 900 and 1200 g/cm3. Our results show that the volume of distribution and the infusion back pressure is dependent on agarose gel strength, with 900 g/cm3 better approximating CED delivery in the porcine brain. This information will be useful for future standardized in vitro evaluations of CED procedures.

Supported by: University of Kentucky
Primary Presenter / e-mail: K. Sunthankar / kpsu223@g.uky.edu
Mentor or Senior Author / e-mail: L. H. Bradley / lhbradley@uky.edu

#92 Abstract Title: **A Neuroprotective Mechanism of Pioglitazone following Traumatic Brain Injury**

Category: Graduate Student

Author(s):
H. M. Yonutas, SCoBIRC, Anatomy and Neurobiology, U of Kentucky
W. J. Geldenhuys, College of Pharmacy, Northeast Ohio Medical University
R. T. Carroll, College of Pharmacy, Northeast Ohio Medical University
P. G. Sullivan, SCoBIRC, Anatomy and Neurobiology, U of Kentucky

Abstract: A major focus has developed to discover neuroprotective therapeutic agents to help the estimated 1.7million Americans who receive traumatic brain injury, TBI, annually. Tribulations have been encountered along the way due to the complicated set of pathways that are initiated post-injury. To target this complicated multifaceted signaling cascade, the most promising therapeutic target multiple pathways involved in the secondary injury cascade, such as neuroinflammation, the generation of ROS and mitochondrial dysfunction. Compelling experimental data demonstrates that mitochondrial dysfunction is a pivotal link in the neuropathological sequelae of brain injury. We have previously reported that Pioglitazone, a known PPAR agonistic, can increase mitochondrial bioenergetics, cortical sparing and functional recovery following TBI but some of these effects seem to be independent of PPAR interaction. We hypothesize that pioglitazone's neuroprotective mechanism is directly related to interactions with the novel mitochondrial protein, mitoNEET. To test this hypothesis, wild-type and mitoNEET null mice (Pioglitazone and NL-1 study) and Sprague Dawley rats (NL-1 study) were subjected to sham or severe controlled cortical impact (CCI) TBI surgery. Preliminary results demonstrate that pioglitazone lacks neuroprotection in mitoNEET knockout mice and that treatment with a specific mitoNEET ligand (NL-1) increases cortical sparing and motor recovery following TBI. Therefore, we believe pioglitazone to be a novel mitochondrial targeting drug which is able to alter mitochondria bioenergetics following TBI. The results of these studies will help to shed light on the fundamental processes involved in TBI neuropathology and may pinpoint potential novel interventions and targets for the treatment of TBI.

Supported by: 'Neurobiology of CNS Injury & Repair' Training Grant: 1T32 NS077889, NIH/NINDS grants R01- NS048191, NS062993 , KSCHIRT (PGS) and P30 NS051220
Primary Presenter / e-mail: H. M. Yonutas / heather.yonutas@yahoo.com
Mentor or Senior Author / e-mail: P. G. Sullivan / patsullivan@uky.edu

Poster Presentation Abstracts

#93 Abstract Title: **Unique Electrophysiological Signatures of Mild Cognitive Impairment and Alzheimer Disease**

Category: Graduate Student

Author(s):
L.S. Broster, Department of Behavioral Science, U of Kentucky
J. Li, Institute of Psychology, Chinese Academy of Sciences
R.H. Haney, Department of Behavioral Science, U of Kentucky
A.N. Khan, Department of Behavioral Science, U of Kentucky
C.D. Smith, Department of Neurology, U of Kentucky
G.A. Jicha, Department of Neurology, U of Kentucky
F.A. Schmitt, Department of Neurology, U of Kentucky
M. Heflin, Department of Behavioral Science, U of Kentucky
N.B. Munro, Oak Ridge National Laboratory, Oak Ridge, TN
L.M. Hively, Oak Ridge National Laboratory, Oak Ridge, TN
Y. Jiang, Department of Behavioral Science, U of Kentucky

Abstract: We measured behavior and cognitive event-related potentials (cERPs) to repetition effects (RE) of working memory (WM) generated by 37 older participants to identify the mechanism of maintained behavioral RE in the course of Alzheimer disease (AD). Changes in working memory are among the earliest clinical symptoms of patients with the stage of AD termed amnestic mild cognitive impairment (aMCI). Behaviorally, the normal older control (NC) and aMCI groups performed similarly, though the aMCI group showed disproportionately slow reaction times for non-matching stimuli. The AD group was slower and had poorer accuracy than both other groups, but all groups showed comparable RE. Cognitive ERPs identifies significant REs and a significant WM x RE interaction at frontal sites during the late time-window (ps < 0.01); RE were associated with reduced amplitude, and RE was greater for WM-matching stimuli (ps < 0.05). During the early time-window, cERPs revealed significant RE, a significant WM x RE interaction, and a significant WM x RE x Clinical Group interaction at posterior electrodes (ps < 0.05). Unlike in the late time-window, RE here was linked to increased mean P3 amplitude, andRE was larger for WM-nonmatching stimuli (ps < 0.01). The WM X RE interaction was greater posteriorly persons with AD (ps < 0.05). Persons with aMCI showed heterogeneous responses. This study suggests that persons with AD show compensatory cognition such that the posterior RE assumes functions typically reserved for the anterior RE, perhaps due to disproportionate anterior RE disruption in persons with AD.

Supported by: Department of Energy (DE-AC03-OR22725), the National Institute of Health (P50 AG05144-21; AG00986; 5P30AG028383; 5 T32 AG 242-18; UL1RR033173; UL1TR000117), and a pilot grant from the University of Kentucky Department of Behavioral Science.

Primary Presenter / e-mail: L.S. Broster / lucas.broster@uky.edu

Mentor or Senior Author / e-mail: Y. Jiang / yjiang@uky.edu

#94 Abstract Title: **Complication Avoidance in Deep Brain Stimulation: A Novel Intracranial Lead Fixation Technique**

Category: Graduate Student

Author(s):
B. W. Brown, Department of Neurosurgery, U of Kentucky
C. G. van Horne, Department of Neurosurgery, U of Kentucky

Abstract: Deep brain stimulation (DBS) has demonstrated effective symptom relief for Parkinson's disease, essential tremor, dystonia, and may be an emerging treatment approach for Alzheimer's disease, depression, and obsessive-compulsive disorders. However, as with all device related procedures, complications are unavoidable. There are numerous reports in the literature regarding complications from DBS; however, there are few regarding complication prevention. In this study, the authors performed a review of published techniques for lead fixation as well as to present their anchoring technique. The novel lead fixation technique utilizes a silastic tubing to protect the lead, an injectable calcium phosphate cement (HydroSet®), and a titanium craniofacial miniplate. The HydroSet® serves as a bone void filler and hinders unwanted lead migration while the miniplate retains the lead in its final position. The described technique has been utilized in 44 patients for implanted electrodes in the subthalmic nucleus, thalamus, or globus pallidus for a total of 66 lead placements without incidence of lead damage or migration.

Supported by: The content is solely the responsibility of the authors. The authors have no disclosures.

Primary Presenter / e-mail: B. W. Brown / bwbrow3@uky.edu

Mentor or Senior Author / e-mail: C. G. van Horne / craigvanhorne@uky.edu

#95 Abstract Title: **Combined Thalamic and Subthalamic Nucleus Stimulation in Parkinson Disease**

Category: Graduate Student

Author(s):
W. Stafford, Department of Neurosurgery, U of Kentucky
F. Zahir, Department of Neurology, U of Kentucky
J. Gurwell, Department of Neurology, U of Kentucky
C. Van Horne, Department of Neurosurgery, U of Kentucky

Abstract: Background: Deep brain stimulation (DBS) is a FDA approved therapy for the symptomatic treatment of movement disorders including essential tremor, Parkinson's disease, and dystonia. Effective treatment depends upon patient selection, the appropriate selection of the target for stimulation, and post-operative programming. Typically, patients will have electrodes placed into a single unilateral target for unilateral symptoms and a single target bilaterally for bilateral symptoms. In this report, we present two PD patients who have been implanted with three electrodes representing a single unilateral target, the VIM of the thalamus to control tremor, and a single bilateral target, the subthalamic nucleus STN, to control the progressive parkinsonian symptoms. Clinical Details: One patient with idiopathic PD initially had good response to unilateral tremor with a left ViM thalamic lead, subsequently developed severe left-sided dyskinesias and underwent right STN lead placement with good response. Ten years after his initial surgery the patient had progressive right sided dyskinetic side effects and motor fluctuations on his right and underwent left STN placement. Interestingly, the patient had significantly better symptom control with all three leads activated. A second PD patient underwent right ViM placement for tremor symptoms, followed by left STN placement for bradykinetic symptoms. She developed worsening left sided bradykinesia and rigidity and a right STN lead was added. Similarly, this patient's symptoms have been well controlled with all three leads activated. Discussion: These cases demonstrate that stimulation of new targets does not necessarily replace effective stimulation at existing targets and can provide additional therapeutic improvements.

Supported by:
Primary Presenter / e-mail: W. Stafford / wlst225@uky.edu
Mentor or Senior Author / e-mail: C. Van Horne / craigvanhorne@uky.edu

---

#96 Abstract Title: **Selenium supplementation for the treatment of traumatic brain injury**

Category: Graduate Student

Author(s):
C. Crowdus, Department of Anatomy and Neurobiology, U of Kentucky
J. Pandya, Department of Anatomy and Neurobiology, U of Kentucky
L. Power, Department of Anatomy and Neurobiology, U of Kentucky
A. Sebastian, Department of Anatomy and Neurobiology, U of Kentucky
H. Yonutas, Department of Anatomy and Neurobiology, U of Kentucky
D. Hopkins, Department of Pharmaceutical Sciences, U of Kentucky
J. Jones, Department of Pharmaceutical Sciences, U of Kentucky
J. Pauly, Department of Pharmaceutical Sciences, U of Kentucky
P. Sullivan, Department of Anatomy and Neurobiology, U of Kentucky
R. Power, Alltech J. Geddes, Department of Anatomy and Neurobiology, U of Kentucky

Abstract: Traumatic brain injury continues to be a prevalent clinical problem, especially in high-risk groups such as professional athletes and military personnel. These groups may benefit from a prophylactic supplement that would ameliorate the secondary neurodegenerative effects as soon as the trauma occurs. Dietary selenium, a known cofactor for antioxidant enzymes, was supplemented in the diets of male Sprague-Dawley rats prior to receiving a moderate (1.75mm) CCI brain injury or sham craniotomy. Twenty-four hours following injury, the impact site was collected and mitochondria isolated from these tissues. Mitochondrial respiration was measured using oxygen consumption rates in response to mitochondrial substrates. A separate cohort of animals, receiving the same severity of injury, were evaluated for behavior and histology. Ten days following surgery, animals were tested for spatial memory for five days using the Morris Water Maze task. Following the final task, the animals were euthanized and brain tissues obtained for histological analysis. Mitochondrial respiration studies showed a damaging injury effect but no significant changes in mitochondrial function following selenium supplementation as compared to rats on a control diet (n=8 per group). The behavioral analysis showed a trend towards improvements in memory of platform location and a significant ($p<0.05$) improvement in distance traveled to the platform on the final day of trial testing. Histological analysis showed no significant difference in cortical tissue sparing between the two treatment groups. The improvements in memory suggest that dietary selenium supplementation may be beneficial for traumatic brain injury, but more sensitive markers are necessary to determine the method of action.

Supported by: Alltech
Primary Presenter / e-mail: C. Crowdus / cacrow3@uky.edu
Mentor or Senior Author / e-mail: J. Geddes / jgeddes@uky.edu

#97 Abstract Title: **The Effects of Chronic Methylphenidate Treatment on Tonic and Phasic Glutamate in Prefrontal Cortical Regions of a Rodent Model of ADHD**

Category: Graduate Student

Author(s):
E. M. Miller, Department of Anatomy and Neurobiology, U of Kentucky
G. Quintero, Department of Anatomy and Neurobiology, U of Kentucky
F. Pomerleau, Department of Anatomy and Neurobiology, U of Kentucky
P. Huettl, Department of Anatomy and Neurobiology, U of Kentucky
G. A. Gerhardt, Department of Anatomy and Neurobiology, U of Kentucky
P. E. A. Glaser, Department of Anatomy and Neurobiology, U of Kentucky

Abstract: Recent clinical research has implicated glutamate in the etiology of attention-deficit/hyperactivity disorder (ADHD). Using proton magnetic resonance spectroscopy, it was discovered that children and adults with ADHD exhibited increased levels of a marker for glutamine/glutamate in the prefrontal cortex (PFC). The stimulant medication methylphenidate (MPH), a dopamine reuptake inhibitor, was found to lower these levels. Previous evaluations of the spontaneously hypertensive rat, a rodent model of ADHD, suggest that altered glutamatergic neurotransmission may exist in the PFC and data from our lab in anesthetized animals revealed higher glutamate levels in the PFC of the SHR than in its progenitor strain, the Wistar Kyoto (WKY). To connect this glutamatergic dysfunction to the ADHD-like behaviors of the SHR, we used a novel double-sided glutamate biosensor, which allowed for glutamate recordings from several PFC sub-regions simultaneously in an awake animal. First, we discovered that a clinically relevant dose of MPH (2 mg/kg) acutely increased locomotion in the SHR but not the WKY, whereas chronic treatment (11 days) increased locomotion in both strains. Next, we sought to examine the effects of chronic MPH treatment on glutamate and we found that chronic, but not acute, treatment reduced tonic while increasing phasic glutamate in the SHR. These results establish glutamate dysfunction as a potential target for novel therapeutics for the treatment of ADHD. Finally, this experimental paradigm provides us an avenue in which the exploration of the links between behavior, PFC sub-regions, glutamatergic neurotransmission, and pharmacotherapy is possible.

Supported by: USPHS grants MH070840, AG13494, 5T32AG000242-13, NSF EEC-0310723, and DARPA N66001-09-C-2080.

Primary Presenter / e-mail: E. M. Miller / emmo222@uky.edu

Mentor or Senior Author / e-mail: P. E. A. Glaser / pglas0@email.uky.edu

#98 Abstract Title: **Effects of Time Interval Variation Between Repeated Mild Traumatic Brain Injuries in Mice**

Category: Graduate Student

Author(s):
A.N. Bolton, Spinal Cord and Brain Injury Research Center, Department of Physiology, U of Kentucky
B.C. Tuttle, Spinal Cord and Brain Injury Research Center, U of Kentucky
J.P. Brelsfoard, Spinal Cord and Brain Injury Research Center, U of Kentucky
K.E. Saatman, Spinal Cord and Brain Injury Research Center, Department of Physiology, U of Kentucky

Abstract: Due to increasing concern about cumulative effects of war and sports-related mild traumatic brain injuries (mTBI), the development of a translatable model with which to assess the histological and behavioral outcomes associated with repetitive mTBI is necessary. A pneumatic controlled cortical impact device modified with a compliant 5mm diameter tip was used to impact the intact mouse cranium along the dorsal midline suture to produce bilateral hippocampal pathology in the absence of cortical contusion underlying the impact site. The severity of astrocytosis and amount of neurodegeneration in the hippocampus increased as a function of impact depth (0.5mm-3.0mm; n=3-4/depth). In order to assess how the length of time between repeated injuries affects neuropathological outcomes, mice were given five mTBI spaced at either 24hr or 48hr intervals and were then euthanized 24hrs after their final head injury (n=8/group). Five mTBI at 24hr intervals resulted in greater astrocytosis in the hippocampus and entorhinal cortex (ERC), and increased axonal injury, microgliosis, and neural death in the ERC compared to five mTBIs at 48hr intervals. The ERC plays a critical role in the memory circuit, and an injury in this location provides a novel tool to assess memory deficits due to repetitive head injuries. Mice receiving three mTBIs spaced at 24hr intervals (n=10) displayed memory deficits on a novel object recognition task 4wks after injury that had resolved by 8wks post-injury compared to sham control animals (n=4). This model will help further the exploration of mechanisms underlying the pathology and behavioral impairment after repeated mTBI.

Supported by: NIH PO1 NS058484, P30 NS051220, and 1T32 NS077889

Primary Presenter / e-mail: A.N. Bolton / amanda.bolton@uky.edu

Mentor or Senior Author / e-mail: K.E. Saatman / k.saatman@uky.edu

Poster Presentation Abstracts

#99 Abstract Title: **Transcriptional Regulation by Her Proteins during Vertebrate Retinal Development and Regeneration**

Category: Graduate Student

Author(s):
S. G. Wilson, Department of Biology, U of Kentucky
M. A. Forbes-Osborne, Department of Biology, U of Kentucky
A. C. Morris, Department of Biology, U of Kentucky

Abstract: Purpose: Retinal neurogenesis results from complex interactions of regulatory networks and spatiotemporally controlled gene expression events. Hairy/Enhancer of Split Related (her) transcription factors are expressed during embryonic neurogenesis and regeneration of the zebrafish retina. Many her genes are direct targets of Notch-Delta signaling and repress transcription of pro-neural genes. Here we investigated the roles of her4 and her9 during retinal development and regeneration, and characterized these genes in the context of genetic pathways. Methods: Expression patterns of her4 and her9 were characterized using in situ hybridization (ISH) during embryonic retinal development and in an adult rod degeneration model. Knockdown of the Notch pathway was accomplished using pharmacological inhibition and transgenic mind bomb zebrafish. Translation blocking morpholinos were used to knock down expression of specific her genes. Dual-luciferase assays were used to identify targets of her mediated repression. Results: Her4 and her9 were expressed in proliferative zones of the retina during development and regeneration. Manipulation of the Notch-Delta pathway resulted in expression changes of her4 but not her9. Knockdown of her4 results in premature depletion of progenitor cells, and knockdown of her9 results in loss of retinal vasculature. Dual luciferase assays showed that the her genes directly repress pro-neural genes in vitro. Conclusions: Our results show that knockdown of her4 phenocopies knockdown of the Notch pathway during retinal development, suggesting that it is a primary effector of Notch signaling. This is consistent with the hypothesis that her genes repress neurogenesis and are required for stem cell maintenance in the retina. In addition misexpression of her9 results in vasculature defects, suggesting it plays a role in vasculogenesis.

Supported by: NIH award: RO1EY021769
Primary Presenter / e-mail: S. G. Wilson / stephenwilson@uky.edu
Mentor or Senior Author / e-mail: A. C. Morris / ann.morris@uky.edu

---

#100 Abstract Title: **Tomosyn Dysregulation Leads to Aberrant Glutamate Release in the Dentate Gyrus of the Hippocampus in a Mouse Model of Epileptogenesis**

Category: Graduate Student

Author(s):
S.R. Batten, Department of Anatomy & Neurobiology, U of Kentucky
E.A. Matveeva, Department of Molecular & Cellular Biochemistry, U of Kentucky
S.W. Whiteheart, Department of Molecular & Cellular Biochemistry, U of Kentucky
T.C. Vanaman, Department of Molecular & Cellular Biochemistry, U of Kentucky
P.E.A. Glaser, Departments of Psychiatry, Pediatrics, and Anatomy & Neurobiology, U of Kentucky
G.A. Gerhardt, Department of Anatomy & Neurobiology, U of Kentucky
J.T. Slevin, Neurology Service Veterans Affairs Medical Center, Departments of Neurology, and Molecular & Biomedical Pharmacology, U of Kentucky

Abstract: Epilepsy affects approximately 2.3 million adults and 467, 711 children each year in the United States with 150,000 new cases being diagnosed each year. Despite this, the aberrant molecular processes that initiate and propagate epilepsy (epileptogenesis) are unknown. Dysregulation in the release of the major excitatory neurotransmitter, glutamate, as well as in the function of several presynaptic proteins associated with neurotransmitter release have been indicated as potential causes of epileptogenesis. One of the proteins implicated is a negative regulator of glutamate release, tomosyn. Here we use glutamate biosensors to measure tonic, KCl evoked, and spontaneous glutamate transients in distinct sub-regions of the hippocampus (dentate gyrus [DG], CA3, and CA1) in tomosyn wild type (Tom+/+; n = 7), tomosyn heterozygous (Tom +/-; n = 6), and tomosyn knockout (Tom -/-; n = 9) mice. We found a significant, linear increase in glutamate release as tomosyn levels were reduced across genotype in the DG for both KCl-evoked and spontaneous transient glutamate measures. These results suggest that the dysregulation of proteins controlling glutamate synaptic transmission as well as aberrant glutamate release may contribute to epileptogenesis. Thus, the development of novel pharmacotherapies that work to modulate presynaptic proteins that regulate glutamate release may provide beneficial therapies to treat epilepsy in humans.

Supported by: Department of Veterans Affairs, Defense Advanced Research Projects Agency (N66001-09-C2080), and the National Institute of Health (HL56652 and HL091893)
Primary Presenter / e-mail: S.R. Batten / seth.batten@uky.edu
Mentor or Senior Author / e-mail: P.E.A. Glaser / pglas0@email.uky.edu

Poster Presentation Abstracts

#101 Abstract Title: **Astrocytic Calcineurin and Connexin 43 Gap Junctions in Neuroinflammation and Alzheimer's Disease**

Category: Graduate Student

Author(s):
M. M. Pleiss, Department of Molecular and Biomedical Pharmacology, U of Kentucky
J. L. Furman, Department of Neurology, Washington University
H. M. Abdul, Sanders Brown Center on Aging, U of Kentucky
C. M. Norris, Sanders Brown Center on Aging, U of Kentucky

Abstract: Astrocyte activation arises early in the progression of Alzheimer's disease (AD), possibly leading to chronic neuroinflammation, synapse dysfunction, and neurodegeneration. Pro-inflammatory cytokines inhibit intracellular communication between astrocytes by impairing the function of gap junction proteins, including connexin 43 (Cx43). Earlier work found that Cx43 is dephosphorylated and disrupted by calcineurin (CN), a protein phosphatase upregulated in activated astrocytes during AD and involved in immune/inflammatory signaling. However, the extent to which CN interacts with Cx43 during AD is not known. In the present study, we prepared hippocampal membrane fractions from non-demented human subjects (n = 10), and subjects diagnosed with mild cognitive impairment (MCI, n =14) or AD (n =21) and used Western blot to assess levels of total and dephosphorylated Cx43. The results revealed a slight, though insignificant reduction in Cx43 in the MCI and AD groups relative to non-demented controls. In contrast, levels for the dephosphorylated form of Cx43 exhibited an ~58% increase during MCI ($p < 0.01$), but returned to near control levels during AD. This pattern of change was similar to that shown previously by NFAT1, another critical CN substrate found in activated astrocytes. The results suggest that neuroinflammation arising in the early stages of AD disrupts astrocytic gap junctional coupling, in part, through the activation of CN.

Supported by: NIH RO1 AG027297 and the Kleberg Foundation
Primary Presenter / e-mail: M. M. Pleiss / melanie.pleiss@uky.edu
Mentor or Senior Author / e-mail: C. M. Norris / cnorr2@uky.edu

---

#102 Abstract Title: **Insulin-like Growth Factor-1 Overexpression Enhances Neurogenesis by Promoting Neuronal Differentiation after Traumatic Brain Injury**

Category: Graduate Student

Author(s):
S.W. Carlson, Department of Physiology, SCoBIRC, U of Kentucky
S.K. Kizhakke Madathil, Department of Physiology, SCoBIRC, U of Kentucky
J. Chen, Stark Neurosciences Research Insitute, Indiana U., Indianapolis, IN
K.E. Saatman, Department of Physiology, SCoBIRC, U of Kentucky

Abstract: Traumatic brain injury (TBI) produces neuronal loss in the hippocampus, which can culminate in lasting cognitive impairment. Insulin-like growth factor-1 (IGF-1) is a potent neurotrophic factor capable of mediating neuroreparative processes. We hypothesized that elevating brain levels of IGF-1 would promote hippocampal neurogenesis after brain injury. Astrocyte-specific IGF-1 conditionally overexpressing mice (IGF-1 TG) and wild-type (WT) mice were subjected to a 1mm depth controlled cortical impact (CCI) (n=8/genotype) or sham (n=4/genotype) injury and received 50mg/kg BrdU (i.p.) 4hr prior to being euthanized at 3d post-injury to assess hippocampal cellular proliferation and acute immature neuron loss. A second cohort of mice (n=14 CCI/genotype and n=8 sham/genotype) received daily 50mg/kg BrdU injections for 7d beginning 1hr after injury and was euthanized 10d post-injury to evaluate cellular proliferation and recovery of immature neurons in the dentate gyrus. Immature neurons (DCx+), proliferated cells (BrdU+), and trauma-induced newborn neurons (DCx+/BrdU+) were quantified. Brain injury significantly increased BrdU+ cell density at 3 and 10d post-injury ($p<0.001$, compared to sham-injury); however, IGF-1 overexpression did not increase the density of proliferating cells after CCI. DCx+ cell density was significantly reduced at 3d post-injury independent of genotype ($p<0.01$). At 10d after CCI, DCx+ cell density recovered to baseline in WT mice, but levels in IGF-1 TG mice were significantly above baseline and levels in WT injured mice ($p<0.01$). We hypothesized this recovery was the result of IGF-1 enhanced neuronal differentiation. IGF-1 overexpression produced a significant increase in the numbers of newborn neurons (DCx+/BrdU+) generated after injury ($p<0.0001$, compared to all other groups). These results demonstrate that elevated brain levels of IGF-1 enhance hippocampal neurogenesis by promoting neuronal differentiation of the newly proliferated cells within the first 10d following CCI.

Supported by: T32 DA022738, NIH R01 NS072302, KSCHIRT 7-20, P30 NS051220, and R21 NS072631
Primary Presenter / e-mail: S.W. Carlson / swcarl2@uky.edu
Mentor or Senior Author / e-mail: K.E. Saatman / k.saatman@uky.edu

Poster Presentation Abstracts

#103 Abstract Title: **Increase in Doublecortin and NeuroD Indicates an Increase in Progenitor Cells and Neurogenesis After Binge Ethanol Exposure in Adolescent Rats**

Category: Graduate Student

Author(s):
C.R. Geil, Department of Pharmaceutical Sciences, U of Kentucky
J.A. McClain, Department of Pharmaceutical Sciences, U of Kentucky
M.A. Deeny, Department of Pharmaceutical Sciences, U of Kentucky
K. Nixon, Department of Pharmaceutical Sciences, U of Kentucky

Abstract: Alcohol use disorders are prevalent in adolescents and result in hippocampal neurodegeneration, though these deficits may recover with abstinence. Neural stem cells are instrumental to hippocampal structure and function. Recently, we discovered a reactive increase in neurogenesis after 7 days of abstinence from binge ethanol exposure in adolescent rats using the exogenous marker bromodeoxyuridine (BrdU). Therefore, we confirmed increased neurogenesis with an endogenous marker of adult neurogenesis, Doublecortin (DCX). Then, we investigated NeuroD, a marker of proliferating neural progenitor cells, in the subgranular zone of the hippocampal dentate gyrus in a time course following ethanol exposure. Adolescent male Sprague-Dawley rats (PND 35) were administered 25% (w/v) ethanol or isocaloric control diet via gavage every 8 hours for 4 consecutive days according to the Majchrowicz model. Animals received an average of 12.1 ± 0.2 g/kg/day of ethanol and had an average blood ethanol concentration of 347.5 ± 12.5 mg/dl. Animals were perfused and processed for DCX and NeuroD immunohistochemistry. DCX was quantified using densitometry (pixles/mm2) and t-test revealed a 60% increase over controls at 14 days of abstinence ($p<0.05$), which confirmed the increase in neurogenesis previously observed with BrdU. NeuroD+ cells were increased by 70% over controls at 14 days of abstinence ($p<0.05$). However, there was no difference between ethanol and control groups at 7 or 30 days. These data are consistent with our hypothesis that the progenitor cells proliferate around day 7 then differentiate, resulting in increased differentiated progenitors (NeuroD+ and DCX+ cells) by day 14. Therefore, reactive neurogenesis could be a mechanism of hippocampal recovery in abstinence.

Supported by: NIAAA: R01AA016959
Primary Presenter / e-mail: C. R. Geil / Chelsea.Geil@uky.edu
Mentor or Senior Author / e-mail: K. Nixon / Kim-Nixon@uky.edu

#104 Abstract Title: **Development of an Avian Model to Study Individual Differences in Drug Addiction**

Category: Graduate Student

Author(s):
B.A. Rice, Department of Behavioral Neuroscience and Psychopharmacology, U of Kentucky
H. Husain, Kentucky Young Researcher's, Paul Laurence Dunbar H.S.
C. K. Akins, Department of Behavioral Neuroscience and Psychopharmacology, U of Kentucky

Abstract: Rodents that show increased sign tracking over goal tracking behavior are, in theory, thought to have stronger addictive behaviors. Quail have been used in previous drug addiction studies because they have the added benefit of vision that is similar to humans. The purpose of the current study is to identify individual male Japanese quail as either sign or goal trackers. The test chamber consisted of a 4 foot by 2 foot white chamber that contained a blue light at one end and a window through which males could view a female at the other end. In a Pavlovian task, each trial consisted of a 10 sec light cue (sign) followed by 10 sec of visual access to a female quail (goal). Five trials were conducted per day across 20 days. Each light cue and female presentation was spaced at a 90 sec random time interval. Sign trackers were identified as birds that spent a greater amount of time in a 1 foot area closest to the light. Goal trackers were identified as having spent a greater amount of time in a 1 foot area closest to the female. Preliminary results indicate that of the 16 birds tested, 7 were identified as sign trackers, 9 as goal trackers, and 1 bird as neither. The current results demonstrate that an avian model may be more likely to demonstrate clear sign or goal tracking in fewer trials than rodents. The model may be of additional benefit to rodent models in studying individual differences in drug addiction.

Supported by: 'NIDA Grant #DA 0022451 awarded to CKA'
Primary Presenter / e-mail: B.A. Rice / bethannrice01@gmail.com
Mentor or Senior Author / e-mail: C.K. Akins / ckakin1@email.uky.edu

Poster Presentation Abstracts

#105 Abstract Title: **Sex Differences in the Locomotor-Enhancing Effects of Cocaine in Japanese quail**

Category: Graduate Student

Author(s): K. E. Gill, Department of Psychology, U of Kentucky
C. K. Akins, Department of Psychology, U of Kentucky

Abstract: In rodents, females may be more sensitive to the locomotor-enhancing effects of cocaine than males. This increased sensitization in females may be due to estrogen. Japanese quail may be an alternative model to test cocaine-induced locomotor activity. In quail, circulating hormones may be manipulated via photostimulation or photocastration. The purpose of the current experiment was to explore sex differences in cocaine-induced locomotor activity in quail and to determine whether these differences were associated with hormones. Male and female quail were housed on either a 16:8 hr light:dark cycle or a 12:12 light:dark cycle for 21 days. Quail were then administered either saline or cocaine (10 mg/kg or 20 mg/kg) ip once daily for 10 days and placed immediately into an open field chamber where distance-travelled was collected for 30 min. Cloacal gland measurements (CGMs), which are directly correlated with circulating steroid hormones, were taken before the experiment. Results showed that males on the longer light cycle given 10 mg/kg cocaine, and males on the dark cycle given 20 mg/kg cocaine had greater distance-travelled across trials (sensitization) compared to other groups. Surprisingly, females did not exhibit sensitization to any dose on either light:dark cycle. A repeated measures ANOVA revealed a significant Sex x Treatment x Cycle x Trials interaction, $F(18, 711) = 1.84$, $p = .018$. Additionally, CGMs were significantly correlated with activity levels on Trial 1, $r(89) = .27$, $p = .01$. The current findings suggest that, contrary to rodents, male quail may be more sensitive to the locomotor-enhancing effects of psychostimulants compared to female quail. This may be the result of differential hormone effects.

Supported by: NIDA Grant #DA 0022451 awarded to CKA
Primary Presenter / e-mail: K. E. Gill / karin.gill@uky.edu
Mentor or Senior Author / e-mail: C. K. Akins / ckakin1@email.uky.edu

#106 Abstract Title: **Lobelane analogs inhibit vesicular monoamine transporter-2 function to inhibit the effect of methamphetamine**

Category: Graduate Student

Author(s): Z. Cao, Department of Pharmaceutical Sciences, College of Pharmacy, U of Kentucky
G. Zheng, Department of Pharmaceutical Sciences, College of Pharmacy, U of Arkansas
A. G. Deaciuc, Department of Pharmaceutical Sciences, College of Pharmacy, U of Kentucky
P. A. Crooks, Department of Pharmaceutical Sciences, College of Pharmacy, U of Arkansas
L. P. Dwoskin, Department of Pharmaceutical Sciences, College of Pharmacy, U of Kentucky

Abstract: Methamphetamine (METH) abuse is a serious problem in the United States. Currently, no pharmacotherapies are available for the treatment of METH abuse. Vesicular monoamine transporter-2 (VMAT2), located on synaptic vesicles, uptakes cytosolic dopamine (DA) into the vesicles for storage and subsequent release within presynaptic terminals. METH acts at VMAT2 to inhibit DA uptake and promote DA release from the vesicles, increasing cytosolic DA available for METH-induced reverse transport through DA transporter. Meanwhile, METH inhibits monoamine oxidase function and the increased cytosolic DA can not be metabolized by the enzyme. The cytosolic DA undergoes METH-induced reverse transport and the subsequent increase of extracellular DA is responsible for the reinforcing effect of METH. Recently, VMAT2 has been studied as the target to develop pharmacotherapies for METH abuse. Both lobeline and lobelane (a chemically defunctionalized saturated lobeline analog) decrease METH self-administration in rats by inhibiting VMAT2. To further refine the structure-activity relationships, lobelane analogs with 0-3 carbons at the C-2 and C-6 linkers of the central piperidine ring were evaluated for inhibition of [3H]dihydrotetrabenazine (DTBZ) binding, vesicular [3H]DA uptake and METH-evoked vesicular [3H]DA release. A positive correlation between the affinity for [3H]DTBZ binding (Ki =0.88-62.5 μM) and [3H]DA uptake (Ki =0.024-4.6 μM) was revealed. Both linkers were required to maintain equivalent or higher affinity for VAMT2 binding and function compared to lobelane. (±)-GZ-729C and (±)-GZ-730B showed 2-fold higher affinity (Ki = 0.025 ± 0.003 and 0.024 ± 0.002 μM, respectively) inhibiting VMAT2 function compared to lobelane (Ki = 0.040 ± 0.004 μM; $p<0.05$). Both compounds inhibited METH-evoked [3H]DA release from synaptic vesicles through a surmountable allosteric mechanism. In summary, lobelane analogs potently inhibit VMAT2 function and METH-evoked [3H]DA release from synaptic vesicles.

Supported by: NIH award: DA13519
Primary Presenter / e-mail: Z. Cao / zheng.cao@uky.edu
Mentor or Senior Author / e-mail: L. P. Dwoskin / ldwoskin@email.uky.edu

#107 Abstract Title: **The NRF2-ARE Pathway as a Therapeutic Target for Acute Traumatic Brain Injury: Dose Response of Carnosic Acid**

Category: Graduate Student

Author(s):
D.M. Miller, Spinal Cord & Brain Injury Research Center, U of Kentucky College of Medicine
I.N. Singh, Spinal Cord & Brain Injury Research Center, U of Kentucky College of Medicine
J.A. Wang, Spinal Cord & Brain Injury Research Center, U of Kentucky College of Medicine
E.D. Hall, Spinal Cord & Brain Injury Research Center, U of Kentucky College of Medicine

Abstract: Traumatic brain injury (TBI) currently signifies a substantial health and socioeconomic dilemma in the United States with 50,000 cases resulting in death yearly. The pathophysiological importance of oxidative damage after TBI has been extensively demonstrated. The transcription factor Nrf2 mediates transcription of antioxidant/cytoprotective genes by binding to the antioxidant response element (ARE) within DNA. Upregulation of these genes constitutes a pleiotropic cytoprotective-defense pathway. Previously, we demonstrated the in vivo post-injury time-course of Nrf2-ARE mediated gene expression in the cortex and hippocampus of male CF-1 mice utilizing a unilateral controlled cortical impact (CCI) injury model. Interestingly, increased Nrf2-ARE mediated expression was not observed until 24 hours, whereas our recent work showed oxidative damage also peaking 24-48 hours post-TBI. Additionally, we recently demonstrated that pre-treatment 48 hours prior with either of the Nrf2-ARE activating drugs sulforaphane (5.0 mg/kg) or carnosic acid (1.0 mg/kg) could provide protection to cortical mitochondria challenged by the toxic lipid peroxidation byproduct 4-hydroxy-2-nonenal (4-HNE) ex vivo. Thus, we now sought to determine the in vivo dose response of the potent Nrf2-ARE activator carnosic acid and assess its neuroprotective potential in a mouse model of TBI. Young adult male CF-1 mice were administered carnosic acid (CA) at one of three different doses – 0.3, 1.0, or 3.0 mg/kg I.P. or vehicle at 15 minutes post-injury. At 48 hours post-injury, the ipsilateral cortex and hippocampus tissues were dissected out and levels of the oxidative damage marker 4-HNE were assessed by Western blotting. In the cortex, both 1.0 and 3.0 mg/kg doses of CA significantly ($p<0.05$) reduced levels of 4-HNE as compared to vehicle animals, whereas the 0.3 mg/kg dose did not. In the hippocampus, only the 1.0 mg/kg dose of CA significantly ($p<0.05$) reduced 4-HNE levels compared to vehicle, whereas the 0.3 and 3.0 mg/kg doses did not. The 1.0 mg/kg dose of CA was also that which we previously demonstrated to be effective at attenuating 4-HNE induced dysfunction in cortical mitochondria. Therefore, ongoing and future studies will determine the efficacy of this optimal 1.0 mg/kg CA dosing administration on attenuating post-TBI behavioral deficits and neurodegeneration. Collectively, these data demonstrate that carnosic acid may be a promising therapeutic agent for the treatment of TBI and warrants further investigation.

Supported by: NIH-NIDA 1T32 DA022738, NIH-NINDS 1T32 NS-77889, NIH-NINDS 2P30 NS051220-01, and funds from the Kentucky Spinal Cord & Head Injury Research Trust.

Primary Presenter / e-mail: D.M. Miller / dmmi223@uky.edu

Mentor or Senior Author / e-mail: E.D. Hall / edhall@uky.edu

#108 Abstract Title: **PICALM SNP Associated with Alzheimer's Disease: Expression and Splicing**

Category: Graduate Student

Author(s):
I. Parikh, Department of Physiology and Sanders-Brown Center of Aging, U of Kentucky
J. Simpson, Department of Physiology and Sanders-Brown Center of Aging, U of Kentucky
S. Estus, Department of Physiology and Sanders-Brown Center of Aging, U of Kentucky

Abstract: Objectives: GWAS have identified a series of single nucleotide polymorphisms (SNP)s that are associated with Alzheimer´s disease. We studied SNP, rs3851179, near the gene phosphatidylinositol-binding clathrin assembly protein (PICALM) for its effect on expression and splicing of PICALM. Methods: Expression: Quantified total PICALM mRNA in 60 brain cDNA samples, using qPCR. Splicing: Over 700 clones were sequenced to evaluate the abundance and relative distribution of splice variants present. We targeted the latter part of the gene, exon 17-20, to investigate allelic expression imbalance (AEI) using semiconductor- sequencing technology. Individuals heterozygous for rs76719109, located in exon 17, were used to study the ratio of G/T allele in cDNA and genomic DNA. Results: Expression: In linear regression analyses of PICALM that included microvessel markers, AD, sex and rs3851179; microvessel content ($p< 0.001$) associated with PICALM expression. Splicing: Sequencing the cloned isoforms we found that exons 13, 14,15,18 and 19 were variably spliced and isoform lacking exon 13 is the most abundant isoform. For AEI, we analyzed the G : T allelic ratio, the variant lacking exons 18 and 19 showed unequal allelic expression (p-value < 0.001). One individual was an outlier, showing overall AEI. Conclusions: PICALM is highly expressed in microvessels. Rs3851179 is not associated with PICALM expression. PICALM has multiple splice variants, which lack exons encoding functional protein motifs. The isoform lacking exon 18-19 appears to be under genetic control and is the subject of current investigation.

Supported by: NIH for funding: P01-AG030128

Primary Presenter / e-mail: I. Parikh / ishita.parikh@uky.edu

Mentor or Senior Author / e-mail: S. Estus / steve.estus@uky.edu

29th Annual Spring Neuroscience Research Day (BGSFN)

Poster Presentation Abstracts

8th Annual CCTS Spring Conference
April 8, 2013

#109 Abstract Title: **Aging Attenuates Bmal1 Expression in Hamster Hippocampus, Cortex, and SCN but not Skeletal Muscle**

Category: Faculty

Author(s):
M.J. Duncan, Department of Anatomy and Neurobiology, U of Kentucky
D.H. Cook, College of Arts and Sciences, U of Kentucky
K.M. Franklin, Department of Anatomy and Neurobiology, U of Kentucky
J.T. Smith, College of Public Health, U of Kentucky
J. Prochot, College of Arts and Sciences, U of Kentucky

Abstract: Deletion of the core clock gene, Bmal1, not only ablates circadian rhythms but also induces an early aging phenotype, characterized by tissue atrophy (e.g., skeletal muscle) and cognitive deficits (Kondratov et al., 2006, 2010). These findings suggest that Bmal1 participates in the regulation of memory and muscle function, both of which decline during aging. We hypothesized that aging reduces Bmal1 expression in neural memory substrates (e.g., hippocampus and cingulate cortex), skeletal muscle (gastrocnemius), and the master circadian pacemaker (suprachiasmatic nucleus [SCN]). Young (3-5 mos) and old (16-18 mos) male hamsters (N=8-14/age) exposed to a 14:10 light:dark cycle were euthanized at zeitgeber time (ZT) 1, 6, 13, or 19 (ZT12=lights-off), for detection of Bmal1 rhythms. Muscle tissue was homogenized and RNA was purified for real-time RT-PCR; amplification was quantified using SYBR Green chemistry. Brain sections were processed for in situ hybridization using P33-labeled oligonucleotide probes complementary to Bmal1 mRNA. X-ray films were exposed to the slides and radioactive standards to generate autoradiograms. Bmal1 expression in the SCN, cingulate cortex, and hippocampus (CA1, CA2, CA3, and dentate gyrus [DG]), was measured by computerized microdensitometry of the autoradiograms. Bmal1 expression in all brain regions examined showed time of day variations ($P<0.05$), and was lower in old hamsters ($P<0.01$). Only the CA2 showed a time by age interaction ($P<0.05$). In skeletal muscle, only time of day ($P<0.0001$) affected Bmal1 expression. In conclusion, these findings suggest that aging differentially affects Bmal1 expression in skeletal muscle and brain, and that age-related attenuation of Bmal1 expression in the hippocampus and cingulate cortex may contribute to age-related cognitive defects.

Supported by: NIH: 2R01AG13418 (MJD)

Primary Presenter / e-mail: J. T. Smith / jtsmit4@g.uky.edu

Mentor or Senior Author / e-mail: M.J. Duncan / marilyn.duncan@uky.edu

#111 Abstract Title: **Lobectomy and Wedge Resection for Non Small Cell Lung Cancer: A Short Term Outcomes Analysis, UK Experience**

Author(s): D. Kim, College of Medicine, U of Kentucky
S. Saha, Department of Cardiothoracic Surgery, U of Kentucky

Abstract: Purpose: To examine the short term outcomes of patients that underwent lobectomy or wedge resection at the University of Kentucky from 2002-2006. The study will allow us to compare our data from the university experience with literature rates for lobectomy and wedge resection, determining what factors may affect long term survival of these patients and find any statistically relevant complications for further examination. Methods: Subjects for the study were identified using the Cardiothoracic Surgery patient database and the Kentucky Cancer registry. A retrospective chart review of 514 patients was performed using charts from UK Chandler hospital and the Markey Cancer Center, both paper and SCM. Patients met the study categories only if they had primary non small cell lung cancer and had a lobectomy or wedge resection performed to remove their tumor. Follow up data linkage was performed with the Kentucky Cancer Registry for long term survival data. Results: UK rates of morbidity and mortality were not significantly different than literature rates. Pleural leak as a complication exceeded expected occurrence, resolved without intervention by discharge. UK patients had a lower length of stay perioperatively than literature rates for both wedge resection and lobectomy. Conclusions: Resection offers the best chance of cure for non-small cell lung cancer. Lobectomy and wedge resections are the most frequently used techniques for that purpose. These procedures carry very low morbidity and mortality in this review. Long term survival data will be in our next report.

Supported by: PSMRF
Primary Presenter / e-mail: D. Kim / daniel.kim@uky.edu
Mentor or Senior Author / e-mail: S. Saha / ssaha2@uky.edu

#112 Abstract Title: **Enhancing Lung Cancer Screening: The Potential of Autoantibody Profiling to Complement Screening CT Scans**

Author(s): K. Trudgen, College of Medicine, Pulmonary and Critical Care Medicine, U of Kentucky
N. H. Khattar, Pulmonary and Critical Care Medicine, U of Kentucky
E. Bensadoun, Pulmonary and Critical Care Medicine, U of Kentucky
S. Arnold, Medical Oncology, U of Kentucky
A. J. Stromberg, Department of Statistics, U of Kentucky
E. A. Hirschowitz, Pulmonary and Critical Care Medicine, U of Kentucky & Lexington VA Medical Center

Abstract: Recommendations for lung cancer screening present a tangible opportunity to integrate predictive blood-based assays with radiographic imaging. This study explores performance of autoantibody markers from prior discovery in sample cohorts from two CT screening trials using a training-testing validation approach. One-hundred eighty non-cancer and 6 screening detected cancer cases from the Mayo Lung Screening Trial were used to optimize assay composition, define a normal range and assign cutoff values for class prediction. High and low cutoffs were applied in blinded fashion to 256 samples drawn annually for three years from 95 participants in the Kentucky Regional Lung Screening Trial. Predetermined cutoffs offered predictable rates of cancer detection in the Kentucky cohort that decreased commensurate with increasing measurements. When unblinded, data revealed a discrepancy in quantile distribution between the two apparently comparable sample sets, which skewed the assay's dynamic range towards specificity. A low cutoff offered 60% sensitivity, 65% specificity, and accurate classification of 40% of occult cancer cases up to three years prior to radiographic appearance. High cutoff offered 96% specificity with 40% sensitivity. Data must be interpreted with caution because of the small number of cancers in both training and testing cohort. An apparent ceiling in assay sensitivity is likely to limit the utility of this assay in a conventional screening paradigm. This report does not draw conclusions about other logical applications for autoantibody profiling in lung cancer diagnosis and management, nor its potential when combined with other biomarkers that might improve overall predictive accuracy.

Supported by: These studies were supported by the National Institutes of Health R01 # CA10032-01, the Centers for Disease Control, HRSA and the Veteran's Administration.
Primary Presenter / e-mail: K. L. Trudgen / k.trudgen@uky.edu
Mentor or Senior Author / e-mail: E. A. Hirschowitz / Eahirs2@uky.edu

#113 Abstract Title: **Down-regulation of the polymeric immunoglobulin receptor may be a risk factor for the development of colitis-associated cancer in ulcerative colitis patients.**

Author(s):
M. E. Bruno, Department of Microbiology, Immunology & Molecular Genetics, U of Kentucky
A. L. Frantz, Department of Microbiology, Immunology & Molecular Genetics, U of Kentucky
E. W. Rogier, Department of Microbiology, Immunology & Molecular Genetics, U of Kentucky
D. A. Cohen, Department of Microbiology, Immunology & Molecular Genetics, U of Kentucky
J. S. Bryson, Internal Medicine, Hematology and Blood & Marrow Transplantation, U of Kentucky
J. A. Brandon, Internal Medicine, Hematology and Blood & Marrow Transplantation, U of Kentucky
A. J. Stromberg, Department of Statistics, U of Kentucky
R. Arsenescu, Internal Medicine, Gastroenterology, Hepatology & Nutrition, The Ohio Sate U, Columbus, OH
W. J. deVilliers, Internal Medicine, Division of Gastroenterology, Digestive Diseases & Nutrition, U of Kentucky
C. D. Jennings, Department of Pathology & Laboratory Medicine, U of Kentucky
J.L. Ebersole, Center for Oral Health Research, College of Dentistry, U of Kentucky
C. S. Kaetzel, Department of Microbiology, Immunology & Molecular Genetics, U of Kentucky

Abstract: Secretory IgA (SIgA) antibodies promote intestinal homeostasis by limiting microbial access to immune cells in the lamina propria and shaping the composition of the gut microbiota. SIgA, locally synthesized by plasma cells in the lamina propria, is transported across intestinal epithelial cells (IEC) by the polymeric immunoglobulin receptor (pIgR). Analysis of pIgR mRNA levels in colonic biopsies revealed that pIgR was significantly down-regulated in patients with ulcerative colitis (UC) compared to healthy controls. We previously reported that pIgR is down-regulated in sporadic colon cancer. Because UC patients are at high risk of developing colitis-associated cancer (CAC), we hypothesized that down-regulation of pIgR may contribute to the development of chronic colitis and CAC. To test this hypothesis, we used a murine model of chronic colitis and CAC, involving multiple cycles of oral administration of the epithelial-disrupting agent dextran sulfate sodium (DSS), with or without prior injection with the carcinogen azoxymethane. We found that down-regulation of pIgR mRNA was an early and sustained event in the development of chronic colitis, and that pIgR protein was substantially reduced in dysplastic and neoplastic colon tissues. Finally, we found that pIgR-deficient mice exhibited more severe colitis after multiple rounds of DSS than did wild-type mice. Our findings suggest that down-regulation of pIgR expression in IEC may contribute to the development of chronic colitis and CAC.

Supported by: Crohn's & Colitis Foundation of America Senior Research Award (CSK) American Cancer Society Institutional Research Grant # IRG-85-001-11(MEB) NIH/NIDCR: 5P20RR020145 (JLE)
Primary Presenter / e-mail: M. E. Bruno / mebrun2@uky.edu
Mentor or Senior Author / e-mail: C. S. Kaetzel / cskaet@uky.edu

#114 Abstract Title: **Effect of withaferin, an anti-cancer agent from a medicinal plant, on normal lymphocytes, lymphoma and leukemia cells**

Author(s):
M. K. McKenna, Markey Cancer Center and Dept of Microbiol, Immunol and Molec Genetics
S. Alhakeem, Markey Cancer Center and Dept of Microbiol, Immunol and Molec Genetics
Beth W. Gachuki, Markey Cancer Center and Dept of Microbiol, Immunol and Molec Genetics
K. Z. Oben, Markey Cancer Center and Dept of Microbiol, Immunol and Molec Genetics
V.M. Rangnekar, Markey Cancer Center and Microbiol, Immunol and Molec Genetics, Radiation Medicine, U of Kentucky
N. Muthusamy, Comprehensive Cancer Center and Dept of Internal Medicine, Ohio State University, Columbus, OH
J. C. Byrd, Comprehensive Cancer Center and Dept of Internal Medicine, Ohio State University, Columbus, OH
R. C. Gupta, James Graham Brown Cancer Center, University of Louisville, Louisville, KY
Subbarao Bondada,Markey Cancer Center and Dept of Microbiol, Immunol and Molec Genetics

Abstract: Withaferin A, a withanolide from the plant, Asvagandha (Withania Somnifera) used in Ayurvedic medicine, has been found to be valuable in the treatment of several medical ailments. Withanolides, oxidation products of steroids, are known to have growth inhibitory effects on certain insect larvae. Withaferin A, the first isolated withanolide, has been found to have anticancer activity in breast. prostate, pancreatic and colon cancer models, but its effects on hematological malignancies have not been studied in detail. Here we examined the effect of highly purified Withaferin A on the survival of diffuse large B cell lymphoma lines. Withaferin A strongly inhibited the survival of Ramos, SUDHL6, LY10, and A20luc B cell lymphoma lines as well as the murine immature B lymphoma cell line BKS-2. Interestingly withaferin also reduced the proliferation of normal splenic B cells and T cells stimulated via antigen receptors or mitogens. Surprisingly, withaferin did not inhibit the growth of Jeko, a mantle cell lymphoma but inhibited survival of chronic lymphocytic leukemia cells from the Emu-Tcl1 transgenic mice. Investigations will be performed to determine if resistance to Withaferin A is a property of all mantle cell lymphoma cell lines. We demonstrated that withaferin A inhibited nuclear translocation of NF-κB in the SUDHL-6 large B cell lymphoma line. We found that withaferin A inhibited activation of Akt and Src family kinases after 24 hours of incubation. Since previous studies implicated withaferin affects heat shock proteins and their chaperone activity via ATP-independent mechanisms, we are investigating if the growth inhibition in lymphoma cell lines is also dependent on this pathway.

Supported by: 1R01CA165469
Primary Presenter / e-mail: M. K. McKenna / mkmckenna@uky.edu
Mentor or Senior Author / e-mail: S. Bondada / bondada@email.uky.edu

#115 Abstract Title: Targeting Androgen Receptor in Castration Resistant Prostate Cancer with N-Terminal Anti-Androgens and Microtubule-Stabilizing Chemotherapy

Author(s): S.K. Martin, Department of Molecular and Cellular Biochemistry, U of Kentucky
J. Wang, Department of Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada
M.D. Sadar, Department of Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada
N. Kyprianou, Department of Molecular and Cellular Biochemistry and Urology, U of Kentucky

Abstract: Taxane-based chemotherapy was the only clinically effective treatment for castration resistant prostate cancer (CRPC) via stabilization of microtubules. Recent evidence identified the contribution of microtubules to androgen receptor (AR) signaling enabling new insights into inhibition of AR activity by taxane-impaired nuclear translocation in prostate cancer. The N-terminus was identified as a key domain mediating translocation. This domain is effectively targeted by the novel anti-androgen, EPI-001. This small molecule interacts with the AF-1 domain of the AR N-terminus, limits protein-protein interactions and blocks transactivation of AR target genes. Impairing AR activity enables a targeting platform for taxane-based chemotherapy during CRPC. This study pursued the consequences of combination strategy of taxanes with EPI-001 towards improved therapeutic response in a CRPC xenograft model. Combination treatment of DTX and EPI-001 significantly reduced tumor growth compared to single treatment and untreated controls. These findings were corroborated by the increased number of apoptotic cells found in combination treated xenografts indicating that enhanced apoptosis drives the tumor suppression. There was significant reduction in tumor vascularity in response to combination of EPI-001 and DTX. Evaluation of AR expression revealed the combination treatment led to significant decrease in AR (N-terminus) compared to untreated tumors. There was a down-regulation of tubulin expression in xenografts in response to the combination with DTX. Assessing epithelial to mesenchymal transition (EMT) profile in these prostate tumors indicate that untreated tissue exhibit a more mesenchymal phenotype (increased N-cadherin and diminished E-cadherin levels), that is targeted by the combination of DTX and EPI-001. This study demonstrates that utilization of taxanes and N-terminal targeting anti- androgens may more effectively address CRPC.

Supported by: Department of Defense, CIHR MOP79308 (MDS), SKM recipient of Max Steckler Graduate Fellowship
Primary Presenter / e-mail: S. K. Martin / skmart3@uky.edu
Mentor or Senior Author / e-mail: N. Kyprianou / N.Kypr2@email.uky.edu

#116 Abstract Title: Actin Cytoskeleton Remodeling in a Transgenic Mouse Model of Prostate Cancer

Author(s): S. Larkin, College of Medicine, U of Kentucky
H. Pu, Dept of Surgery/Urology, U of Kentucky
N. Kyprianou, Dept of Surgery/Urology, U of Kentucky

Abstract: Purpose: Cofilin is a small, 19KD actin depolymerizing factor vital to cell motility, and plays a key role in actin filament dynamics. Cofilin has been shown to play a role in early cell motility by promoting actin depolymerization, allowing cell migration toward chemokines and various growth factors. Cofilin is regulated via phosphorylation at a serine residue at position 3; phosphorylation of this residue inhibits the actin binding and depolymerizing role of cofilin. Methods: The TRansgenic Adenocarcinoma of the Mouse Prostate (TRAMP) model was used in this study as a model featuring the clinicopathological characteristics of prostate cancer progression to metastasis. Immunohistochemical (IHC) staining was performed to detect the expression and topological localization of cofilin and phosphorylated cofilin throughout the progression of prostate cancer in the TRAMP mouse model. In order to quantify IHC intensity, the H-scoring method was used on all specimens. Results/Conclusions: There was significant increase in the expression levels of total cofilin and cofilin in its active form in prostate tumors compared to normal prostate, that correlated with progression to metastasis. These findings implicate the involvement of the actin cytoskeleton organization as a contributor to prostate cancer metastasis. Furthermore the study suggests a potential value of cofilin as a biomarker of prostate cancer metastasis and mutation at position S3 as predictor of therapeutic response in human prostate cancer.

Supported by: James F. Hardymon Endowment National Center for Advancing Translational Sciences, UL1TR000117
Primary Presenter / e-mail: S. Larkin / spencer.larkin@uky.edu
Mentor or Senior Author / e-mail: N. Kyprianou / nkypr2@email.uky.edu

#117 Abstract Title: **Activation of VEGFR2 leads to expansion of VEGFR2+lin- population and activates MAPK2/4 and JNK modules in oct3/4+ and SSEA4+ stem cells.**

Author(s): A. V. Karapetyan, Department of Internal Medicine and Cardiology, U of Kentucky
Y. Klyachkin, Department of Cardiology, U of Kentucky
A. Abdel-Latif, Department of Cardiology, U of Kentucky

Abstract: We noticed that after acute myocardial infarction (AMI) the concentration of VEGF in peripheral blood and the number of VEGFR2+lin- stem cells rises in highly correlated manner. To understand if these two processes are dependent we investigated the influence of activation of VEGFR2 on VEGFR2 expressing populations. Earlier we have find out that the incubation of mobilized peripheral blood or bone marrow white cells with anti-KDR-1 antibody activates phosphorylation of MAPK2/4 and JNK in oct3/4 and SSEA4+ populations. It allowed using this antibody to specifically activate VEGFR2. We demonstrated that VEGFR2+ Lin- populations including CXCR4 or/and CD105 positive subpopulations of cord or mobilized peripheral blood or bone marrow white cells largely expand in response to the incubation with anti-hKDR-1(VEGFR2) antibody during 2-5 days. qRT-PCR of cord blood samples incubated with anti-KDR1 for 2-3days showed multifold alterations in mRNA expression levels of GATA4, Nkx2.5, VE-cadherin , NANOG and oct4 with subtle but constant elevation of CXCR4 expression. Based on these experiments we speculate that VEGFR2 activation enhances self expression in paracrine manner. This rises question what initially triggers the activation of VEGFR2 receptors? Our preliminary data pointing on : a) possible activation of VEGFR2 signaling pathways via cross-talk with activated S1P3 receptors; b) Involvement of innate immunity because the relative concentration maximum of IL-6 in plasma after AMI precedes the maxima of both G-CSF and VEGF.

Supported by: University of Kentucky Clinical and Translational Science Pilot Award (UL1TR000117)
Primary Presenter / e-mail: A.V.Karapetyan / karapetian1@gmail.com
Mentor or Senior Author / e-mail: A.V.Karapetyan / karapetian1@gmail.com

#118 Abstract Title: **Descriptive Analysis of Patients with Left Ventricular Assist Device Receiving Intermittent Hemodialysis**

Author(s): C. Areephanthu, College of Medicine, U of Kentucky
J. McAbee, Division of Nephrology, Bone and Mineral Metabolism, U of Kentucky
B. George, Department of Internal Medicine, U of Kentucky
B. Peter Sawaya, Division of Nephrology, Bone and Mineral Metabolism, U of Kentucky

Abstract: Left Ventricular Assist Device (LVAD) has emerged as a common treatment for patients with advanced heart failure. It is not uncommon that these patients suffer from renal failure requiring dialysis. In general, intermittent hemodialysis (IHD) is the most practical and widely used renal replacement therapy. However, due to potential hemodynamic instability of these patients, IHD has been performed only on an inpatient basis with intensive nursing involvement and high medical cost. The purpose of this study is to assess hemodynamic parameters and ability to complete the prescribed HD treatment in a series of patients who underwent a rather large number of dialysis sessions. Ten patients with LVAD received a total of 182 IHD treatments since 2010 at the UKMC. The systolic blood pressure (SBP, mmHg) and heart rate (beats/min) pre and post IHD in these patients were as follows (mean ± SD): 96 ± 16 and 95 ± 20 (NS); 86 ± 18 and 89 ± 20 (NS), respectively. The lowest SBP during IHD was 83 ± 18 ($p < 0.001$ vs. pre SBP). The mean prescribed ultrafiltration (UF) to be removed was 2.6 ± 1.8L and the UF that was actually achieved was 2.7 ± 2L (NS). There were only 13 documented minor events during the 182 IHD treatments: low BP (5), shortness of breath (2), nausea (2), mechanical issues with LVAD (2), early termination of treatment (1), and tachycardia (1). These results indicate that patients with LVAD tolerate IHD very well and are likely able to be treated on an outpatient basis.

Supported by: The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117 as part of the Professional Student Mentored Research Fellowship. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.'
Primary Presenter / e-mail: C. Areephanthu / christopher.areephanthu@uky.edu
Mentor or Senior Author / e-mail: B. Peter Sawaya / petersawaya@uky.edu

#119 Abstract Title: **Changes in Calcium Cycling And Twitch in Isolated Unloaded Cardiomyocytes at Different Temperature and Transmural Region**

Author(s): C. S. Chung, Department of Physiology and Center for Muscle Biology, U of Kentucky
K. S. Campbell, Department of Physiology and Center for Muscle Biology, U of Kentucky

Abstract: Measurement and characterization of myocardial properties is typically taken at sub-physiologic temperatures and without regard to myocardial region. We hypothesized that calcium transients and sarcomere length (SL) twitches in unloaded myocytes are different both in response to temperature and from different transmural region. Methods: Myocytes were enzymatically digested and isolated from 3 mo female Sprague-Dawley rats and separated into three transmural (epi-[exterior], mid-, and endocardial [inner]) regions. Cells were loaded with Fura-2AM, a cell permeable fluorescent calcium indicator dye, paced at 0.5Hz and individual cells measured at three temperatures (25, 31, and 37oC) using an experimental design balancing temperatures and transmural region. Calcium transients and sarcomere length during twitch (shortening and relengthening) were measured for 10 beats and averaged. Results: Calcium transients were >50% shorter at physiologic vs room temperature and are different transmurally. Timing of SL twitches were also >50% shorter at physiologic vs room temperature but were not dependent on transmural region. In contrast, twitch magnitude varies with transmural layer but not temperature, with the epicardial cells showing the largest magnitude twitch. Control experiments suggest that temperature dependent changes are not related to rundown or uncontrolled pH. A novel finding is that sarcomeric twitch properties are not strongly correlated with calcium timing. This suggests that sarcomeric (crossbridge) interactions, not calcium, control shortening and relaxation rates. Summary: These experiments suggests temperature and transmural region dependence in calcium excitation and sarcomere length contraction and relaxation properties. These experiments also provide a novel perspective into the excitation twitch relationship.

Supported by: R01HL090749
Primary Presenter / e-mail: C.S. Chung / charles.chung@uky.edu
Mentor or Senior Author / e-mail: K.S. Campbell / k.s.campbell@uky.edu

#120 Abstract Title: **Comparative effects of different combination antiretroviral therapies on the risk for myocardial infarction among HIV patients enrolled in Medicaid: a new user, active comparator cohort study**

Author(s): E.S. Brouwer, Departments of Pharmacy Practice and Science and Epidemiology, U of Kentucky
S Napravnik, Departments of Medicine and Epidemiology, U of North Carolina
J. J. Eron, Jr, Department of Medicine, U of North Carolina
B. Stalzer, Department of Medicine, U of North Carolina
M. Floris-Moore, Department of Medicine, U of North Carolina
R. J. Simpson, Department of Medicine, U of North Carolina
T. Sturmer, Department of Epidemiology, U of North Carolina

Abstract: Background: Cohort studies have demonstrated greater risk of myocardial infarction (MI) associated with specific antiretroviral use, while meta-analyses of randomized controlled trials have not. Inherent biases may be related to using observational data and the study design or limited duration of randomized trials. We conducted a new user, active comparator cohort study emulating a randomized controlled trial comparing initiation of specific antiretrovirals as part of combination antiretroviral therapy (cART) and MI. Methods: We included North Carolina (NC) Medicaid beneficiaries infected with HIV between 2002 and 2008 previously untreated with cART. We compared hazard rates (HR) and 95% confidence intervals (CI) of MI between abacavir to tenofovir recipients, and lopinavir-ritonavir or atazanavir recipients to non-nucleoside reverse transcriptase inhibitor (NNRTI) recipients. Confounding was adjusted for using standardized morbidity/mortality ratio (SMR) weights. Results: There were 3,481 NC Medicaid new cART recipients that contributed 6,399.25 person-years and experienced 38 MI events. Receiving abacavir as part of cART was associated with an increased rate of MI compared to tenofovir in unadjusted and adjusted models (HR: 2.70 [95% CI: 1.24, 5.91], HR: 2.05 [95% CI: 0.72, 5.86] respectively). Point estimates suggest a relationship between receipt of atazanavir or lopinavir-ritonavir compared to an NNRTI and MI, however, estimates were imprecise. Conclusions: We found an increased rate of MI among patients initiating abacavir compared to tenofovir that decreased after confounding adjustment. Without a very large prospective comparative clinical trial, a much larger observational study of patients initiating cART is needed to better define this apparent association.

Supported by: Agency for Healthcare Research and Quality Award: R01 HS018731 National Center of Research Resources, NIH: M01RR00046, UL1RR025747 NIH: R01 AG023178 NIH: K12 DA035150
Primary Presenter / e-mail: E.S. Brouwer / emily.brouwer@uky.edu
Mentor or Senior Author / e-mail: T. Sturmer / sturmer@unc.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#121 Abstract Title: Role of ABCC1 in protecting the heart against doxorubicin (DOX)-induced oxidative stress

Author(s):
J. Deng, Graduate Centre for Toxicology, U of Kentucky
D. Coy, Graduate Centre for Toxicology, U of Kentucky
M. Sunkara, Saha Cardiovascular Research Centre, U of Kentucky
A. Morris, Saha Cardiovascular Research Centre, U of Kentucky
C. Wang, Markery Cancer Centre, U of Kentucky
L. Chaiswing, Pathology and Laborary Medicin, U of Wisconsin-Madison, Madison, WI
T. Oberley, Pathology and Laborary Medicin, U of Wisconsin-Madison, Madison, WI
M. Vore, Graduate Centre for Toxicology, U of Kentucky

Abstract: We investigated the role of multidrug resistance-associated protein 1 (Mrp1), an ATP-binding cassette transporter (ABCC1), in mouse heart following DOX-induced oxidative stress. Wildtype (WT) and Mrp1-/- (KO) C57BL/6 littermates were administered a single dose of 20 mg/kg DOX or Saline (SAL) intravenously. Hearts were collected 72 h later, and ultrastructural damage measured by electron microscopy (EM) (n=6) and content of the glutathione conjugate of 4-hydroxynonenal (GS-HNE), a substrate of Mrp1, determined by LC-MS (n=6-7). The mRNA of Nrf2 responsive genes, Nqo1, GPX1, GPX3, and GPX4 were quantitated by real time quantitative PCR (n=6). Morphometric analysis of EM data showed a trend ($p = 0.063$) for decreased cytoplasmic + mitochondrial damage in DOX-treated KO mice vs WT, but increased ($p = 0.031$) nuclear injury in KO mice. In contrast, SAL induced more cytoplasmic damage in KO mice ($p = 0.015$). GS-HNE (nmol/g heart tissue) of WT and KO SAL mice were similar, whereas DOX decreased ($p < 0.001$) GS-HNE in WT mice, but had no effect in KO mice. The basal level of GS-HNE in naïve KO mice was lower ($p = 0.013$) than in naive WT mice (n=8). DOX increased mRNA of Nqo1 and GPX3 in hearts of WT and KO mice similarly, but had little influence on GPX1 and GPX4 mRNA. Nevertheless, in naïve mice, basal levels of Nqo1, GPX3, and GPX4 mRNA were lower in KO than in WT ($p = 0.001$, 0.011, 0.022, respectively). These data imply that the elevated GSH level in hearts of KO mice is able to protect against some forms of DOX-induced injury, but not others. (CA139844)

Supported by: NIH award: R01CA139844
Primary Presenter / e-mail: J. Deng / jun.deng4@uky.edu
Mentor or Senior Author / e-mail: M. Vore / maryv@email.uky.edu

#122 Abstract Title: A New Role for Exercise: Examining the Effects of Physical Activity on Polychlorinated Biphenyl-Induced Cardiovascular Disease

Author(s):
M. Murphy, Graduate Center for Nutritional Sciences, U of Kentucky
K. Eske, Graduate Center for Nutritional Sciences, U of Kentucky
S. G. Han, Superfund Research Program, U of Kentucky
B. Newsome, Department of Chemistry, U of Kentucky
K. Esser, Department of Physiology, U of Kentucky
B. Hennig, Graduate Center for Nutritional Sciences, U of Kentucky

Abstract: Cardiovascular disease is the leading cause of mortality in developed countries. Polychlorinated biphenyls (PCBs) are persistent environmental pollutants that contribute to the initiation of cardiovascular disease. Previous work in our laboratory has examined the potential role of nutrition in modulating the toxicity of PCBs in vascular endothelial cells. We hypothesize that, in addition to nutrition, exercise also can modulate the vulnerability to environmental insults. There is strong evidence that exercise can reduce the risk of cardiovascular disease; however, whether exercise can modulate PCB-induced cardiovascular inflammation and dysfunction is unknown. Results from our preliminary study suggest that exercise can antagonize the progression of atherosclerosis induced by exposure to PCB 77. Mice were allowed voluntary exercise prior to PCB exposure. In this study, exercise also prevented elevated cholesterol and insulin associated with PCB treatment. A follow-up study was initiated where male ApoE-/- mice were divided into sedentary and exercise groups and allowed to develop atherosclerosis over a 12 week period. Half of each group was exposed to PCB 77 at a dose of 170 μmoles/kg mouse during weeks 1, 2, 9 and 10. The dosing schedule is based on previous studies that have demonstrated glucose intolerance and increased levels of atherosclerosis in this mouse model. This study determined the effects of voluntary exercise on PCB77 exposure in relation to body weight, body composition, blood pressure, distribution of PCB in tissues, glucose tolerance, serum cholesterol, systemic inflammation, and atherosclerosis. Results from this study provide novel findings suggesting that regular physical activity could be utilized as a therapeutic approach for the prevention of adverse cardiovascular health effects induced by environmental pollutants such as PCBs.

Supported by: Superfund Research Program., grant number P42ES007380.
Primary Presenter / e-mail: M. Murphy / momurp3@uky.edu
Mentor or Senior Author / e-mail: B. Hennig / bhennig@uky.edu

#123 Abstract Title: **Associating Pseudopod Extension of Leukocytes in the Presence of Red Blood Cells with their Rheological Flow Behavior**

Author(s): N. Horrall, Biomedical Engineering, U of Kentucky
H. Shin PhD, Biomedical Engineering, U of Kentucky

Abstract: In addition to releasing antibacterial and protein degradative agents, neutrophils flowing in blood extend pseudopods upon activation by agonists. Under chronic inflammation (a common denominator for cardiovascular disease), the circulating blood exhibits sustained levels of activated neutrophils with pseudopods which influence their flow behavior in vessels. The goal of this study was to determine how much neutrophil activation in blood influences vasculature circulation and in which vessels their activation status had the greatest impact. For this purpose, we hypothesized that pseudopod extension differentially influences neutrophil flow behavior in small and larger diameter vasculature. To test this hypothesis, we used viscosity as measured by a cone-plate rheometer to measure the impact of neutrophil flow behavior in macrocirculation-related vessels and a Millipore filter-based flow system (pore diameter of 10μm) to simulate microvascular flow. Notably, the viscosity of suspensions of activated cells was significantly higher compared to that of non-activated cell suspensions. However, the presence of red blood cells at a hematocrit of 10% abolished this effect. In micropore filter-based microvascular mimics, we used the impact of cell suspensions on pore pressure to detect the effects of cell activation on neutrophil flow behavior. In this case, while activated cells in suspension had little effect on micropore resistance, suspensions of activated neutrophils in 10% hematocrit had a significantly larger effect on the flow resistance of micropore filters compared to that of non-activated cells. These results confirm that erythrocytes serve multiple purposes including a biofluid mechanics-related role in modulating the leukocyte transport within blood vessel lumens. Moreover, they contribute key insight into the importance of the shear-sensitive control of neutrophil activity in microvascular blood flow regulation.

Supported by: NSF Kentucky EPSCoR BioEngineering Initiative
Primary Presenter / e-mail: N. Horrall / nmhorr2@g.uky.edu
Mentor or Senior Author / e-mail: H. Shin / hy.shin@uky.edu

#124 Abstract Title: **Factors Associated With Early Readmission Among Patients With Heart Failure**

Author(s): N. Srihakim, College of Nursing, U of Kentucky
D. Kuchmy, College of Nursing, U of Kentucky
R. Dekker, College of Nursing, U of Kentucky

Abstract: Background: Little is known about the psychosocial factors in early readmissions for patients with heart failure. By identifying early readmission factors, including psychosocial, we could design more effective and comprehensive interventions to prevent early readmissions. Objective: This study compared characteristics between hospitalized patients with heart failure in an early readmission group (readmitted or died within three months) and a non-early readmission group (not readmitted and alive within three months). Method: This prospective design study followed 113 patients hospitalized with heart failure (47% female, mean age 61±13, 63% NYHA class III/IV) for three months to determine cardiovascular events and death. Demographics, clinical characteristics, and psychosocial status were measured at baseline. Independent t-tests were used to compare the mean differences in continuous variables. Chi-square was used for categorical variables. Results: Thirty-five percent of patients were readmitted or died within three months. The early readmission group had a higher proportion discharged on antidepressants (41% vs. 12%, $p = .006$), a lower proportion discharged on calcium channel blockers (5% vs. 21%, $p = .028$), a lower proportion with a history of hypertension (74% vs. 90%, $p = .022$), and a lower proportion of African Americans (8% vs. 25%, $p = .026$). The early readmission group had lower mean systolic and diastolic blood pressure on admission (123.49 ± 24.83 vs. 136.63 ± 28.46, $p < .017$), (73.13 ± 15.81 vs. 81.61 ± 17.72, $p < .015$) and lower mean ejection fraction (32.82 ± 10.47 vs. 39.96 ± 17.17, $p < .031$). No other characteristic differed between groups. Conclusion: There may be a link between antidepressant use and early readmission among patients with heart failure. We plan to identify independent risk factors using regression analyses with larger samples and to design a comprehensive intervention.

Supported by: The project described was supported by Rebecca Dekker, PhD, APRN, College of Nursing, University of Kentucky.
Primary Presenter / e-mail: N. Srihakim / nattarose@uky.edu
Mentor or Senior Author / e-mail: R. Dekker / rdekker@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#125 Abstract Title: Developing a Tissue Bank from Patients with Heart Failure: Clinical Characteristics

Author(s):
P. Nataraj, College of Medicine, CCTS PSMRF program, U of Kentucky
P. Shekar, Department of Physiology, U of Kentucky
C. Hoopes, Department of Surgery, Division of Cardiothoracic Surgery, U of Kentucky
S. Smyth, Department of Internal Medicine- Cardiology, U of Kentucky
K. Campbell, Department of Physiology, U of Kentucky

Abstract: Heart failure affects around 5 million Americans and costs approximately 33 billion dollars each year. As people continue to make poor lifestyle choices, this number will only increase. Ventricular assist devices (VAD) are emerging as a viable therapeutic option for patients with advanced heart failure who fail medical therapy. Some patients demonstrate recovery of myocardial function after VAD implantation. As of right now, we do not have clear predictors to tell if a patient will benefit from VAD implantation. We are creating a tissue bank of heart specimens obtained from patients at the time of open heart surgery. My project is aimed at developing tools to collect information about the clinical characteristics of the patients whose specimens are in the tissue bank. Data collection will include patients who enrolled in the study from 2008 to 2012.

Supported by: PSMRF award; 'The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.'

Primary Presenter / e-mail: P. Nataraj / pnata2@uky.edu

Mentor or Senior Author / e-mail: S. Smyth / ssmyt2@uky.edu

#126 Abstract Title: The number and the content of ectosomes and the structural changes of cytochrome b558 might predict the disease.

Author(s):
R.M. Simonyan, Division of Protein Chemistry,Institute of Biochemistry named after H. Buniatyan NAS Republic of Armenia
A.V. Karapetyan, Chemistry Department, U of Kentucky
AF. Miller, Chemistry Department, U of Kentucky
M.A. Simonyan, Division of Protein Chemistry,Institute of Biochemistry named after H. Buniatyan NAS Republic of Armenia

Abstract: During ischemia, erythrocytes release elevated numbers of ectosomes enriched with cytochromeb558. Cytochromeb558 forms complexes with hemoglobin and solubilizes into plasma. The content, altered absorption spectrum and activity of plasma cytochromeb558 might be early predictors of ischemia. The concentration of cytochromeb558 in plasma may influence the progression of disease. Ectosomes are small vesicles shed from various types of cells. The content of ectosomes depends on the type of cell producing them. Our studies and several others showed that during ischemia erythrocyte membranes lose their integrity due to peroxidation of membrane lipids and release hemoglobin. Simultaneously the quantity of ectosomes in plasma substantially increases, however their role in diseases is not well understood. We proposed that the main source of ectosomes in plasma during ischemia is erythrocytes. This is consistent with the elevated concentrations of oxidants observed in plasma during ischemia, considering that cytochromeb558 is a potential oxidant, due to its superoxide generating activity in the presence of NAD(P)H. Moreover cytochromeb558 has the relevant properties of methemoglobin reducing activity and ability to strongly bind nitric oxide. We demonstrated that during ischemia the concentration and superoxide generating activity of cytochromeb558 in plasma greatly depend on the stage of disease, and are elevated with progression of inflammation. The absorption spectrum of cytochromeb558 from the plasma of patients after a heart attack possesses characteristic changes. The mechanism of release of cytochromeb558 from microvesicle membranes may be facilitated by free hemoglobin in plasma and will be further investigated in detail.

Supported by: The project described was sponsored by State Committee of Sciences of the Ministry of Science and Education of RA.

Primary Presenter / e-mail: R.M.Simonyan / ruzan.simonyan@gmail.com

Mentor or Senior Author / e-mail: M.A. Simonyan / maxim.simonyan@gmail.com

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#127 Abstract Title: Neuroprotection for Acute Ischemic Stroke: From Review to Preview

Author(s): S. Grupke, Department of Neurosurgery, U of Kentucky
J. F. Fraser, Department of Neurosurgery, U of Kentucky

Abstract: Acute ischemic stroke is a major cause of mortality and disability worldwide, and as of now the only pharmacological therapy for treatment in the acute setting centers around thrombolysis for reperfusion of brain. Neuroprotection for ischemic stroke is an emerging and rapidly growing field, built upon the elucidation of the biochemical pathways of ischemia. Means by which to pharmacologically intervene and counteract these pathways have been sought, and there have been promising results published with use of neuroprotective agents in experimental animal models. Unfortunately, this has been met with little success in proving benefit in the clinical setting. For the purpose of our discussion, neuroprotective agents refer to medications used to preserve or protect the ischemic penumbra after an acute stroke, excluding treatments designed to re-establish perfusion. This excludes mechanical or pharmacological thrombolytics, anti-thrombic medications, or anti-platelet therapies. This review aims to outline the key biochemical steps in ischemic injury that are candidate pathways for intervention, and to summarize previously trialed neuroprotective agents, including but not limited to glutamate neurotransmission blockers, anti-oxidants, GABA agonists, leukocyte migration blockers, various small cation channel modulators, narcotic antagonists, and phospholipid membrane stabilizers. Through a systemic evaluation of the accomplishments and failures in neuroprotection research, we propose new methodologies and techniques which we plan to implement in a clinical setting in an attempt to elucidate potential benefit for human stroke patients.

Supported by:
Primary Presenter / e-mail: S. Grupke / stephen.grupke@uky.edu
Mentor or Senior Author / e-mail: J.F. Fraser / jfr235@uky.edu

#128 Abstract Title: ACE2 Activation by Diminazene Aceturate Lowers Angiotensin II-Induced Abdominal Aortic Aneurysms in Hyperlipidemic Mice

Author(s): S. E. Thatcher, Graduate Center of Nutritional Sciences, U of Kentucky
X. Zhang, Department of Toxicology, U of Kentucky
D. A. Howatt, Saha Cardiovascular Center, U of Kentucky
E. Lewis, Department of Molecular and Biomedical Pharmacology, U of Kentucky
M. Karounos, Graduate Center of Nutritional Sciences, U of Kentucky
A. Daugherty, Saha Cardiovascular Center, U of Kentucky
L. A. Cassis, Department of Molecular and Biomedical Pharmacology, U of Kentucky

Abstract: Objective: Angiotensin converting enzyme 2 (ACE2) is a monocarboxypeptidase that converts angiotensin II (AngII) to angiotensin 1-7 (Ang-(1-7)). However ACE2's role in the development of AngII-induced abdominal aortic aneurysms (AAAs) has not been discerned. Furthermore, the ability to use ACE2 activators to increase the catabolism of AngII has not been evaluated in AAA models and may provide a therapeutic tool for treatment. In these studies, whole body ACE2 deficiency and an ACE2 activator, diminazene aceturate (DIZE), were evaluated to see if ACE2 could augment AngII-induced AAAs. Methods and Results: Whole body ACE2 deficient mice were bred to a low-density lipoprotein receptor null background (LDLr-/-) and given AngII by osmotic pump for 28 days. ACE2-deficient animals that developed an AAA displayed greater luminal diameters by ultrasound when compared to wildtype littermates. Ex-vivo diameters were also significantly increased in comparison to wildtypes. DIZE or vehicle (VEH) was administered to Ace2+/y or -/y LDLr-/- mice daily under AngII-infusion. Ace2+/y mice had lower luminal diameters when compared to either DIZE-treated Ace2-/y mice or VEH wildtypes. Ex-vivo diameters as well as AAA incidence was also decreased in DIZE-treated mice. Conclusions: Whole body ACE2 deficiency in hyperlipidemic mice increases the size of the AAA and the ACE2 activator, DIZE, can lower the size of the AAA indicating that ACE2 is a therapeutic target of AAAs.

Supported by: NIH P01 HL080100 (AD, LAC) NIH R01 HL62846 (AD, LAC) F32 HL095281(SET).
Primary Presenter / e-mail: S. Thatcher / seanthatcher@uky.edu
Mentor or Senior Author / e-mail: L. Cassis / lcassis@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#129 Abstract Title: Calpain cleaves methionine aminopeptidase 2 in a rat model of ischemia.

Author(s):
T. Clinkinbeard, Gerontology and Physiology at Sanders-Brown Center on Aging, U of Kentucky
S. Ghoshal, Gerontology at Sanders-Brown Center on Aging, U of Kentucky
S. Craddock, Sanders-Brown Center on Aging, U of Kentucky
L.C. Pettigrew, Neurology and Physiology at Sanders Brown Center on Aging, U of Kentucky
R.P. Guttmann, Center on Aging, U of West Florida, Pensacola, FL

Abstract: Ischemic stroke results in multiple injurious signals within the cell including dysregulation of calcium homeostasis. Consequently, there is an increase in the enzymatic activity of the calpains, calcium dependent cysteine proteases thought to contribute to neuronal injury. In addition, cellular stress due to ischemia/reperfusion triggers a decrease in protein translation through dissociation of methionine aminopeptidase 2 (MetAP2) from eukaryotic initiation factor 2 alpha (eIF2α). Because levels of phosphorylated eIF2α (an indication of dissociated MetAP2) are increased in ischemic stroke and calpain has been shown to cleave eIF4γ, we tested the hypothesis that calpain cleaves MetAP2 directly. To test this hypothesis, homogenates of brain tissue were prepared and digested with either calpain 1 or calpain 2, in vitro. In vitro studies showed the production of a stable 57kDa calpain-mediated fragment. We further showed that this fragment was produced in a rat middle cerebral artery occlusion (MCAO) model of ischemia/reperfusion. These data suggest that calpain activation in stroke may play a role in the MetAP2 mediated decrease in translation and therefore in the subsequent death of cells in the penumbral area.

Supported by: NIH award: P01NS05848
Primary Presenter / e-mail: T. Clinkinbeard / tdclin2@uky.edu
Mentor or Senior Author / e-mail: R.P. Guttmann / rpg007@aol.com

#130 Abstract Title: Mrp1 Protects Against Doxorubicin-induced Cardiotoxicity in vitro

Author(s):
Wei Zhang, Graduate Center for Toxicology, U of Kentucky
Donna Coy, Graduate Center for Toxicology, U of Kentucky
Jun Deng, Graduate Center for Toxicology, U of Kentucky
Mary Vore, Graduate Center for Toxicology, U of Kentucky

Abstract: Doxorubicin (DOX), an anthracycline antibiotic commonly used as a cancer chemotherapeutic agent, is well known for its ability to induce acute and chronic cardiotoxicity, leading to irreversible cardiomyopathy. In the present study, we investigated the role of multidrug resistance-associated protein 1 (Mrp1), an ATP-binding cassette efflux transporter, in DOX induced cardiotoxicity. We cultured cardiomyocytes (CM) and cardiac fibroblasts (CF), which were isolated from C57BL/6J (WT) or Mrp1 knock out (KO) mice (1 - 3 days old). The cells were treated with DOX (0.5 – 3 μM) and examined 24 hrs later. DOX enhanced Mrp1 mRNA (~2 fold) and protein (~2.6 fold) expression similarly in both CM and CF. The MTS assay showed that the CM from KO mice were more sensitive to DOX than WT, with an IC50 in KO of 0.94 μM (95% CI: 0.74 – 1.18) versus 1.60 μM (95% CI: 1.20 – 2.11) in WT. Furthermore, CM and CF from KO mice showed increased caspase 3 and PARP cleavage following DOX treatment, consistent with increased apoptosis in cells from KO. These results imply that Mrp1 protects against DOX induced cardiotoxicity in cultured CM and CF.

Supported by: NIH award: R01CA139844
Primary Presenter / e-mail: W. Zhang / weizhang6011@uky.edu
Mentor or Senior Author / e-mail: M. Vore / maryv@email.uky.edu

#131 Abstract Title: **TGF-β Neutralization Augments Development of Angiotensin II-induced Aneurysms in Both Ascending and Abdominal Aortic Regions**

Author(s):
X. Chen, Saha Cardiovascular Research Center, U of Kentucky
D. L. Rateri, Saha Cardiovascular Research Center, U of Kentucky
D. A. Howatt, Saha Cardiovascular Research Center, U of Kentucky
A. Balakrishnan, Saha Cardiovascular Research Center, U of Kentucky
J. J. Moorleghen, Saha Cardiovascular Research Center, U of Kentucky
L. A. Cassis, Saha Cardiovascular Research Center, U of Kentucky
A. Daugherty, Saha Cardiovascular Research Center, U of Kentucky

Abstract: Introduction and Objectives: Angiotensin II (AngII) infusion induces ascending and abdominal aortic aneurysms (AAs) in mice. In a mouse model of Marfan Syndrome expressing Fbn1C1039G/+, ascending AAs were reduced by administration of a transforming growth factor-β (TGF-β) neutralizing antibody. In contrast, administration of TGF-β neutralizing antibodies to AngII-infused mice increased aortic rupture. The purpose of this study was to compare the effects of TGF-β neutralization on formation and progression of AngII-induced ascending and abdominal AAs. Methods and Results: Male C57BL/6 mice were fed a normal diet and infused subcutaneously with AngII (1,000 ng/kg/min). To determine the effects of TGF-β neutralization on the formation of AngII-induced AAs, 5 days prior to initiating infusion, mice were injected i.p. with either a mouse monoclonal TGF-β antibody (1D11) or an isotype matched IgG at a dose of either 0.3 or 5 mg/kg x 3/per week. 1D11 administration significantly decreased serum TGF-β concentrations. TGF-β neutralization at 5 mg/kg greatly increased the incidence of aortic rupture, which was attributed to rupture in both the ascending and abdominal regions. For mice that remained viable after 28 days of infusion, there were equivalent increases in aortic dilation in both the ascending and abdominal regions. Prior to rupture, aortic diameters determined by ultrasound demonstrated no significant effect on AngII-induced dilation of the ascending or abdominal aorta. We also studied the effects of TGF-β neutralization in mice with established AngII-induced AAs following AngII-infusion for 28 days. C57BL/6 mice were injected with the mouse TGF-β neutralizing antibody or IgG control (5 mg/kg x 3/per week, n=10 per group), while AngII infusion was continued for a further 28 days. Although TGF-β antibody administration significantly decreased serum TGF-β concentrations in mice with established AAs, there was no effect on aortic rupture or dilation of either the ascending or abdominal aortic region. Conclusion: TGF-β inhibition augmented AngII-induced aortic rupture in both the ascending and abdominal regions but had no effect on dilation. Furthermore, TGF-β neutralization had no effect on either aortic rupture or expansion in established AAs.

Supported by: This work is supported by a McKusick Fellowship grant from the National Marfan Foundation (NMF) to Xiaofeng Chen.

Primary Presenter / e-mail: X. Chen / xch224@uky.edu

Mentor or Senior Author / e-mail: A. Daugherty / alan.daugherty@uky.edu

#132 Abstract Title: **Suppression of Nonsense Mutations in Laforin as a Therapeutic Option for Lafora Disease and a Bioassay for Laforin Activity**

Author(s):
A. R. Sherwood, Department of Molecular and Cellular Biochemistry, U of Kentucky
A. V. Delgado-Escueta, Department of Neurology, U of California Los Angeles
M. B. Johnson, Department of Molecular and Cellular Biochemistry, U of Kentucky
M. S. Gentry, Department of Molecular and Cellular Biochemistry, U of Kentucky

Abstract: Lafora disease (LD; OMIM #254780) is a fatal disorder in which patients exhibit progressive degeneration of the central nervous and motor systems concurrent with myoclonic, tonic-clonic, and focal occipital seizures. A distinguishing characteristic of LD is the presence of insoluble glucan deposits called Lafora bodies (LBs) within the cells of most tissues, although only neurological effects are observed. LD results from recessive mutations in the EPM2A gene encoding the glucan phosphatase laforin. Laforin consists of a carbohydrate-binding module (CBM) and a dual-specificity phosphatase domain (DSP). Approximately 16% of LD patients possess nonsense mutations in laforin, creating truncated and nonfunctional protein products. Currently, there is no long-term treatment option for LD outside of palliative therapeutics. However, for the subset of LD patients with nonsense mutations in laforin, aminoglycosides may lead to the production of full-length, functional protein. We explored the response of different nonsense mutations in laforin to several readthrough-promoting compounds, including the aminoglycosides gentamicin and amikacin and the functional analog PTC124. We found that each mutation responded differently to treatment, with a varied response similar to in vivo results of cystic fibrosis and Duchenne's muscular dystrophy patients with nonsense mutations. In addition, we developed a sensitive bioassay for the detection of endogenous laforin based on the unique activity of laforin as a glucan phosphatase. This bioassay for laforin will prove useful for the detection of functional laforin in LD patients who receive therapies such as aminoglycosides to induce functional laforin production.

Supported by: This work was supported by National Institutes of Health Grants R00NS061803, P20RR020171, and R01NS070899 and University of Kentucky College of Medicine startup funds to M.S.G. The project described was also supported by the National Center for Advancing Translational Sciences, UL1TR000117.

Primary Presenter / e-mail: A. R. Sherwood / amanda.sherwood@uky.edu

Mentor or Senior Author / e-mail: M. S. Gentry / matthew.gentry@uky.edu

#133 Abstract Title: RNA Degradation is Elevated with Age-, but not Disuse-Associated Skeletal Muscle Atrophy

Author(s): A. Shah, Department of Biology, College of Arts and Sciences, U of Kentucky
A. L. Confides, Department of Rehabilitation Sciences, College of Health Sciences, U of Kentucky
J. L. R. White, Department of Rehabilitation Sciences, College of Health Sciences, U of Kentucky
E. E. Dupont-Versteegden, Rehab Sciences, College of Health Sciences, Div of Physical Therapy, Center for Muscle Biology, U of Kentucky

Abstract: Aging and inactivity are both associated with decreased muscle size and protein content. The possible role of RNA degradation in the loss of protein has not yet been investigated. Therefore, we hypothesized that RNA degradation was elevated with muscle atrophy in aging and disuse. Brown Norway/Fisher344 male rats at 6 and 32 months were hindlimb suspended (HS) for 14 days to induce muscle atrophy or remained weight bearing (WB). Cytosolic extracts from gastrocnemius muscles were prepared for Western analysis of decapping protein-2 (DCP-2, a marker of p-bodies) and RNA degradation assay. In vitro total RNA decay assay was performed using 30□g of total RNA (from tibialis anterior) incubated with 20□g of S15 extracts from gastrocnemius. In addition, cDNA was prepared from the assay product for real-time reverse-transcription polymerase chain reaction to determine the relative gene expression of MyHC and MAFbx mRNAs. RNA integrity was determined using the Agilent Technologies algorithm to calculate the RNA Integrity Number ; decay rate and half-life were calculated for each sample. Results indicated an increase in DCP-2 protein with age, but not disuse. Additionally, an almost 2-fold increase in decay rate and 48% decrease in half-life of total RNA was observed in muscle from 32 month old rats. However, no significant difference in decay rate and half-life was observed with disuse at either 6 or 32 months. Also, no significant difference in decay rate and half-life of MyHC and MAFbx mRNA was evident with age or disuse. We conclude that muscle atrophy associated with aging, but not disuse, may be due to decreased RNA availability because of increased total RNA degradation.

Supported by: NIH/NIA grants: AG028925 to Esther E. Dupont-Versteegden American Physiological Society Undergraduate Summer Research Fellowship to Aman Shah

Primary Presenter / e-mail: A. Shah / aman2048@hotmail.com

Mentor or Senior Author / e-mail: E. E. Dupont-Versteegden / eedupo2@uky.edu

#134 Abstract Title: The Effects of Physical Activity on Trunk Mechanical and Neuromuscular Behaviors

Author(s): B. Koch, Center for Biomedical Engineering, U of Kentucky
A. Agarwal, Center for Biomedical Engineering, U of Kentucky
M. Vazirian, Center for Biomedical Engineering, U of Kentucky
B. Bazrgari, Center for Biomedical Engineering, U of Kentucky

Abstract: The objective of this study was to quantify changes in trunk mechanics following one day of low/high level of physical activity and the recovery after ~12 hours of rest. Four males (high exposure group) of the University's Ultimate Frisbee team were tested before and after a daylong tournament. Six males (low exposure group) of the University's students and staff were tested before and after a sedentary work day. Both groups were also tested the following morning to evaluate recovery. During each test participants performed a maximum voluntary extension (MVE) of their back and two series of randomized perturbations while maintaining either 10% or 30% (±2%) of their MVE. MVEs in the high exposure group decreased ($t(6)=-3.07$; $P=0.026$) by 22% after the exposure but then increased (recovered) ($t(6)= 3.67$; $P=0.016$) by 14% during the rest period, whereas MVEs were similar across all time points for the low exposure group. Mean (SD) intrinsic stiffness with 30% effort across all time points were 16408 (2255) N/m and 13739 (2093) N/m for high and low exposure group respectively. Despite the recovery of MVEs following the rest period in the high exposure group, intrinsic trunk stiffness with 30% effort was 20% higher ($t(6)=2.25$; $P=0.042$) than initial values (i.e., before exposure). Such an increase in stiffness, despite recovery in MVE, suggests an alteration (e.g., higher co-activation) in the activity pattern of trunk muscles during pulling efforts.

Supported by: This publication was supported by CDC-NIOSH grant number R21OH010195

Primary Presenter / e-mail: B. Koch / Brian.Koch@uky.edu

Mentor or Senior Author / e-mail: B. Bazrgari / Babak.Bazrgari@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#135 Abstract Title: Satellite Cells Regulate the Skeletal Muscle Environment by Inhibiting Fibroblast Function

Author(s):
C. S. Fry, College of Health Sciences, U of Kentucky
J. D. Lee, College of Health Sciences, U of Kentucky
J. R. Jackson, College of Health Sciences, U of Kentucky
T. J. Kirby, Department of Physiology, , U of Kentucky
E. E. Dupont-Versteegden, College of Health Sciences, U of Kentucky
J. J. McCarthy, Department of Physiology, U of Kentucky
C. A. Peterson, College of Health Sciences, U of Kentucky

Abstract: Interaction between satellite cells and the skeletal muscle extracellular matrix (ECM) has been demonstrated, but a role for satellite cells in regulating the ECM during hypertrophy has not been defined. We utilized mouse primary myoblasts and fibroblasts in co-culture in addition to a genetically modified mouse model (Pax7-DTA) to investigate the role of satellite cells in the regulation of muscle ECM. The Pax7-DTA mouse allows for the conditional depletion of satellite cells in adult muscle following tamoxifen administration. Vehicle/tamoxifen treated animals were randomized to sham or synergist ablation surgery, leading to overload of the plantaris muscle for 1 and 8 weeks. Microarray analysis after 1 week of surgery showed the loss of satellite cells was associated with increased expression of numerous collagens and ECM structural genes. Depletion of satellite cells also led to attenuated hypertrophy and fibrosis of the plantaris with increases in both ECM deposition and fibroblast number following 8 weeks of overload. Co-culturing mouse myoblasts with fibroblasts led to decreased mRNA expression of Col Ia2, IIIa1, VIa2 and Fibronectin compared to fibroblasts co-cultured with fibroblasts, suggesting a paracrine role of myoblasts that inhibits fibroblast ECM production. We conclude that a novel function of satellite cells both at rest and during hypertrophy is to regulate muscle fibroblasts and the ECM.

Supported by: NIAMS R01AR060701, R21AG34453 and the Jeane B. Kempner Postdoctoral Award.
Primary Presenter / e-mail: C. S. Fry / cfr223@uky.edu
Mentor or Senior Author / e-mail: C. A. Peterson / cpete4@uky.edu

#136 Abstract Title: Selective Fiber Infiltration of M1 Macrophages at Six Hours in Skeletal Muscle Following Eccentric Exercise: A Pilot Study

Author(s):
C. Waters-Banker, Rehabilitation Sciences, U of Kentucky
W. Swann, Kinesiology and Health Promotion, U of Kentucky
T.A. Butterfield, Rehabilitation Sciences, U of Kentucky

Abstract: Recent studies have demonstrated potential influences of massage at the cellular level however, a lack of sound scientific data to support efficacy of massage remains. The purpose of this pilot study was to assess effects of massage on the temporal inflammatory response following eccentric exercise (EEX). Four male rats were divided into 2-groups: 6hr (n=2) and 24hr (n=2). Nerve-cuff electrodes were surgically implanted on the peroneal nerve of each limb. Following 1wk recovery, each limb underwent a single-bout of EEX. Immediately following EEX, the right limb of each animal received a 30min bout of massage using a customized cyclic-compressive loading device (massage memetic). Rats were euthanized according to group time point. Tibialis Anterior muscles were harvested and cryogenically preserved for tissue analysis. Main outcomes of this study were to immunohistochemically quantify neutrophils, M1, and M2 macrophages, and general cellular abundance utilizing H&E staining. The most notable result from this pilot investigation was identification of M1 macrophages at 6hrs following EEX and EEX+Massage (0.75±0.75 per 0.150mm2 and 5.25±1.25 per 0.150mm2 respectively). General cellular abundance was significantly higher in the 6hr vs. 24hr group (43.0±6.0 and 16.13±2.88 respectively, p=0.04). Supraphysiologic models of muscle injury (e.g. freeze-injury, cardiotoxin) have predominantly shaped the inflammatory time-course in skeletal muscle. M1s have largely been reported at 12hrs post injury, however our pilot data show selective fiber infiltration of M1's as early as 6hrs. An important finding that may challenge current dogma associated with macrophage action, the inflammatory response, manual therapy, and growth/regeneration of skeletal muscle.

Supported by: NIH T32 Institutional Training Grant (University of Kentucky) NATA Research Foundation
Primary Presenter / e-mail: C. Waters-Banker / chris.waters@uky.edu
Mentor or Senior Author / e-mail: T.A. Butterfield / tim.butterfield@uky.edu

#137 Abstract Title: **Dynamic Contributions of Respiration, Phonation, and Resonance during Normal and Perturbed Voice Production**

Author(s):
D. J. Croake, Department of Rehabilitation Sciences, U of Kentucky
R. Andreatta, Department of Rehabilitation Sciences, U of Kentucky
J.C Stemple, Department of Rehabilitation Sciences, U of Kentucky

Abstract: Voice physiology literature is replete with implications that voice production is dependent on a relative balance of the subsystems of respiration, phonation, and resonance. Furthermore, it is commonly believed that these systems function in a synergistic manner where alteration of one subsystem causes concomitant alterations in the other subsystems. Few studies have simultaneously examined all three voice subsystems in order to provide information about the dynamic nature of voice production. Dynamic systems theory (DST) provides a useful heuristic in the study of biological systems, enabling description of how multi-component systems converge into preferred performance patterns within a particular context. DST postulates that complex systems may converge in variant ways, which continue to yield invariant outcomes. The proposed project will expand on previous investigations by simultaneously measuring all three vocal subsystems in 15 males and 15 females with normal voice. We will examine the relationships among the subsystems to determine 1) if unique system profiles exist among normal voiced individuals, 2) if differences exist in the system strategies of men and women, and 3) if perturbations to the subsystems result in identifiable compensatory system profiles. We hypothesize that individuals will demonstrate differing strategies of subsystem activation resulting in identifiable profiles which all yield normal healthy voice output. This study will be the first to identify the determinants which result in normal voicing in all three subsystems and the effects of perturbation on subsystem relationships. Understanding individuals' strategies in normal and perturbed voice production will directly influence clinical treatment of disordered voices.

Supported by:
Primary Presenter / e-mail: D. J. Croake / djcroa2@uky.edu
Mentor or Senior Author / e-mail: J. C. Stemple / joseph.stemple@uky.edu

#138 Abstract Title: **Discrimination of Attempted Movements from Rest Using an EEG Brain-Machine Interface for Rehabilitation from Neural Injury**

Author(s):
E. Salmon, Center for Biomedical Engineering, U of Kentucky
K. Chelette, Department of Physical Medicine and Rehabilitation, U of Kentucky
L. Sawaki, Department of Physical Medicine and Rehabilitation, U of Kentucky
S. Sunderam, Center for Biomedical Engineering, U of Kentucky

Abstract: Neurological trauma, as in spinal cord injury and stroke, can severely impair normal motor functions. Brain-machine interfaces (BMIs) have been developed to decode brain signals into control commands for prosthetic devices. The sensorimotor, or Rolandic "mu", rhythm of the electroencephalogram (EEG) is commonly used for BMI control. This idling rhythm (seen at rest) is suppressed by actual/imagined movement. Beyond their use as assistive devices, BMIs could facilitate motor recovery. Studies suggest that repetitive exercises induce beneficial neuroplastic changes in motor cortex and afferent peripheral nerve stimulation can augment this recovery. We hypothesize that stimulation-induced plastic changes could be enhanced further by selectively rewarding attempted movement with closely timed stimulation. Detection of effort directly from the brain and contingent stimulation could be accomplished using an EEG-BMI. Here, we test the feasibility of detecting cued hand movements from continuously recorded EEG. We measured EEG and grasping force in five healthy volunteers over three weekly sessions with IRB approval. Subjects responded to intermittent visual cues (6-10s apart) by squeezing a dynamometer with the left/right hand. Their EEG was classified offline based on spectral band power and other features using a linear classifier, trained on each subject's data pooled from two sessions and tested on the third. In four of five subjects with acceptable signal quality, rest, sham, left, and right samples were classified with mean accuracy of 79% (76-84%) during cross-validation within the training set, and 62% (40-73%) on the test set. Hence, EEG detection of motor intent for the proposed rehabilitation trials is feasible.

Supported by: University of Kentucky Startup Funds
Primary Presenter / e-mail: E. Salmon / elizabeth.salmon@uky.edu
Mentor or Senior Author / e-mail: S. Sunderam / ssu223@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#139 Abstract Title: Peripheral Nerve Stimulation Dose-Response Relationship in Chronic Stroke: Early Results from an Ongoing Trial

Author(s):
E. Salyers, Department of Physical Medicine and Rehabilitation,University of Kentucky
K.C. Chelette, Department of Physical Medicine and Rehabilitation, University of Kentucky
C. Carrico, Department of Physical Medicine and Rehabilitation, University of Kentucky
L. Nichols, Department of Physical Medicine and Rehabilitation, University of Kentucky and Cardinal Hill Rehabilitation Hospital, Lexington, KY
C. Henzman, College of Medicine, University of Louisville, Louisville, KY
L. Sawaki, Department of Physical Medicine and Rehabilitation, University of Kentucky

Abstract: Objective: To better understand the dose-response relationship of peripheral nerve stimulation (PNS) as an adjunctive intervention paired with upper extremity motor training for subjects with severe post-stroke motor deficit. Design: Twenty-eight subjects with chronic stroke were randomly assigned to 1 of 5 groups in an ongoing double-blind study (projected total enrollment: n=60). Each subject received PNS and upper extremity motor training on a robot-assisted device. The intervention varied with respect to PNS intensity (ie, eliciting compound action muscle potentials (CMAPs) either above or below 100μv, or sham (ie, 0μv)) and PNS timing (ie, delivered either before or during training). Baseline evaluation preceded 10 consecutive weekdays of intervention. We used the Fugl-Meyer Assessment Scale (FMA; primary outcome measure) and the Stroke Impact Scale (SIS) to measure motor performance and recovery of function. Results: At completion evaluation, all groups showed improvement in total motor scores on the FMA. The Below/During group had greater improvement than all other groups (significant in comparing “Below/During” with “Below/Before,” “Above/During,” and “Sham.”). SIS scores generally followed the same pattern as FMA scores, with “Below/During” showing significantly more improvement than “Sham” at completion evaluation. Conclusions: Our preliminary data suggest that variation of PNS intensity and timing relative to motor training carries great potential to advance neurorehabilitation strategies to promote functional recovery for stroke survivors with chronic, severe upper extremity motor deficit.

Supported by: Cardinal Hill Endowment for Stroke and Spinal Cord Injury Research
Primary Presenter / e-mail: E. Salyers / elsa223@g.uky.edu
Mentor or Senior Author / e-mail: L. Sawaki / lumy.sawaki@uky.edu

#140 Abstract Title: Effects of a Cavity-Filling Mutation in the Enzyme Choline Acetyltransferase

Author(s):
J. Batra, Molecular and Cellular Biochemistry and Center for Structural Biology, U of Kentucky
C.D. Ester, Molecular and Cellular Biochemistry and Center for Structural Biology, U of Kentucky
Y. Cai, Molecular and Cellular Biochemistry and Center for Structural Biology, U of Kentucky
D.W. Rodgers, Molecular and Cellular Biochemistry and Center for Structural Biology, U. of Kentucky

Abstract: Choline acetyltransferase (ChAT) synthesizes the neurotransmitter acetylcholine, and point mutations in the enzyme cause congenital motor disorders. We hypothesize that the susceptibility of ChAT to point mutations at sites distributed over the enzyme is due to its unusually large number of core packing defects or cavities. Using site directed mutagenesis, a point mutation converting serine 106 to a leucine residue was introduced in order to partially fill a cavity near two known congenital mutation sites. The wild type and S106L mutant proteins were expressed, purified, and analyzed for activity and thermal stability. The S106L mutation reduced maximal activity of the enzyme by approximately two fold and increased the thermal stability by almost 5 degrees Celsius, demonstrating that internal cavities are linked with enzyme function and stability. We are now testing the effect of the cavity-filling S106L mutation on the decrease in enzyme function caused by a nearby congenital mutation (L102P). If filling packing cavities reduces the effects of congenital mutations, small ligands that bind in cavities may be useful in treating the motor disorders.

Supported by: NIH Awards: R03NS079818 and P20RR20171
Primary Presenter / e-mail: J. Batra / Jyotica.Batra@uky.edu
Mentor or Senior Author / e-mail: D.W. Rodgers / David.Rodgers@uky.edu

8th Annual CCTS Spring Conference

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#141 Abstract Title: Sarcopenia and Aged Skeletal Muscle Hypertrophy are Independent of Lifelong Satellite Cell Depletion

Author(s): J.D. Lee, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
J. Mula, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
C.S. Fry, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
T.J. Kirby, Physiology, College of Medicine, U of Kentucky
J.R. Jackson, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
J.A. Beggs, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
M.S. Campbell, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
T.E. Kmiec, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
E.E. Dupont-Versteegden, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
J.J. McCarthy, Physiology, College of Medicine, U of Kentucky
C.A. Peterson, Rehabilitation Sciences, College of Health Sciences, U of Kentucky

Abstract: Aging is associated with the loss of muscle stem cells, satellite cells, a process assumed to contribute to sarcopenia. However, no definitive evidence exists showing that satellite cells are necessary for muscle maintenance or adaptation with age. To directly address these issues, we developed the Pax7-DTA mouse that allows conditional and specific deletion of Pax7+ satellite cells with tamoxifen administration. Four month old mice were treated with tamoxifen or vehicle and allowed to recover for one (young) or 20 (old) months, followed by synergist ablation (SA; two weeks of overload) or sham surgery. Tamoxifen-treated muscles showed >90% satellite cell depletion after 1 month and no recovery after 20 months, such that the aged mice lived the majority of their lives with a significantly reduced satellite cell pool. With age, vehicle-treated muscles demonstrated an expected reduction (-52%) in Pax7+ satellite cells. Further, an age-associated loss of muscle mass and attenuated muscle hypertrophy in response to overload was observed in 24 month old mice; however, neither was affected by lifelong satellite cell depletion. During overload in old mice, tamoxifen prevented myonuclear accretion and the appearance of small, regenerating myofibers, but did not influence overall muscle hypertrophy. These data provide convincing evidence that loss of satellite cells does not exacerbate sarcopenia, nor are satellite cells required for myofiber hypertrophy even in old age. Thus, satellite cell loss does not play a causal role in sarcopenia or in diminished muscle adaptability observed with age.

Supported by: Funding: NIH R01AR060701 and R21AG34453. This research was conducted while Jonah Lee was an Ellison Medical Foundation/American Federation of Aging Research Fellow EPD12102. Acknowledgement of the Center for Muscle Biology Single Fiber Function Core Services

Primary Presenter / e-mail: J.D. Lee / jle238@uky.edu

Mentor or Senior Author / e-mail: C.A. Peterson / cpete4@uky.edu

#142 Abstract Title: Satellite Cell Depletion Negatively Impacts Voluntary Wheel Running Performance in Mice

Author(s): J.R. Jackson, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
C.S. Fry, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
T.J. Kirby, Physiology, College of Medicine, U of Kentucky
J.D. Lee, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
J.H.Werker, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
C.S. Dean, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
J.J. McCarthy, Physiology, College of Medicine, U of Kentucky
E.E. Dupont-Versteegden, Rehabilitation Sciences, College of Health Sciences, U of Kentucky
C.A. Peterson, Rehabilitation Sciences, College of Health Sciences, U of Kentucky

Abstract: Satellite cells have long been thought to be responsible for muscle plasticity. Recent studies in the field using genetically-modified mouse models that allow for conditional satellite cell ablation have challenged this dogma. Although these studies confirmed that satellite cells are required for muscle regeneration, they surprisingly show that they are not required for muscle growth. While the role that muscle stem cells play in muscle growth and regeneration are being defined, their role in muscle response to aerobic exercise remains unexplored. Therefore the purpose of the current study is to assess the involvement of satellite cells in response to voluntary wheel running. Female Pax7-DTA mice were satellite cell depleted following tamoxifen administration. Mice were either ambulatory, or were wheel run for 8 weeks. Satellite cell depleted animals ran ~27% less km/day and 17% slower than non-depleted animals. Succinate dehydrogenase was significantly elevated in plantaris muscles with running, but staining intensity tended to be attenuated in satellite cell-depleted muscle. Myosin heavy chain isoforms were significantly altered with running, independent of satellite cell ablation. Similarly, fiber vascularization, quantified using the endothelial marker CD31, was elevated with running, but was unaffected by satellite cell depletion. In conclusion, the presence of satellite cells appears to be beneficial to voluntary running performance. The metabolic processes that may be altered in the absence of satellite cells that contribute to decreased endurance are currently under investigation.

Supported by: NIAMS R01AR060701

Primary Presenter / e-mail: J.R. Jackson / jfr232@uky.edu

Mentor or Senior Author / e-mail: C.A.Peterson / cpete4@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#143 Abstract Title: ED2 Macrophage Number is Dependent upon Loading Conditions in Aged Muscle

Author(s):
S.D. Moore, Division of Athletic Training, U of Kentucky
C. Waters-Banker, Division of Athletic Training, U of Kentucky
T. Butterfield, Division of Athletic Training, U of Kentucky
E. Dupont-Versteegden, Division of Physical Therapy, U of Kentucky

Abstract: Aging has been associated with impaired recovery of muscle size following disuse, the reasons for which are unknown. The regulation of the inflammatory response may be locally altered in aging muscle, likely resulting in a different inflammatory environment compared to young muscle. Therefore, the goal of this project was to examine inflammatory cells in muscle tissue following atrophy and recovery in young and old rats. We hypothesized that aged rats would display different numbers of the cells of interest compared to young rats under different loading conditions. Six and 32 month old Brown Norway/F344 rats were assigned to 3 groups: (1) control: rats remained ambulatory for two weeks; (2) hindlimb-suspended (HS): rats were tail suspended to induce atrophy for 14 days; (3) reloaded (RE): rats were allowed normal ambulation for 14 days after HS for 14 days. Soleus muscles were used for analysis. Muscle cross sections were immunoreacted for ED1 macrophages (CD68), ED2 macrophages (CD163), and neutrophils (CD43). The number of ED2 macrophages was counted and expressed per number of muscle fibers. Two-way ANOVA and Pearson correlations were conducted. ED1 macrophages and neutrophils were not detectable in the muscle regardless of age or condition. ED2 macrophages were elevated in aged muscle compared to young in all loading conditions. Furthermore, the number of ED2 macrophages was lower with HS compared to control and RE only in aged. In the young muscle, no significant correlation was observed between number of ED2 macrophages and muscle weight, but aged muscle demonstrated a significant positive correlation ($r = .499$, $p = .018$). These findings suggest that aged muscle has a different inflammatory environment than young muscle. Also, in aged muscle the inflammatory environment is dependent on loading condition. These differences support the need for further investigation into interventions (e.g. massage) that positively modulate the inflammatory environment in the aged. Supported by NIH AG028925.

Supported by: Supported by NIH AG028925
Primary Presenter / e-mail: S.D. Moore / sdmo222@uky.edu
Mentor or Senior Author / e-mail: E. Dupont-Versteegden / eedupo2@uky.edu

#144 Abstract Title: Noncontact Diffuse Optical 3-D Imaging of Hemodynamic Contrasts in Breast Tumor: Geometrical Reconstruction and Alignment of Optical Sources and Detectors

Author(s):
C. Huang, Center for Biomedical Engineering, U of Kentucky
Y. Lin, Center for Biomedical Engineering, U of Kentucky
L. He, Center for Biomedical Engineering, U of Kentucky
Y. Shang, Center for Biomedical Engineering, U of Kentucky
D. Irwin, Center for Biomedical Engineering, U of Kentucky
M. Szabunio, Markey Cancer Center, University of Kentucky
G. Yu, Center for Biomedical Engineering, U of Kentucky

Abstract: Functional alterations in tumors usually occur in advance of morphological changes and give early evidence of responses to treatment. We have recently developed a unique noncontact 3-D near-infrared functional imaging system for the quantification of blood flow and oxygenation distributions in breast tumors. The noncontact probe head consisted of 2 laser sources and 11 detectors, which were projected onto tissue surface by optical lenses. Experimental protocol involved rotating the probe perpendicular to tissue surface with marks indicating the positions of sources and detectors. Previous studies using the noncontact system have demonstrated that the curvature of tissue surface caused significant measurement errors. In this study, a 3-D laser scanner was used to capture the breast surface with marks. These scanning procedures were repeated sequentially in the breasts of a plastic mannequin and a female subject. The output surface was then converted to a solid breast model in a consistent coordinate system by SolidWorksÒ. The sources and detectors were then aligned on the surface of the breast model based on the marks. The reconstructed solid breast model had the same shape and dimensions as the mannequin, and position errors in the alignment of sources and detectors were less than 6.5%. From the human subject, we also obtained a solid breast model with the sources and detectors aligned on its surface. A mesh with desired node size was created in the solid breast model using ANSYSÒ, which can be used as input in a software package (NIRFAST) for image reconstruction of breast hemodynamics.

Supported by: UK Center for Clinical and Translational Science
Primary Presenter / e-mail: C. Huang / chong.huang@uky.edu
Mentor or Senior Author / e-mail: G. Yu / guoqiang.yu@uky.edu

#145 Abstract Title: **A Microscopic Real-Time 3D Impedance Imaging Technique for Precise and Accurate Tumor Remove**

Author(s):
C. Kim, Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA
Chengjie Zhu, Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA
Jie Zhang, Department of Radiology, College of Medicine, University of Kentucky
Hua Wang, Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA

Abstract: One unmet need in tumor surgery is to remove all the cancer cells and to preserve as much healthy tissues as possible, which minimizes the cancer recurrence rate after the surgical intervention while minimizing the loss of functionalities of the patient. To achieve this goal, we propose a high-performance imaging technique, providing real-time information of tumor boundaries during surgical procedure. The technology is based on microscopic 3D impedance imaging of the tissues close to the surgical cutting tool, which can be readily adopted in guide-surgery to achieve complete surgical removal of tumors. We develop a tissue impedance sensor array (>10,000 electrodes). The large-scaled electrode array is built in a Complementary Metal-Oxide-Semiconductor (CMOS) Integrated Circuit (IC) chip (< 2mm) to perform the tissue impedance mapping. This technique registers the tissue impedance information as voxels, which resolves the actual tissue anatomical structure with a single-cell resolution. Our simulation study shows great promise. The simulation impedance mapping results have successfully demonstrated the delineation of the tissue boundaries between tumor and healthy tissues which are shown as user-friendly false-colored 2D images. It can also be rendered into interactive 3D plots for guided surgery. Since 3D impedance full scan can be performed within seconds, our method is readily to achieve real-time 3D tumor detection. The proposed real-time 3-D sensing technique for precise and accurate tumor removal provides a radical solution for surgeons. This technology enables high-precision guided surgery, particularly in minimally invasive brain tumor surgery. Moreover, the proposed broadband impedance sensor can be easily integrated with existing cutting tool for full tissue characterization.

Supported by: Currently Funded by Professor Hua Wang's Start-Up Fund at Georgia Institute of Technology
Primary Presenter / e-mail: C. Kim / choongsoon@gatech.edu
Mentor or Senior Author / e-mail: H. Wang and J. Zhang / hua.wang@ece.gatech.edu

#146 Abstract Title: **The Role of Cardiac CT for the Diagnosis of Pulmonary Vein Thrombus; an Illustrative Case Report**

Author(s):
R. Embertson, College of Medicine, U of Kentucky
D. Kim, College of Medicine, U of Kentucky
P. Von Hermmann, Dept of Radiology, U of Kentucky
M. Winkler, Dept of Radiology, U of Kentucky

Abstract: INTRODUCTION: The risk of death from intracardiac thrombus is significant. Emboli can break free from the thrombus and manifest as embolic stroke. Intracardiac thrombi are generally treated with anticoagulation therapy. METHODS: The medical records and images of a patient with pulmonary vein thrombus were reviewed by the authors. The literature relating to this topic was reviewed. RESULTS: A 54-year-old male was admitted to the hospital with chief complaints of shortness of air and blood tinged sputum. He also noted transient numbness and weakness in the left arm and face, recent weight loss, and decreased appetite. An MRI of the brain were performed soon after admission demonstrating scattered peripheral hyperintense foci on DWI consistent with embolic infarcts. A Non-Gated CTpulmonary angiogram was ordered for hypoxia. No pulmonary embolus was seen. However, the scan was concerning for left atrial and pulmonary venous thrombus vs flow artifact. A TTE was performed which did not visualize any thrombus in the left atrium. An ECG-Gated CTA of the thorax was then obtained which definitely demonstrated a highly mobile, disorganized, and friable thrombus in the left atrium extending from three of four pulmonary veins [figure 1]. The patient was started on enoxaparin and discharged. Ten days later he returned with increasing SOA, new onset arm weakness, confusion and respiratory distress. He was intubated and admitted to the ICU. A repeat MRI of the head showed that the foci of DWI hyperintensity in his brain had progressed dramatically in size and number since the first MRI. A gradient echo sequence demonstrated the presense of acute and subacute infarcts. The patient passed away five days after his admission to the ICU. CONCLUSION: Any intracardiac thrombus confers a risk of stroke or other end organ ischemic event. In this case discordant results between CT and TTE prompted an ECG-CT, which definitively established the presence of thrombus. Although anticoagulation remains the standard of care at this time, it is not always successful, as this case illustrates.

Supported by:
Primary Presenter / e-mail: D. Kim / daniel.kim@uky.edu
Mentor or Senior Author / e-mail: M. Winkler / michael.winkler@uky.edu

#147 Abstract Title: **Noncontact 3-D Imaging of Small Animal Tumors with Combined Diffuse Optical, Correlation, and Fluorescence Tomography: Preliminary Results in Phantoms**

Author(s):
D. Irwin, College of Engineering, Center for Biomedical Engineering, U of Kentucky
Y. Lin, College of Engineering, Center for Biomedical Engineering, U of Kentucky
L. He, College of Engineering, Center for Biomedical Engineering, U of Kentucky
C. Huang, College of Engineering, Center for Biomedical Engineering, U of Kentucky
Y. Shang, College of Engineering, Center for Biomedical Engineering, U of Kentucky
M. Zhao, College of Engineering, Center for Biomedical Engineering, U of Kentucky
G. Yu, College of Engineering, Center for Biomedical Engineering, U of Kentucky

Abstract: Recently, our lab incorporated near-infrared diffuse optical and correlation tomography (DOT/DCT) into a noncontact acquisition system. These technologies produce three-dimensional deep tissue (up to several centimeters) oxygenation and blood flow data, respectively. Laser light is focused by lenses onto tissue and, after interacting, is detected several centimeters away via lenses. Of interest for many researchers is monitoring fluorescence-based parameters, but available in-vivo fluorescent imaging devices may have limitations such as lack of functional information. This study aims to amalgamate the noncontact system with components to obtain diffuse fluorescent tomography (DFT) and DOT/DCT simultaneously. The final objective is collection of in-vivo data on small animal tumors through collaborations. Initial system evaluation was performed with a tissue-like liquid phantom (background) and solid phantom (anomaly). The solid phantom with volume=0.95cm3 was placed at ~3mm depth below the center of the scanning area. Experimental protocol involved rotating the lens focusing apparatus, located perpendicular to liquid surface, 60° at 6° intervals over anomaly site. Actual contrast between background and anomaly flow index values is -100%. Reconstructed contrast was -88.25% and reconstructed anomaly volume was 0.82cm3. These results were similar to actual, exhibiting potential to identify anomalies in real tissue. Future investigations include DOT aspects, DFT integration, phantom testing, and small animal tumor monitoring.

Supported by: NIH award: R01 CA149274 NIH award: R21 AR062356 NIH award: UL1 RR033173
Primary Presenter / e-mail: D. Irwin / daniel.irwin@uky.edu
Mentor or Senior Author / e-mail: G. Yu / guoqiang.yu@uky.edu

#148 Abstract Title: **Thickness of the Lower Trapezius and Serratus Anterior Using Ultrasound Imaging During a Repeated Arm Lifting Task**

Author(s):
J. M. Day, Department of Rehabilitation Sciences, U of Kentucky
T. L. Uhl, Department of Rehabilitation Sciences, U of Kentucky

Abstract: The purposes of this study were to establish the reliability for measuring scapular muscle thickness, and to examine how scapular muscle thickness changes with respect to external loads. Participants were asymptomatic subjects recruited from a sample of convenience. Thickness Measures were taken using rehabilitative ultrasound imaging (RUSI) under 11 conditions, rest and 10 progressive loads, for the Lower Trapezius (LT) and Serratus Anterior (SA). The procedures were repeated 1 week later to determine reliability. Bland and Altman limits of agreement and Interclass correlation coefficients (ICC) were used to determine reliability. Separate repeated measure ANOVAs were performed to determine differences in muscle thickness for both muscles across 3 conditions; rest and the 2 loaded conditions that represented the lowest and highest torque values. Results demonstrate good within and between day reliability for the LT (ICC = .86 to .99) and SA (ICC = .88 to .99). For the LT and SA, there were significant differences between the resting thickness and 2 lifting conditions ($p \leq .01$) but not between the two lifting conditions. It was concluded that RUSI is reliable in measuring scapular muscle thickness. RUSI is sensitive enough to detect absolute changes in thickness from resting to a contracted state but unable to detect differences between loads imposed on the shoulder.

Supported by:
Primary Presenter / e-mail: J. M. Day / joseph.day@uky.edu
Mentor or Senior Author / e-mail: T. L. Uhl / tluhl2@email.uky.edu

#149 Abstract Title: **Noninvasive diffuse optical monitoring of hemodynamic changes in head and neck tumors throughout radiation therapy**

Author(s):
L. Dong, Center for Biomedical Engineering, U of Kentucky College of Engineering
M. Kudrimoti, Department of Radiation Medicine, U of Kentucky Chandler Hospital
Y. Lin, Center for Biomedical Engineering, U of Kentucky College of Engineering
C. Huang, Center for Biomedical Engineering, U of Kentucky College of Engineering
R. Cheng, Center for Biomedical Engineering, U of Kentucky College of Engineering
Y. Shang, Center for Biomedical Engineering, U of Kentucky College of Engineering
S. D. Stevens, Department of Radiology, U of Kentucky Chandler Hospital
B. J. Shelton, Markey Cancer Center, Medicine, Biostatistics, Public Health, U of Kentucky
G. Yu, Center for Biomedical Engineering, U of Kentucky College of Engineering

Abstract: Radiation therapy is a principal modality in treatment of head and neck cancers, and its efficacy is associated with tumor oxygen status. Functional assessment of tumor physiological status before, during, and after therapy holds potential for pretreatment planning, early prediction of therapy outcomes, and longitudinal evaluation of tumor responses to therapy. This study explored using a hybrid near-infrared diffuse optical instrument combining a commercial frequency-domain tissue oximeter (Imagent, ISS) and a novel diffuse correlation spectroscopy (DCS) flowmeter, which allows for simultaneous measurements of blood flow and blood oxygenation in head and neck tumors. The hemodynamic measurement was performed by placing a fiber-optic probe connected to the hybrid instrument on the surface of the lymph node for 3 minutes, and followed by a control measurement on forearm flexor muscle for 2 minutes. Seventeen patients were continually measured once a week over a treatment period of seven weeks. Large inter-patient variations in tumor hemodynamic responses to therapy were observed and different trends/patterns were found in different hemodynamic parameters and for different tissues (i.e., tumor and forearm muscle). More patients are being recruited and long-term clinical outcomes are being collected to investigate the sensitivities of the measured hemodynamic parameters in the prediction of treatment outcomes. Our long-term goal is to develop robust scientific collaborations for establishing the hybrid diffuse optical system as an alternative clinical tool for objective response evaluation in various tumors and for optimizing cancer therapies by improving tumor hemodynamic status with real-time early adjustment of the treatment plan.

Supported by: R01 CA149274 (GY), R21 AR062356 (GY), and UL1RR033173 (GY)
Primary Presenter / e-mail: L. Dong / lixin.dong@uky.edu
Mentor or Senior Author / e-mail: G. Yu / guoqiang.yu@uky.edu

#150 Abstract Title: **Noncontact Diffuse Optical 3-D Imaging of Hemodynamic Contrasts in Breast Tumor: Computer Simulation**

Author(s):
L. He, UK Center for Biomedical Engineering
Y. Lin, UK Center for Biomedical Engineering
C. Huang, UK Center for Biomedical Engineering
D. Irwin, UK Center for Biomedical Engineering
M. Szabunio, UK Markey Cancer Center
G. Yu, UK Center for Biomedical Engineering

Abstract: Background: Near-infrared diffuse optics is a simple, fast, portable, inexpensive method for noninvasive quantification of deep tissue hemodynamics, which can be used for early diagnosis of breast cancer. The conventional contact measurements with the placement of fiber-optic probes on the skin cause noises and artifacts associated with the imperfect coupling between the fibers and breast. The probe-tissue contact pressure may also result in the distortion of tissue property distribution. Our lab has recently developed a noncontact diffuse optical system for 3-D imaging of tumor optical properties and blood flow. This study is to examine the imaging capability of the developed system using computer simulations. Methods: A slab mesh considered as background tissue was created and a sphere mesh whose optical property and flow index were different from the background was suspended inside the slab to mimic a tumor inside normal tissues. A noncontact fiber-optic imaging probe scanned over the tumor. The simulation algorithms consisted of forward and inverse models. In the forward model, photon fluence rate at each detector position on tissue surface was calculated according to photon diffusion equation. For the inverse problem, optical property and flow index inside the tumor and background tissues were reconstructed using the measured light fluence rate. Simulations were performed with different tumor volumes located at different depths. Results and Conclusions: The accuracy of image reconstruction depended on tumor depth and volume as well as hemodynamic contrasts assigned. Simulation results demonstrated the feasibility of using this noncontact optical system for 3-D imaging of tumor hemodynamics, and provided information for the optimization of imaging system.

Supported by: University of Kentucky Center for Clinical and Translational Science
Primary Presenter / e-mail: L. He / lhe228@g.uky.edu
Mentor or Senior Author / e-mail: G. Yu / gyu2@email.uky.edu

#151 Abstract Title: **Patients with Tetralogy of Fallot suffer from Abnormal Synchrony of Contraction in the Heart: A Magnetic Resonance Imaging Study**

Author(s):
L. Jing, Center for Biomedical Engineering, University of Kentucky
C. M. Haggerty, Departments of Pediatrics, Physiology and Medicine, University of Kentucky
T. Geva, Department of Pediatrics, Harvard Medical School, Boston, MA
A. J. Powell, Department of Pediatrics, Harvard Medical School, Boston, MA
B. K. Fornwalt, Depts of Pediatrics, Physiology and Medicine, Center for Biomedical Engineering, U of Kentucky

Abstract: Background– Despite many therapeutic advances, congenital heart disease remains responsible for more than double the years of life lost due to all of childhood cancer. New therapies are urgently required. We hypothesized that MRI-based measures of cardiac synchrony would be abnormal in patients with congenital heart disease, suggesting that these patients may benefit from a life-prolonging treatment called cardiac resynchronization therapy. Methods– Thirteen patients with tetralogy of Fallot (46% female, age 26±16 years) and 17 healthy control subjects (12% female, age 29±7 years) underwent cardiac MRI. Regional circumferential strain curves were generated from each ventricle by tracking 12 evenly spaced points throughout the cardiac cycle using a displacement-based optical flow algorithm. Synchrony was quantified as cross-correlation delays expressed as a percentage of the cardiac cycle length, which were calculated between regional strain curves and the reference curve determined by a QT-clustering algorithm. Inter-ventricular synchrony was quantified as the cross-correlation delay between the volume curves from the two ventricles. Results– Left ventricular delays were increased in the patients (2.9±1.3% vs 0.2±0.5%, $p<0.001$). Inter-ventricular synchrony was also different in the patients: the right ventricle contracted 4±3% later than the left ventricle in the patients and 1±4% earlier than the left ventricle in the controls ($p<0.001$). Right ventricular synchrony was not different between patients and controls. Conclusions– Patients with tetralogy of Fallot have abnormal synchrony in the heart compared to healthy subjects. These patients may therefore benefit from cardiac resynchronization therapy, but additional studies including the relationship between synchrony and outcomes are required.

Supported by: NIH KL2 RR033171 and NIH DP5 1DP5OD012132-01
Primary Presenter / e-mail: L. Jing / lji222@uky.edu
Mentor or Senior Author / e-mail: B. K. Fornwalt / b.f@uky.edu

#152 Abstract Title: **Comparison of Ultrasound Imaging and Skinfold Caliper Measurements of Subcutaneous Adipose Tissue Thickness**

Author(s):
M. Zhao, Center for Biomedical Engineering, U of Kentucky
Y. Shang, Center for Biomedical Engineering, U of Kentucky
B. A. Henry, Center for Biomedical Engineering, U of Kentucky
G. Yu, Center for Biomedical Engineering, U of Kentucky

Abstract: Objective: The subcutaneous adipose tissues overlaying the skeletal muscle affect the measurement accuracy of muscle blood flow by near-infrared diffusion correlation spectroscopy. The adipose tissue contribution can be corrected using multi-layer models with the knowledge of top layer thickness. Although skinfold caliper has been broadly used to measure the top layer thickness of adipose tissues, its accuracy needs to be determined by comparing with other established methods. For this reason, we compared the thickness measurements of the adipose layer on top of calf muscle measured by the skinfold caliper and ultrasound imaging (as a standard). Methods: Seven subjects (5 males and 2 females) participated in this study. Caliper measurements were performed 3 times on top of bilateral calf muscle in each subject and thickness data were averaged. The top layer thickness at the same location was also quantified by ultrasound imaging, where the adipose tissue appeared brighter than the muscle. Linear regression was used to compare the two measurements. Results: Significant correlation was observed between the two measurements [$R2 = 0.74$, $p = 8.45e\text{-}5$, Y (caliper) = 0.80 * X (ultrasound) + 1.58]. However, the adipose layer thicknesses measured by the caliper were lower than those measured by the ultrasound (regression slope = 0.80). Conclusions: Although the skinfold caliper is a simple, inexpensive and easy-to-use tool, the thicknesses of the adipose layer were generally underestimated by its measurements (regression slope < 1). Such underestimation is likely due to the compression of the adipose tissue by the caliper head. Therefore, a caution should be made when using the skinfold caliper to quantify adipose layer thickness.

Supported by:
Primary Presenter / e-mail: M. Zhao / mingjun.zhao@uky.edu
Mentor or Senior Author / e-mail: G. Yu / gyu2@email.uky.edu

#153 Abstract Title: MR Spectroscopy to Measure Hepatic Fat Quantification

Author(s): P. A. Hardy, Department of Radiology U of Kentucky
B. Noblitt, U of Kentucky Medical School
J. T. Lee, Department of Radiology U of Kentucky

Abstract: Introduction: Noninvasive hepatic fat quantification is important for diagnosing and monitoring hepatic diseases, such as Nonalcoholic Fatty Liver disease (NAFLD). The purpose of our study was to validate Single Voxel MR Spectroscopy (SVS) to measure liver fat content. The secondary purpose was to measure the dependence of the amplitudes of the fat and water peaks on acquisition technique and tissue iron concentration as iron accumulation is believed to accompany the development of NAFLD. Methods: Using a 7.0 T small animal Imager and a SVS STEAM sequence we measured the fat fraction (FF) in calibrated samples of Intralipid®. We scanned the samples at a series of TE and TR times to construct decay curves to calculate T1 and T2. The FF was defined as the ratio of the predominant fat peak (1.3 ppm) to the total amplitude of the fat and water (4.7 ppm) peaks. Secondly, livers from 19 hybrid C57Bl/6 and CD1/129 mice with 9 mice homozygous for db were measured to estimate their FF. The iron concentration of each sample was measured using ICP-OES. Results: The IntraLipid samples demonstrated a highly linear relationship between the measured and the known FF. However, the fat fraction depended upon TE and TR indicating the need to compensate for relaxation times to obtain the most accurate FF estimate. The wild type animals had a significantly increased liver iron concentration. The T2* measured with imaging correlated with the iron concentration indicating it was sufficient to affect the T2* of the water signal.

Supported by: Partial support for this work was provided by the Office of the Vice President of Research and the Federal Work Study program.
Primary Presenter / e-mail: P. A. Hardy / peter.hardy@uky.edu
Mentor or Senior Author / e-mail: J. T. Lee / jtlee3@uky.edu

#154 Abstract Title: Identification of Coronary Artery Calcification and Diagnosis of Coronary Artery Disease by Abdominal CT; a Continuous Quality Improvement Project

Author(s): P. Clark, College of Medicine, U of Kentucky
D. Kim, College of Medicine, U of Kentucky
R. Embertson, College of Medicine, U of Kentucky
R. Charnigo, Deparment of Radiology, U of Kentucky
M. Winkler, Department of Radiology, U of Kentucky

Abstract: Introduction: Coronary artery disease (CAD) is the leading cause of death in the US. It is well established that coronary artery calcification (CAC) visible on a CT scan is pathognomonic of CAD. In July 2009, the Departments of Radiology and Cardiology instituted an Advanced Cardiac Imaging (ACI) rotation for trainees. As part of the ACI rotation, trainees are taught to identify CAC on CT scans and report this finding consistently. As a continuous quality improvement project, periodic measurement of reporting of CAC and CAD on CT scans of the abdomen was implemented to assess the impact of ACI training on reporting of studies not targeted to evaluation of the heart. Methods: The initial 500 sequential abdominal CT scans performed at University of Kentucky Gill Imaging Center for 2009, 2011, and 2013 were studied. Of each set of 500, the images and companion reports for patients age > 45 yrs were retrospectively reviewed by a Cardiac Imaging Specialist. Results: 375 scans from 2009, 361 from 2011, and 403 from 2013 met the inclusion criteria.Between 2009 and 2011, the sensitivity of reporting of CAC increased from 1% to 72%. The sensitivity for making a diagnosis of CAD, defined by inclusion of this diagnosis in the report impression, increased from 0% to 8%. Between 2011 and 2013 the sensitivity of reporting CAC increased further from 72 to 90% and the diagnosis of CAD from 8% to 13%. Conclusion: Incorporation of formal CI training into resident education improves reporting of CAC on abdominal CT scans. The rate of improvement in the diagnosis of CAD on abdominal CT scans lags behind improvement in reporting of CAC. This discrepancy, as well as the clinical impact of improved reporting and diagnosis of CAC and CAD on abdominal CT scans, are topics identified for further study.

Supported by:
Primary Presenter / e-mail: P. Clark / pdclar2@uky.edu
Mentor or Senior Author / e-mail: M. Winkler / michael.winkler@uky.edu

#155 Abstract Title: Obesity Reduces Cardiac Strains, Torsion, and Synchrony in Mouse Models: a Cardiac Magnetic Resonance Imaging Study

Author(s):
S. Kramer, Pediatrics, Cardiology, and Physiology, UK College of Medicine
D. Powell, Center for Biomedical Engineering, UK
C. Haggerty, Pediatrics, Cardiology, and Physiology, UK College of Medicine
C. Binkley, Pediatrics, Cardiology, and Physiology, UK College of Medicine
A. Mattingly, Pediatrics, Cardiology, and Physiology, UK College of Medicine
L. Cassis, Graduate Center for Nutritional Sciences, UK College of Medicine
F. Epstein, Biomedical Engineering, University of Virginia, Charlottesville, VA
B. Fornwalt, Pediatrics, Cardiology, Physiology, and Biomedical Engineering, UK College of Medicine

Abstract: Background– Obesity affects one-third of adults in the US and increases risk of cardiovascular mortality. The mechanisms underlying this increased risk are not well understood but are thought to involve direct effects on the heart such as lipid deposition and fibrosis. However, the effect of obesity on cardiac function has not been well defined. We hypothesized that diet-induced obesity in mice leads to reduced strain, torsion, and synchrony in the heart. Methods– Ten 12-week-old mice were randomized to a high-fat or low-fat diet. After 5 months on the diet, mice were imaged with a 7T MRI using cine DENSE for quantification of strains, torsion, and synchrony in the left ventricle. Results– Subepicardial strain was lower in the obese mice with decreases of 40% circumferentially ($p<0.001$), 19% longitudinally ($p=0.03$), and 53% radially ($p=0.06$). By contrast, subendocardial strain was modestly reduced in the obese mice in the circumferential direction by 12% ($p=0.01$), and no different in the radial ($p=0.63$) or longitudinal ($p=0.44$) directions. Peak torsion was reduced by 34% ($p=0.06$). The synchrony of contraction was also reduced ($p=0.01$) with a time delay in the septal to lateral direction. Finally, mass was increased by 15% ($p=0.02$) with no change in ventricular volumes or ejection fraction. Conclusions– Diet-induced obesity reduces left ventricular strains and torsion in mice. These effects are mostly limited to the subepicardium. Obesity also leads to reduced synchrony of contraction and hypertrophy. These new findings help to elucidate the mechanisms underlying the link between the obesity epidemic and increased cardiovascular mortality.

Supported by: NIH COBRE grant (Cassis: 8P20 GM103527-05)
Primary Presenter / e-mail: S. P. Kramer / s.kramer@uky.edu
Mentor or Senior Author / e-mail: B. K. Fornwalt / b.f@uky.edu

#156 Abstract Title: Diffuse Optical Monitoring of Cerebral Hemodynamics During Obstructive Sleep Apnea

Author(s):
Y. Hou, Center for Biomedical Engineering, U of Kentucky and Shenyang Ligong U, China
Y. Shang, Center for Biomedical Engineering, U of Kentucky and College of Science
R. Cheng, Center for Biomedical Engineering, U of Kentucky and College of Science
Y. Qin, Center for Biomedical Engineering, U of Kentucky and Shenyang Ligong U, China
D. Hayes, Jr., College of Medicine, Ohio State U
G. Yu, Center for Biomedical Engineering, U of Kentucky and College of Science

Abstract: Obstructive sleep apnea (OSA) is characterized by repetitive pausing of breath resulted from upper airway obstruction during sleep and diagnosed through monitoring of overnight sleep with a polysomnography. The impeded airflow during OSA may cause cerebral ischemia and disturb cerebral blood flow (CBF). Although hemodynamic parameters (e.g., CBF and cerebral oxygenation) are usually coupled and interactive, current studies during OSA have mostly been limited to evaluating a single hemodynamic parameter due to the lack of adequate techniques. In this study, we utilized a novel near-infrared diffuse correlation spectroscopy (DCS) flow-oximeter recently developed in our lab to continuously and simultaneously monitor relative changes of CBF, oxy- and deoxy- hemoglobin concentrations in 18 subjects with OSA for ~8 hours overnight. Two fiber-optic probes connected to the DCS flow-oximeter were taped on both sides of the forehead for cerebral monitoring during sleep. To minimize the disturbance to patients, we remotely operated the optical measurements in a control room and designed special fiber-optic connectors to dis- or re- connect the probes when the patient went to bathroom overnight. Large fluctuations in CBF were observed during the episodes of apnea. By contract, cerebral oxygenation changes were not evident. Upcoming work will investigate the differences in cerebral hemodynamics between the apnea and non-apnea episodes, and correlate the homodynamic responses with the severity of OSA. We believe that this study reports, for the first time, the simultaneous and continuous monitoring of CBF and cerebral oxygenation changes overnight during OSA.

Supported by: American Heart Association (BGIA 2350015) and University of Kentucky Research Support Funds
Primary Presenter / e-mail: Y. Hou / yajun.hou@uky.edu
Mentor or Senior Author / e-mail: G. Yu / guoqiang.yu@uky.edu

#157 Abstract Title: **Simultaneous measurement of deep tissue blood flow and oxygenation using noncontact diffuse correlation spectroscopy flow-oximeter**

Author(s):
Y. Lin, Center for Biomedical Engineering, U of Kentucky
T. Li, Center for Biomedical Engineering, U of Kentucky
Y. Shang, Center for Biomedical Engineering, U of Kentucky
L He, Center for Biomedical Engineering, U of Kentucky
C. Huang, Center for Biomedical Engineering, U of Kentucky
M. Szabunio, Markey Cancer Center, U of Kentucky
G. Yu, Center for Biomedical Engineering, U of Kentucky

Abstract: Characterization of tissue blood flow, oxygenation and oxidative metabolism is important for the diagnosis and therapeutic assessment of vascular/cellular diseases. Our group has recently developed a portable and relatively inexpensive diffuse correlation spectroscopy (DCS) flow-oximeter for simultaneous quantification of relative changes of blood flow (rBF) and oxygenation (Δ[oxygenation]). This study reports a novel noncontact DCS flow-oximeter which can measure both rBF and Δ[oxygenation] without distorting tissue hemodynamics. The noncontact probe built with optical lenses was compared against a contact probe in tissue-like liquid phantoms and forearm muscles (n = 10). Both rBF and Δ[oxygenation] responses in forearm muscles during 5-minute arterial occlusion measured by the two probes were highly correlated, and the magnitudes of rBF responses were also highly consistent. However, the magnitudes of Δ[oxygenation] measured by the noncontact probe were significantly lower than those measured by the contact probe (regression slope = 0.44 ± 0.12 < 1). Monte Carlo (MC) simulations and phantom experiments revealed that the forearm curvature caused a significant underestimation (~-20%) for the noncontact measurements in Δ[oxygenation], but not in rBF. The underestimation was corrected using a MC-based calibration algorithm. The calibrated regression slopes (0.56 ± 0.10) were significantly higher than the original slopes (0.44 ± 0.12). Further comparisons with other established technologies are needed to identify other factors for the residual discrepancies. Nevertheless, our research paves the way for simultaneous and noncontact monitoring of blood flow and oxygenation in soft (e.g., breast) and vulnerable (e.g., ulcerous) tissues without distorting tissue hemodynamics.

Supported by: NIH award: R01-CA149274, R21-AR062356 and UL-1RR033173 and pilot funding from UK Center for Clinical and Translational Science

Primary Presenter / e-mail: Y. Lin / yu.lin@uky.edu
Mentor or Senior Author / e-mail: G. Yu / guoqiang.yu@uky.edu

#158 Abstract Title: **Integration of Diffuse Optical Spectroscopies with Muscular Stimulator for Noninvasive Evaluation of Electrical Stimulation Impacts on Muscle Hemodynamics**

Author(s):
Y. Shang, Center for Biomedical Engineering, University of Kentucky
Y. Lin, Center for Biomedical Engineering, University of Kentucky
B.A. Henry, Center for Biomedical Engineering, University of Kentucky
R. Cheng, Center for Biomedical Engineering, University of Kentucky
C. Huang, Center for Biomedical Engineering, University of Kentucky
K.R. Swartz, Department of Neurosurgery, University of Kentucky
S.S. Salles, Department of Physical Medicine and Rehabilitation, University of Kentucky
G. Yu, Center for Biomedical Engineering, University of Kentucky

Abstract: Electrical stimulation (ES) can promote muscle blood flow and oxygenation. However, muscle hemodynamics during ES is rarely measured due to the lack of appropriate technologies. This study integrated a muscular stimulator with a DCS (diffuse correlation spectroscopy) flow-oximeter to noninvasively evaluate hemodynamic improvements in skeletal muscle created by ES at different frequencies. Ten healthy volunteers participated in this study. The subject laid supine on bed, and a muscular stimulator delivered biphasic electrical current to right leg quadriceps muscle via a pair of electrodes. Two fiber-optic probes connected to a novel custom-made DCS flow-oximeter were taped on both legs to monitor muscle blood flow and oxygenation. To minimize motion artifacts of muscle fibers during ES, optical data were only recorded at the time points of muscle fiber relaxation judged by the output current from the muscular stimulator. ES at 2, 10 or 50 Hz were applied for 20 minutes on each subject in 3 days sequentially, and muscle hemodynamics was monitored continuously throughout ES. Muscle blood flow was significantly elevated during and after ES. At 20-minute post ES, blood flow increases with 2, 10 and 50 Hz stimulations were 71.5 ± 19.8%, 74.4 ± 16.2%, and 63.1 ± 19.7%, respectively. However, only ES at 10 Hz created a large and significant increase in oxy-hemoglobin concentration (5.0 ± 1.9 μM, p = 0.03). Our results indicate that ES at medium frequency (i.e., 10 Hz) improves both muscle blood flow and oxygenation efficiently. This study demonstrates the potential of diffuse optical technologies in the evaluation of ES treatments for diseases caused by poor muscle blood circulation and oxygenation (e.g., pressure ulcer).

Supported by: NIH award: R21 AR062356-01

Primary Presenter / e-mail: Y. Shang / yu.shang@uky.edu
Mentor or Senior Author / e-mail: G. Yu / guoqiang.yu@uky.edu

#159 Abstract Title: A Near-infrared Broadband Spectroscopy for Tissue Blood Oxygenation Measurement

Author(s):
Y.Qin, College of Engineering, U of Kentucky & Shenyang Ligong University, China
X.Luan, College of Engineering, U of Kentucky & Dalian Stomatological Hospital, China
S.Yu, College of Engineering, U of Kentucky
C.Huang, College of Engineering, U of Kentucky
Y.Hou, College of Engineering, U of Kentucky & Shenyang Ligong University, China
G.Yu, College of Engineering, U of Kentucky

Abstract: Near-infrared spectroscopy (NIRS) is a noninvasive method allowing for the measurement of tissue blood oxygenation via detecting light absorption and scattering in the tissue. Continue-wave (CW), frequency-domain (FD) and time-resolved methods with limited number of near-infrared wavelengths have been used to extract tissue optical properties. Some of these methods require large and expensive instrumentation (e.g., FD and time-resolved), and more wavelengths would generate more accurate measurement results. As a portable and inexpensive alternative, a broadband CW spectroscopy has been recently built in our laboratory to detect the tissue absorption coefficient μa, reduced scattering coefficient μs' and tissue blood oxygen saturation (StO2). This system consists of a halogen lamp for light emission and a spectrometer for light detection. The halogen lamp emits broadband light into the tissue and the reflected light traveling through the tissue is collected by the spectrometer via source and detector fibers placed on the tissue surface millimeters to centimeters apart. The μa, μs' and StO2 are calculated by fitting the measured light intensities at the broadband of 600-800 nm to an analytical solution of photon transport equation in a homogeneous tissue with semi-infinite geometry. The system has been tested in human forearm tissues, and the measured StO2 values agree well with those quantified by a commercial FD NIRS device (Imagent, ISS, IL). Varying the source-detector separation from 0.8 to 1.2 cm has minor influence on the optical measurements. Upcoming study will apply this system in different types of tissues with different oxygen levels for diagnostic purposes.

Supported by:
Primary Presenter / e-mail: Y.Qin / yanli.qin@uky.edu
Mentor or Senior Author / e-mail: G.Yu / guoqiang.yu@uky.edu

#160 Abstract Title: Chronic Non-Cancer Pain and Six-Month Follow-Up Outcomes Among Community-Based Opiate Addiction Treatment Clients on Methadone.

Author(s):
E. Stevenson, Center on Drug and Alcohol Research, U of Kentucky
A. Northcutt, Center on Drug and Alcohol Research, U of Kentucky

Abstract: Individuals who seek medication-assisted treatment for opiate addiction are generally prescribed methadone at a licensed opiate treatment program (OTP). For OTP clients who also have chronic non-cancer pain (CNCP), the disease of addiction is treated, but the disease of CNCP may not be addressed. The link between opioid dependence and CNCP may seem obvious since opioids produce both analgesia and euphoria, yet limited data is available on their co-occurrence and the impact on treatment outcomes. This study hypothesized correlations between CNCP and poor 6-month follow-up outcomes among a sample of individuals taking methadone as part of medication-assisted treatment at an OTP. Analyses compared 115 individuals with CNCP to 470 without CNCP, all of whom completed a structured baseline interview between March 2007 and December 2010 and a matching follow-up interview. ANOVA results found no differences between groups arrests at follow-up. CNCP cases reported greater average number of past 30 day use of non-prescribed methadone at follow-up (.92) compared to non-CNCP cases [.17; F (1) =10.005, p<.01]. Crosstab analyses found a lower percentage of CNCP compared to non-CNCP clients were employed at follow-up (58.2% vs. 71.5%, p<.01). More CNCP cases than non-CNCP cases reported depression (22.0% vs. 13.3%; p<.05) or anxiety (39.6% vs. 23.6%; p<.01) at follow-up. For patients with CNCP, co-occurring disorders would certainly counter the recovery efforts of MAT. Addressing co-occurring issues like pain and/or mental health problems will be important for MAT programs to successfully help patients learn to manage their health conditions and maintain sobriety.

Supported by: Kentucky Department of Behavioral Health
Primary Presenter / e-mail: A. Northcutt / jano222@uky.edu
Mentor or Senior Author / e-mail: E. Stevenson / erin.stevenson@uky.edu

#161 Abstract Title: Risk Factors Associated with Fatal Child Maltreatment

Author(s): Adrienne Whitt-Woosley, Center on Trauma and Children, Department of Psychiatry, U of Kentucky
Ginny Sprang, Center on Trauma and Children, Department of Psychiatry, U of Kentucky

Abstract: Awareness of cases of fatal child maltreatment has risen significantly in recent years suggesting the presence of a serious threat to young children despite complex child welfare, clinical and legal responses to the issue. The purpose of this study was to identify differences between high risk child maltreatment and fatal risk cases and associated child protective service efforts. For this study, 50 cases of fatal and near fatal child maltreatment and 50 comparison cases were analyzed using quantitative and qualitative methods to assess risk factors selected according to a transactional model of child maltreatment. Recognition of the combination of having a male perpetrator, in cases of physical abuse, in families with one to two children living in more rural environments notably improved the odds of predicting fatal risk cases. Descriptions of perpetrators, target children and associated patterns of service provision were also reported on to support early intervention and more proactive child protection measures.

Supported by: UK Center on Trauma and Children
Primary Presenter / e-mail: A. Whitt-Woosley / alwhit4@uky.edu
Mentor or Senior Author / e-mail: A. Whitt-Woosley / alwhit4@uky.edu

#162 Abstract Title: Hepatitis C Viremia and Genotype among Nonmedical Prescription Drug Users in Rural Appalachia

Author(s): A. M. Young, Department of Behavioral Science, U of Kentucky College of Medicine
R. A. Crosby, College of Public Health, Department of Health Behavior, U of Kentucky
C. B. Oser, Department of Sociology, U of Kentucky
C. G. Leukefeld, Behavioral Science and Center on Drug and Alcohol Research, U of Kentucky
D. B. Stephens, Department of Behavioral Science, U of Kentucky College of Medicine
J. R. Havens, Behavioral Science and Center on Drug and Alcohol Research, U of Kentucky

Abstract: Introduction: 54% of a large cohort of injection drug users (IDUs) in rural Eastern Kentucky were recently found to be HCV-seropositive. HCV genotype is a robust predictor of both hepatic disease progression and response to pharmacotherapy. Individuals at high risk for infection, such as IDUs, are typically less likely to be screened and treated for HCV. With advances in pharmacotherapy, evidence indicates that treating even active IDUs can be efficacious and cost-effective. However, HCV treatment is plagued by poor uptake and adherence, with pronounced barriers in low-income rural areas like Appalachia. This exploratory study examines HCV viremia, viral load, and genotype in a sample of HCV-seropositive nonmedical prescription drug users in rural eastern Kentucky. Methods: The study sample (n=81) was randomly selected from a pool of 200 HCV-seropositive participants in a longitudinal study of rural drug users. Participants were tested serologically for HCV RNA, viral load, and genotype; behavioral and demographic data were collected by questionnaire. Results: 56 participants (69%) tested RNA-positive, indicative of active infection, and 48 (59%) had viral loads exceeding 800,000 IU/ml. Among RNA+ participants, 66% had genotype 1a; types 2b (16%) and 3a (13%) were less common. Discussion: Highly prevalent active infection in this cohort highlights a growing public health crisis and a need for increased focus on prevention, screening, and treatment in rural populations. Widespread HCV genotype 1a foreshadows heightened burdens of cirrhosis, hepatocellular carcinoma, and healthcare expenditure in the absence of HCV treatment. Further study is needed to better characterize the HCV epidemic in this “hidden” rural population.

Supported by: National Institute on Drug Abuse: Grant R01DA024598; Centers for Disease Control and Prevention: Grant 1U48DP001932-01; National Institute on Drug Abuse (to Dr. Oser): Grant K01DA021309; CCTS T32 Training Grant TL1RR033172 (to D. B. Stephens). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.
Primary Presenter / e-mail: D. B. Stephens / dbst222@uky.edu
Mentor or Senior Author / e-mail: J. R. Havens / jhave2@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#163 Abstract Title: Factors Effecting End of Treatment Symptom Severity for Children Receiving Trauma-Informed Evidence-Based Treatment

Author(s): J. G. Eslinger, Center on Trauma and Children, U of Kentucky
G. Sprang, Center on Trauma and Children, U of Kentucky

Abstract: The purpose of this presentation is to discuss the moderating effects of treatment type on the traumatic stress and behavioral outcomes of children ages 2 -12 receiving trauma-informed evidence –based interventions. Method: Caregivers and children receiving outpatient services (N=134) completed the Child Behavioral Checklist, Trauma Symptom Checklist for Young Children, and the Trauma Symptom Checklist for Children-Alternate Version at baseline and end of treatment. A series of ANCOVA analyses were conducted to examine the relationships between a child's gender, guardianship status, type of treatment received, number of different types of traumas, child age, and end of treatment scores on the above mentioned measures. Results: While statistically significant improvements were found between all baseline and termination outcome scores regardless of treatment type, TF-CBT was found to more successfully reduce externalizing and total problem scores at termination compared to PCIT. Despite the relatively young age of this sample, older age was found to be predictive of elevated externalizing and total problem scores on the CBCL. Implications: Trauma recovery is dependent upon successful matching of client characteristics and need to treatment type. The implications of these findings will be discussed with specific recommendations on how clinicians can achieve this goal.

Supported by: SAMHSA grant # 2 U79SM058230-06 Sprang-PI
Primary Presenter / e-mail: J. G. Eslinger / j.g.eslinger@uky.edu
Mentor or Senior Author / e-mail: G. Sprang / sprang@uky.edu

#164 Abstract Title: Trait Impulsivity, Behavioral Disinhibition, Arousal, and Risky Sexual Behavior

Author(s): K. J. Derefinko, Department of Psychology, University of Kentucky
J. R. Peters, Department of Psychology, University of Kentucky
T. A. Eisenlohr-Moul, Department of Psychology, University of Kentucky
E. C. Walsh, Department of Psychology, University of Madison-Wisconsin
D. R. Lynam, Department of Psychological Science, Purdue University, West Lafayette, Indiana

Abstract: The current study examined how impulsivity-related traits (as assessed by the UPPS impulsivity scale), laboratory measures of impulsivity, and psychophysiological arousal and reactivity relate to risky sexual behaviors in undergraduate men. Correlations indicated that sensation seeking was related to a high number of sexual partners, and ever having engaged in sex with a stranger. In contrast, negative and positive urgency were related to lack of condom use, although partial relations (controlling for other facets of impulsivity) indicated this relation was uniquely related to negative urgency. Correlations between risky sexual outcomes and psychophysiological arousal and laboratory tasks of disinhibition were in expected directions; low resting arousal and tasks of disinhibition were associated with active pursuit of new and different partners, whereas skin conductance reactivity to unpleasant stimuli was associated with lack of condom use. These findings indicate that low arousal individuals who continue to pursue rewards even at risk of punishment are more likely to also engage in risky sexual partner acquisition, whereas individuals who are physiologically reactive to unpleasant stimuli and act impulsively under conditions of negative affect are less likely to use condoms. These findings add to the current understanding of the divergence between different risky sexual behaviors, and may lend utility to the development of individualized HIV prevention programming.

Supported by: This research was supported by grants from the National Institute on Drug Abuse (DA005312 and DA007304)
Primary Presenter / e-mail: K. J. Derefinko / kjdere2@uky.edu
Mentor or Senior Author / e-mail: R. Milich / milich@email.uky.edu

#165 Abstract Title: Recognition of Depression: A literature review

Author(s): K. M. Dekker, College of Nursing, U of Kentucky
R. L. Dekker, College of Nursing, U of Kentucky

Abstract: Background: Depression, a prevalent mood disorder, is linked with chronic illnesses and related negative health outcomes. Currently, no practice guideline for depression screening in chronically ill patients exists. Screening relies on nurse intuition. This becomes problematic if nurses are unable to assess for depression without the use of a depression scale. This could result in underdiagnoses of depression, and increased negative patient outcomes. Purpose: To systematically review the literature and determine whether nurses' ability to recognize depression in chronically ill patients with and without the use of a depression screening tool. Methods: In 2012, we searched PubMed and CINAHL using the key words 1) "nurse" AND "recogni*" AND "depression", and 2) "nurse" AND "identify" AND "depression". Studies were included if they compared nurse recognition of a patient's depression status to the use of a depression screening instrument. We limited studies to those that enrolled adults (inpatient and outpatient) with a medical condition such as cancer, chronic pain, diabetes, heart disease, multiple sclerosis, Parkinson's disease, or stroke. We excluded articles related to pediatric and perinatal depression. Results: Nine articles met the criteria and were included in the review. Results from all of the studies demonstrated that nurses and medical staff were unable to successfully identify depression without the use of a formal screening tool. When no screening tool was used, nurses were only able to identify 23% of adults with depression in the community setting, 43% of adults with depression in hospitals, and 48% of depressed adults in nursing homes. The majority of depression cases were not recognized by nurses, doctors, and social workers. However, nurses can be trained to effectively screen for depression using formal screening instruments. Conclusion: Depression negatively influences many adults, especially those with chronic illnesses. Screening for depression using a standardized tool, is an inexpensive and reliable means of identifying individuals with depression. Once diagnosed, there are multiple treatments that available to improve individual quality of life and disease outcome.

Supported by:
Primary Presenter / e-mail: K. M. Dekker / kmde222@uky.edu
Mentor or Senior Author / e-mail: R. L. Dekker / rebecca.dekker@uky.edu

#166 Abstract Title: The Effect of Prior Month Marijuana Use on Marijuana Self-Administration in the Laboratory

Author(s): M. M. Freeman, Department of Behavioral Science, U of Kentucky
D. C. Lee, Department of Psychology, U of Kentucky
J. A. Lile, Department of Behavioral Science, U of Kentucky
C. A. Martin, Department of Psychiatry, U of Kentucky
T. H. Kelly, Department of Behavioral Science, U of Kentucky

Abstract: Previous research indicates that subjective and performance effects of THC differ depending on the frequency of prior marijuana use. However, it is unclear if frequency of marijuana use predicts drug-taking behavior. This study tested the hypothesis that marijuana self-administration would vary as a function of recent (past month) use frequency. Forty healthy volunteers completed an 8-session, randomized, double-blind study consisting of four 2-session test blocks. During the first session of each block, subjects received 8 uniform puffs from a cigarette containing THC (0, 1.75 or 3.5%). During the second session of each block, subjects could earn up to 8 puffs of marijuana containing the previously sampled THC concentration on a modified progressive-ratio procedure. The first puff was earned by completing 50 responses, and the response requirement for each subsequent puff was doubled, such that 12,750 responses were required to earn all 8 puffs. Verbal-report, performance and cardiovascular assessments were completed before, and hourly for 4 hours after smoking. Results indicated that the change in the number of puffs of the higher THC concentration earned (3.5% - 0%) was positively correlated (r=0.38) with frequency of marijuana use in the month prior to screening. In addition, when subjects were divided into a median split based upon use frequency, more frequent use was associated with higher ratings of like drug, take again, and pay for drug at active THC concentrations. These results validate the use of a modified progressive-ratio procedure to examine the reinforcing effects of marijuana in the laboratory, while also demonstrating that frequent marijuana use in the natural environment is associated with increased self-administration in a laboratory environment.

Supported by: Supported by DA-05312 and RR-15592
Primary Presenter / e-mail: M. M. Freeman / megan.freeman@uky.edu
Mentor or Senior Author / e-mail: T. H. Kelly / thkelly@email.uky.edu

#167 Abstract Title: **Sex Differences in Trait Mechanisms of Childhood Attention-Deficit/Hyperactivity Disorder (ADHD) Comorbidity**

Author(s): M.M. Martel, Department of Psychology, U of Kentucky

Abstract: ADHD is a common and impairing disorder that affects boys three times as often as girls with striking sex differences in associated comorbidity. Yet, explanations for these sex differences remain in short supply. The aim of the present study was to evaluated dispositional traits are one possible mechanism of these effects. Hypotheses were that dispositional traits would differentially mediate associations between ADHD and commonly comorbid childhood problems based on child sex (i.e., moderated mediation). Participants were 109 children ages 3 to 6 (M=5.22;59% male) and their families. ADHD, ODD, and CD child clinical symptoms were assessed using parent-rated symptoms on the Disruptive Behavior Rating Scale and Child Behavior Checklist. Child receptive language problems were assessed using the Peabody Picture Vocabulary Test-4. Dispositional traits were measured from examiner report on the California Q-Sort. Based on moderated mediation analyses using bootstrapped indirect effect mediation tests, negative emotionality significantly partially mediated the association between ADHD and ODD symptoms for girls (boot z=2.12,p=.04), but not boys (boot z=.57,p=.57). Disagreeableness significantly partially mediated the association between ADHD and CD symptoms in boys (boot z=2.32,p=.02), but not girls (boot z=.75,p=.45). Low conscientiousness significantly partially mediated the association between ADHD symptoms and language problems in boys (boot z=-1.96,p=.05), but not girls (boot z=-.69,p=.49). Thus, temperament traits explain comorbidity between ADHD and other common childhood disorders in a sex-specific manner. Early assessment of child traits may be able to inform early intervention strategies that can be personalized based on child sex.

Supported by: This research was supported by National Institute of Health and Human Development Grant 5R03 HD062599-02 to M. Martel. I am indebted to the families who made this study possible.

Primary Presenter / e-mail: M. M. Martel / michelle.martel@uky.edu

Mentor or Senior Author / e-mail: M. M. Martel / michelle.martel@uky.edu

#168 Abstract Title: **Conviction Celerity and Rehabilitation Compliance as Predictors of DUI Recidivism: A Mediation Model of Deterrence**

Author(s): M.F. Dickson, Department of Sociology & Center on Drug and Alcohol Research, U of Kentucky
J.M. Webster, Department of Behavioral Science & Center on Drug and Alcohol Research, U of Kentucky

Abstract: Driving under the influence (DUI) is one of the most frequently committed offenses in the United States and approximately one-third of DUI offenders are recidivists. Researchers have evaluated multiple DUI prevention approaches, most of which have been rooted in deterrence theory. Recently, the criminal justice system has moved away from deterrence-based approaches only and begun employing various forms of rehabilitation to reduce DUI recidivism. This shift in the criminal justice system has lead researchers to also begin exploring the effects of rehabilitation on DUI offenders, including an examination of offender compliance with rehabilitation programs. Whereas each of these areas has been investigated separately, existing studies have not incorporated deterrence-related measures, rehabilitation compliance, and offender recidivism into a single model. Utilizing a statewide sample of Kentucky DUI offenders, the current study examines whether rehabilitation compliance mediates the relationship between conviction celerity and DUI offender recidivism. In addition, bivariate analyses were conducted to explore differences between first time and repeat DUI offenders. Repeat offenders were significantly more likely to be male, report a substance use problem, and comply with treatment recommendations. Mediation analyses revealed that, although conviction celerity was not directly correlated with recidivism, there was a significant indirect effect mediated by rehabilitation compliance. Findings suggest that compliance may be a more accurate predictor of DUI recidivism than deterrence-based variables, demonstrating a need for the criminal justice system to place more emphasis on treatment accessibility and retention of DUI offenders in order to decrease DUI recidivism.

Supported by: Data used for this project was collected as part of a contract with the Kentucky Division of Behavioral Health.

Primary Presenter / e-mail: M.F. Dickson / megan.dickson@uky.edu

Mentor or Senior Author / e-mail: J.M. Webster / matt.webster@uky.edu

#169 Abstract Title: Non-fatal Overdose among Appalachian Probationers with a History of Nonmedical Prescription Drug Use

Author(s): PK Elliston, Center on Drug and Alcohol Research, College of Public Health, U of Kentucky
J.M. Webster, Behavioral Science, Center on Drug and Alcohol Research, U of Kentucky
C. Leukefeld, Behavioral Science, Center on Drug and Alcohol Research, U of Kentucky

Abstract: Nonmedical use of prescription drugs is now considered to be an epidemic, especially in the Appalachian region of the United States. Both fatal and non-fatal overdose involving nonmedical use of prescription drugs has increased steadily over the past ten years, although non-fatal overdose is more prevalent. Predictors of non-fatal overdose include injection drug use and polysubstance use, which are behaviors commonly reported for criminal justice populations. As a result, researchers have examined overdose in criminal justice populations. Periods of abstinence due to incarceration or treatment may lower tolerance and increase risk of overdose among this group. Previous studies have focused on nonmedical use of prescription drugs among rural offenders and non-fatal overdose among recently released prisoners in an urban area but none to our knowledge have investigated non-fatal overdose among Appalachian probationers. The current study examines the correlates of non-fatal overdose among a sample of Appalachian probationers with a history of nonmedical use of prescription drugs (N=613). Analyses revealed that probationers reporting a non-fatal overdose were similar on demographic characteristics, substance use, and incarceration history to those who did not report a non-fatal overdose. However, probationers reporting a non-fatal overdose were more likely to be injection drug users (48.2% vs. 20.0%), report a higher number of mental health issues (2.82 vs. 1.98), and higher scores for trauma (60.30 vs. 48.91) and impulsive behavior (9.34 vs. 7.38). These data suggest that probationers with injection drug use histories and mental health issues may benefit from targeted overdose prevention programming during community supervision.

Supported by: NIDA grant R01 DA13076
Primary Presenter / e-mail: PK Elliston / pk.elliston@uky.edu
Mentor or Senior Author / e-mail: J.M. Webster/C. Leukefeld / webster@uky.edu

#170 Abstract Title: A Pilot Investigation of Tobacco-free Policy Noncompliance

Author(s): R. A. Record, College of Communication and Information, U of Kentucky

Abstract: Although the US smoking rate has been declining, the average smoking rate on college campuses has remained around 20%. Outdoor tobacco-free policies (OTP) are an effective strategy for reducing smoking rates and increasing cessation attempts. However, these policies are only effective if they are complied with. Guided by the EPPM, the purpose of this study was to investigate the public health problem of OTP noncompliance. H1 expected smokers and nonsmokers to differ in their EPPM stage of control. RQ1 investigated what factors predicted outdoor tobacco-free policy noncompliance. RQ2 investigated why smokers chose to either comply or not comply with the policy. One hundred and eleven participants were recruited using a quota sample to obtain 75% smokers. Participants were students, employees, and visitors on the campus. Hypothesis one was supported [$t(109) = 5.75$, $p < 0.001$]. A regression model was built to investigate RQ1. The selected model of best fit significantly explained 26% of the variation in average number of weekly policy violations ($p < .05$). To investigate the third research question, qualitative data was collected. Three themes were found for smokers who do not comply with the policy (i.e., personal rights, addiction, and lack of enforcement) and three for smokers who do comply with the policy (i.e., respect for others, fear of job loss, and sense of control). With a greater sample size, personal characteristics, nicotine dependence, and cessation factors are expected to more strongly predict tobacco-free policy noncompliance. A greater understanding of OTP noncompliance provides direction for future campaign research aimed at increasing compliance.

Supported by:
Primary Presenter / e-mail: R. A. Record / rachael.record@uky.edu
Mentor or Senior Author / e-mail: R. A. Record / rachael.record@uky.edu

#171 Abstract Title: **Risk Behaviors Among IV Drug-Using and Non-IV Drug Using Pregnant and Post-Partum Women in Residential Treatment**

Author(s):
S. L. Biermann, College of Social Work, U of Kentucky
M. Staton-Tindall, College of Social Work, U of Kentucky
C. Yates, Chrysalis House

Abstract: Drug use among pregnant and post-partum women (PPW) is especially concerning, particularly when the women are IV-drug users. The purpose of this presentation is to examine the differences in drug use and sexual risk behaviors between IV- and non-IV-drug using pregnant and post-partum women who have recently entered residential treatment. As part of an ongoing CSAT-funded evaluation of enhanced services provided to pregnant and post-partum women at a residential drug treatment program, face-to-face interviews were conducted with 34 women. Data were collected on topics including drug use and risky sex behaviors. Of the 34 women who consented to the evaluation between August 2012 and February 2013, 19 (55.9%) report ever injecting drugs with a needle while 15 (44.1%) report that they had never injected. The IV-drug-using women were more likely than the non-IV-drug-using women to report more risky sex behaviors including having unprotected sex with IV-drug users (58% IV drug users compared to 6% non-IV drug users). IV-drug using women also reported significantly more days of heroin use, (t= -3.502, p=.0032) and Oxycotin use (t= -2.438, p=.022) compared to non-injectors. These findings have significant implications for women's treatment. Given that IV-drug-using women engage in high-risk behaviors that increase their chances of bloodborne diseases like HIV and HCV, it may be important to implement educational interventions into residential treatment programs. These interventions may be especially important if women have children who could also be influenced by these behaviors.

Supported by: SAMHSA/CSAT award: TI023674-01
Primary Presenter / e-mail: S. L. Biermann / s.leukefeld@uky.edu
Mentor or Senior Author / e-mail: M. Staton-Tindall / mstindall@uky.edu

#172 Abstract Title: **Examination of Appalachian vs. non-Appalachian Assertive Adolescent and Family Treatment Participant Characteristics from 2006 to 2012**

Author(s):
T. Gill, University of Kentucky
E. Stevenson, University of Kentucky
D. Parrish, University of Kentucky
A. Northcutt, University of Kentucky

Abstract: Four cohorts of Center on Substance Abuse Treatment funded Assertive Adolescent and Family Treatment (AAFT) grantee sites collected Global Assessment of Individual Needs (GAIN) baseline data on participating youth between 2006 and 2012. A concatenated secondary dataset was obtained to examine similarities and differences in Appalachian vs. non-Appalachian youth participating in this treatment project. The hypothesis was youth in Appalachian regions would report different drug use patterns and less juvenile justice involvement than non-Appalachian youth. Data were divided into two groups to specifically compare Appalachian (n=250) with non-Appalachian (n=4220) youth ages 11-25. Bivariate comparisons were made on gender, age, race, juvenile justice involvement, mental health, and substance use. Crosstab analyses examined statistical variation between the groups on each variable. Findings included no age or gender distribution differences. Appalachian sites were predominately White (82.0%). Only 28.4% of non-Appalachian participants were White, 16.5% were African-American, and 33.7% were Hispanic. Fewer Appalachian youth were involved in juvenile justice compared to non-Appalachian youth (0.4% vs. 2.1%, p<.05). Significantly fewer Appalachian youth had been in prior substance abuse treatment compared to non-Appalachian youth (28.9% vs. 35.6%, p<.05). There were no differences between the two groups in diagnosed behavioral or emotional disorders. Less than 2% of both groups reported injection drug use. Counselors at intake to treatment identified the most severe substance problem for Appalachian youth compared to non-Appalachian youth was alcohol abuse (21.2% vs. 14.9%, p<.001) and opioid use (8.0% vs. 1.4%, p<.001). Understanding drug use patterns can help focus prevention, treatment, and recovery efforts.

Supported by: SAMHSA/ CSAT
Primary Presenter / e-mail: T. Gill / tagill3@g.uky.edu
Mentor or Senior Author / e-mail: E. Stevenson / erin.stevenson@uky.edu

#173 Abstract Title: Assessing the Risk of Bleeding Complications after Tracheotomy for Patients Taking Anticoagulants

Author(s): E. Alimova, College of Medicine, U of Kentucky
E. Van Meter, Department of Statistics, U of Kentucky
R. K. Aouad, Department of Otolaryngology, U of Kentucky

Abstract: Objective: Tracheotomies have been performed routinely for a variety of reasons since 1909. A large proportion of these have to be performed without the benefit of time to modify patient medications prior to the procedure. Many of the patients undergoing tracheotomies are regularly taking anticoagulants with a potential risk of increased bleeding intra- and post-operatively. Currently, there is no published evidence concerning the difference in the risk of bleeding complications in patients who are taking anticoagulants and those who are not; therefore, we conducted this research study. Method: A retrospective chart review of 100 patients who underwent a tracheotomy procedure at the University of Kentucky within the last 8 years was conducted. Multiple parameters were recorded and they included age, sex, comorbid conditions, anticoagulation status and type of anticoagulant, bleeding outcome (intra-operatively and post-operatively) and size of tracheotomy tube. Results: Our study looked at 100 patients (mean age 60.7 years), 54 men (54%) and 46 women (46%). 38 patients (38%) were on anticoagulants at the time the procedure was performed while 62 patients (62%) were not. One patient on anticoagulation therapy (2.63%) and two patients not on anticoagulation therapy (3.23%) experienced bleeding complcations. Statistical analysis didn't show any significant difference between our 2 groups, despite the relatively the small number of patients included in the study. Conclusion: The risk of bleeding in patients who underwent a tracheotomy procedure didn't significantly increase with anticoagulation at the time of their surgery. We are currently looking for any potential associations of the risk of bleeding with a number of other variables (above) and are also reviewing more charts to increase our sample size to give more power to our analysis.

Supported by: Professional Student Mentored Research Fellowship Grant, CCTS, U of Kentucky.
Primary Presenter / e-mail: E. Alimova / ealim2@uky.edu
Mentor or Senior Author / e-mail: R. K. Aouad / rony.aouad@uky.edu

#174 Abstract Title: Symptom Validity Effects in Neuropsychological Evaluation of Veterans

Author(s): J. P. Harp, Lexington VAMC and Department of Psychology, U of Kentucky
A. L. Shandera-Ochsner, Lexington VAMC and Department of Psychology, U of Kentucky
M. S. Edmundson, Lexington VAMC and Department of Psychology, U of Kentucky
D. T. R. Berry, Department of Psychology, U of Kentucky
T. L. Pape, Edward J. Hines, Jr. Veterans Affairs Hospital
J. L. Babcock-Parziale, Southern Arizona Department of Veterans Affairs Healthcare System
R. E. Schleenbaker, Lexington VAMC and Dept of Physical Medicine and Rehabilitation, U of Kentucky
W. M. High, Jr., Lexington VAMC, Physical Medicine and Rehabilitation, Psychology, and Neurosurgery, U of Kentucky

Abstract: Objective: To determine the association between standalone symptom validity testing and embedded self-report validity indices, and to describe their effects on neuropsychological test performance and their association with diagnostic classification of TBI and PTSD. Participants and Methods: OIF/OEF combat veterans (N=438) were recruited by telephone, mailer, and clinical contact at VA medical centers to complete structured interviews for TBI (SITDOV) and PTSD (CAPS) and neuropsychological testing. Testing included measures of psychiatric symptoms (MMPI-2-RF), attention (CPT-II), verbal memory (CVLT-II), processing speed (WAIS-IV PSI), and executive functions (D-KEFS Trail Making, Verbal Fluency; WCST). Symptom validity was assessed using the standalone Letter Memory Test (LMT) and embedded validity indices (VRIN-r, TRIN-r, F-r, and Fp-r) from the MMPI-2-RF. Results : LMT failure was modestly but significantly associated with MMPI-2-RF symptom exaggeration (φ-sq = .04, χ-sq(1) = 63.50, $p < .001$) but not with content non-responsive invalidity (VRIN-r and TRIN-r). Failure of any validity indicator predicted worse performance on cognitive testing, with large (DKEFS trail making), medium (category fluency, CVLT-II, CPT), and small effects (WCST, letter fluency) across domains ($F(1,437)$, $p < .01$). Validity indicator failure was modestly associated with diagnosis of TBI (φ-sq = .04 , χ-sq(1) = 17.37, $p < .001$) and PTSD (φ-sq = .13, χ-sq(1) = 45.91, $p < .001$). Conclusions : While performance-based symptom validity was related to self-report validity, the two modalities were largely independent and may not measure a unitary construct in this population. Symptom invalidity indicated in either modality predicted worse performance on neuropsychological tests, often reaching clinical significance. Symptom invalidity was also related to diagnoses of TBI and PTSD. These findings suggest that symptom validity testing may provide incremental validity to objective neuropsychological testing and structured diagnostic interviews.

Supported by: Funded by U.S. Dept. of Veterans Affairs
Primary Presenter / e-mail: J. P. Harp / jordanharp@gmail.com
Mentor or Senior Author / e-mail: W. M. High, Jr. / whigh2@email.uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#175 Abstract Title: Integrating Community Engagement into Public Health Research

Author(s): K.M. Butler, College of Nursing, University of Kentucky
E.J. Hahn, Colleges of Nursing and Public Health, University of Kentucky

Abstract: The purpose is to describe the process for integrating community engagement into translational public health research. The project is consistent with the principles of community-based participatory research (CBPR) including the formation of an equitable partnership between traditional experts and community members to move a community toward change. A CBPR project designed to motivate rural smokers to think about quitting using culturally targeted materials forms a case study to illustrate the integration of community engagement into the research process. Equitable partnerships were formed with county extension agents, health department personnel, and community members who identified smoking cessation as a common concern. This group designed the research including community members as focus group participants, and utilized focus group themes to create culturally targeted intervention materials. All materials, including a quilt made by local artisans, remained in the community after the project was completed. Selected members were involved in interpreting results and also determined how the results would be used for action. The intervention was considered by community members to be acceptable, practical, and effective. Participants gained recognition in the community which may serve as relapse prevention. Use of CBPR is a data-rich strategy for the development and testing of public health interventions. A major strength of this process is relationship building; in our exemplar community members enthusiastically assumed ownership and took great pride in the process and outcomes. CBPR can be effectively implemented to enrich translational research and improve public health outcomes.

Supported by: 'The development of the HEEL program was made possible by Senator Mitch McConnell with funds earmarked for the University of Kentucky, College of Agriculture, Lexington, KY and budgeted through the CSREES/USDA Federal Administration.' 'The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.'

Primary Presenter / e-mail: K.M. Butler / karen.butler@uky.edu

Mentor or Senior Author / e-mail: E.J. Hahn / ejhahn00@uky.edu

#176 Abstract Title: MMPI-2-RF Clinical Scale Score Comparisons between Genuine PTSD, Feigned PTSD, and Random Responding Groups

Author(s): L. H. Mason, Department of Psychology, U of Kentucky
A. L. Shandera-Ochsner, Department of Psychology, U of Kentucky
J. P. Harp, Department of Psychology, U of Kentucky
K. D. Williamson, Department of Psychology, U of Kentucky
M. Edmundson, Department of Psychology, U of Kentucky
W. M. High, Jr., Physical Medicine and Rehabilitation, U of Kentucky and Lexington VA Medical Center
D. T. R. Berry, Department of Psychology, U of Kentucky

Abstract: The Minnesota Multiphasic Personality Inventory-2 Restructured Form (MMPI-2-RF) was administered to groups consisting of veterans with genuine posttraumatic stress disorder (PTSD), students feigning PTSD, and students randomly responding. Undergraduate students (n=109) were screened for PTSD and randomly assigned to one of four groups: honest, feigned PTSD, half random (RANDhalf), and full random (RANDfull). Veterans (n=31) diagnosed with PTSD were selected from an archival database to develop clinical MMPI-2-RF profiles. Veterans were diagnosed with PTSD using the Clinician Administered PTSD scale (CAPS), took the MMPI-2-RF, and passed a malingering test. ANOVA results showed significant differences between groups on all clinical scales except for RC9 ($p<.01$). The feigned PTSD group obtained the highest mean T score elevations on 7 of 9 clinical scales and had the highest demoralization score (RCd T=77.54). Completely random protocols obtained higher elevations than FAKE PTSD on 2 scales (RC4 and RC6), but obtained comparable elevations to the genuine PTSD group on several scales. Additionally, the honest group's mean elevations remained within the normal range on all clinical scales and were generally lower did the other groups' scores. These results demonstrate that individuals feigning PTSD may be distinctive due to higher scale scores on an overall greater number of scales than other groups. The results show distinct patterns when compared to completely random, partially random, and genuine PTSD groups. These results may allow clinicians to further differentiate feigned PTSD symptoms from clinical PTSD symptoms when combined with validity scale scores.

Supported by: No external funding- some resources and data provided by the Lexington Veterans Affairs Medical Center

Primary Presenter / e-mail: L. H. Mason / lisa.mason13@gmail.com

Mentor or Senior Author / e-mail: David T. R. Berry / dtrb85@gmail.com

#177 Abstract Title: Cough response triggered by hyperventilation of humid hot air in patients with allergic rhinitis

Author(s):
M. Khosravi, Department of Medicine, U of Kentucky
P. B. Collins, Department of Medicine, U of Kentucky
R.-L. Lin, Department of Physiology, U of Kentucky
D. Hayes, Jr,Department of Pediatrics, Ohio State U, Columbus, OH
L.-Y. Lee, Department of Physiology, U of Kentucky

Abstract: Rationale: Transient receptor potential vanilloid type 1 (TRPV1) is a ligand-gated cation channel that is activated by chemical mediators like capsaicin and is found in vagal sensory C fibers in respiratory system and upper airways. TRPV1 is also activated by an increase in temperature (>39°C). We have previously shown activation of TRPV1 by hyperventilation of humid hot air (HA) results in bronchospasm and cough in asthmatics. Inflammation results in upregulation and sensitization of TRPV1 receptors. We hypothesized that sensitization of TRPV1 develops in the upper airways of patients with allergic rhinitis (AR). We designed the following pilot study to test this hypothesis. Methods: Airway resistance (Raw), spirometry indices, and numbers of coughs were recorded prior, during and after the HA challenge in 5 patients (2 male, 3 female) with moderate allergic rhinitis. Isocapnic hyperventilation (40% MVV) of both humidified HA (49°C) and humidified room air (21°C) (RA) for 4 minutes were performed in separate sessions of random order in the same subject. Data are presented as mean ± SEM; and, analyzed by 2-way repeated-measure ANOVA. Results: The HA challenge consistently triggered cough in the AR patients. Number of coughs increased from 0.11 ± 0.1 coughs/min at baseline to 1.89 ± 0.94 coughs/min during and to 1.51 ± 0.9 coughs/min after the isocapnic hyperventilation of HA ($P<0.01$, $n=5$). In contrast, hyperventilation of RA did not cause any significant tussive effect in the same patients: 0.07 ± 0.07 coughs/min at baseline; 0.22 ± 0.16 coughs/min during and 0.17 ± 0.08 coughs/min after the RA challenge. Airway resistance was mildly but significantly increased after the HA in AR patients: Raw = 2.17 ± 0.19 cmH2O/L/sec at baseline; peak Raw = 2.84 ± 0.29 cmH2O/L/sec after HA challenge ($P<0.05$, $n=5$). Conclusions: These data showed that hyperventilation of humid HA triggered vigorous cough response and a mild increase in Raw in AR patients, indicating the involvement of airway sensory nerves, presumably the TRPV1-expressing C-fibers. Also of interest is the relatively small increase in airway resistance in AR patients after the HA challenge, when compared to asthmatics. This implies that activation of airway sensory nerves and the resulting cough or bronchoconstriction is influenced by the location and degree of inflammation in the airways, which may plays a role in modulating sensitization and/or upregulation of TRPV1 receptors. Further investigation to better define the role and mechanism of TRPV1 activation in triggering cough in AR patients is warranted.

Supported by: Supported by Department of Defense TATRC award W81XWH-10-2-0189
Primary Presenter / e-mail: M. Khosravi / mehdi.khosravi@uky.edu
Mentor or Senior Author / e-mail: L. Y. Lee / lylee@uky.edu

#178 Abstract Title: Discerning Cognitive Decline: Comparing Face-to-Face and Telephone Memory Screening

Author(s):
E. Abner, Sanders-Brown Center on Aging, U of Kentucky
A. Caban-Holt, Sanders-Brown Center on Aging/ Department of Behavioral Sciences, U of Kentucky
B. Dennis, Frazier Rehab and Neuroscience Center A. Henderson, Sanders-Brown Center on Aging, U of Kentucky
R. Kryscio, Sanders-Brown Center on Aging/Departments of Biostatistics and Statistics, U of Kentucky
C. D. Lockard, Sanders-Brown Center on Aging, U of Kentucky
M. Matthews, Sanders-Brown Center on Aging/Department of Neurology, U of Kentucky
F. Schmitt, Sanders-Brown Center on Aging/Department of Neurology, U of Kentucky
J. Turner, Sanders-Brown Center on Aging, U of Kentucky
K. Vallance, Sanders-Brown Center on Aging, U of Kentucky
M. N. Westbrook, Sanders-Brown Center on Aging, U of Kentucky
S. H. Wilson, Sanders-Brown Center on Aging, U of Kentucky

Abstract: The Memory Impairment Screen (MIS) is a brief and efficient first-line screening tool for dementia. Previous research has suggested that telephone-based assessments of cognitive status are comparable to face-to-face (FTF) assessments when used for dementia screenings in geriatric populations (Lipton et al., 2003). The aim of this investigation was to determine whether screening modality is associated with performance on the MIS and Memory Impairment Screen-Telephone version (MIS-T). These data, collected from 3,669 older male participants enrolled in an Alzheimer's disease prevention trial, indicate a significantly higher failure rate ($p<.0001$) for phone-based screenings (4.81%) over FTF screenings (1%). Further analysis indicated that, when compared to age and prior score, screening modality was the most influential predictor for failing the MIS. Worsened performance on the MIS-T given age and prior scores indicates screening modalities must be considered when evaluating screening results.

Supported by: PREADViSE is supported by NIA grant 1 R01 AG019241; SELECT is supported by National Cancer Institute Clinical Trials Identifier NCT00076128
Primary Presenter / e-mail: M. N. Westbrook / mwe235@uky.edu
Mentor or Senior Author / e-mail: F. Schmitt / fascom@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#179 Abstract Title: Streamlining deep brain stimulation surgery to provide immediate therapy

Author(s): W. Asfahani, Department of Neurosurgery, U of Kentucky
G. Quintero, Department of Anatomy and Neurobiology, U of Kentucky
C. Van Horne, Department of Neurosurgery, U of Kentucky

Abstract: Background: Deep Brain Stimulation (DBS) is approved for several clinical indications; however, the sequencing of DBS surgery and the timeline for implementing stimulation therapy are under debate. Objective: In this technical note, we describe a sequence for the implantation of DBS systems that we argue is conducive to minimizing patient anxiety and discomfort while shortening the time between implantation and use of the DBS leads for therapeutic management symptoms. Methods: Surgical implantation of DBS leads were performed during two surgical stages. The first surgical stage (Stage I), under general anesthesia, consisted of implanting the pulse generator. In addition, burr holes were placed under imaging-assisted guidance and lead extensions were tunneled, placed under the skin flaps, and in place for the second stage. The second stage (Stage II) was completed from 24 hours to seven days later. During Stage II, the DBS leads were placed into the subthalamic nucleus (STN), ventralis intermedius (VIM) nucleus of the thalamus, or globus pallidus internus (GPi) under local anesthesia. Results: Stage I surgery lasted approximately 90 minutes while stage II surgeries were approximately 230 minutes long. In stage II, patients typically received only local anesthetic during the head frame placement, microelectrode recordings, test stimulations, and patient exams. Normally, DBS therapy was initiated on the same day as lead implantation. Conclusions: Staging DBS surgery in reverse order from the conventional practice provides operative benefits and permits same-day use of DBS therapy after lead implantation.

Supported by:
Primary Presenter / e-mail: W. Asfahani / whslei2@email.uky.edu
Mentor or Senior Author / e-mail: C. Van Horne / craigvanhorne@uky.edu

#180 Abstract Title: An Assessment of Alzheimer's Caregivers in Northeastern Kentucky

Author(s): D. A. Gross, St. Claire Regional Medical Center, Morehead, KY

Abstract: Background: More than 70% of people with Alzheimer's disease live at home, posing special challenges for family caregivers. For instance, studies have found that more than one-third of Alzheimer's caregivers suffer from high levels of stress or depression and that they have poorer self-reported physical health status than non-caregivers. Nationally, most Alzheimer's caregivers are women, aged 55 or older, and have obtained less than a college degree. Methods: We are collaborating with a multi-county Alzheimer's support group and northeastern Kentucky's largest rural hospital to conduct a caregiver needs assessment (e.g., demographic characteristics, health status, service demands). Results: Preliminary data show that the region's Alzheimer's caregivers track national data in terms of gender and age. Three-quarters of respondents would use in-home respite care if it were available, and more than half would utilize adult day care services. The region's caregivers report being in good health (an average of 2.77 on a 5-point Likert scale, with 1 being "excellent health" and 5 being "poor health"), yet more than half of respondents acknowledge they have delayed treatment for their own conditions or have experienced a worsening health condition as a result of the demands associated with caregiving. Conclusions: Northeastern Kentucky's high rate of delayed treatments and worsened conditions among Alzheimer's caregivers is an important finding. It suggests physicians and other health care professionals should consider using Alzheimer's patients' health care encounters as an opportunity to inquire about caregivers' health, diet, and stress levels (i.e., parallel office visits).

Supported by: 2012-'13 UK CCTS Community Engagement Core Community Development Funding
Primary Presenter / e-mail: D. A. Gross / dagross@st-claire.org
Mentor or Senior Author / e-mail: N. E. Schoenberg / nesch@uky.edu

#181 Abstract Title: Assessing the Outcomes of the 2012 College of Medicine Annual Multicultural Health Fair

Author(s):
E.T. Ighodaro, College of Medicine, University of Kentucky
K. Alimova, College of Medicine, University of Kentucky
S. White, College of Medicine, University of Kentucky
A. Wright, College of Medicine, University of Kentucky
H. Knudsen, Department of Behavioral Science, University of Kentucky

Abstract: Since 2000, first year medical students at the University of Kentucky's College of Medicine have organized an annual Hispanic Health Fair that provides free health screenings and medical education for the Hispanic population in the Lexington community. Over the last 11 years, there have been between 200 and 600 participants each year. This year's health fair, "The Multicultural Community Health Fair," The health fair focus is to provide health services, health screenings, and medical education to the uninsured, low-income, and minority populations of the Lexington area. The objective of this research project is to analyze the demographics of health fair participants and its efforts on education and service providing for the community. The preliminary data analysis focuses on the Hispanic population because the target population for past health fairs was the Hispanic population. Our analysis shows that the Hispanic participants were more likely to not have insurance than non-Hispanic participants. Moreover, they were more likely to obtain a blood pressure screening and vision testing from the health fair compared to non-Hispanic participants in the survey. They were also more likely to say that they would utilize the resources offered to them during the health fair. Currently, we are performing more statistical analysis on other ethnic groups that attended the fair. Afterwards, we will be looking that the data to assess the quality of education that the participants received during the fair.

Supported by: PSMRF Program
Primary Presenter / e-mail: E. Ighodaro / etigho2@uky.edu
Mentor or Senior Author / e-mail: H. Knudsen / hkknud2@uky.edu

#182 Abstract Title: Stress and Coping Behaviors among Undergraduate and Graduate Students

Author(s):
J. Brown, University Health Service, University of Kentucky
M. Ickes, Kinesiology and Health Promotion, University of Kentucky
B. Reeves, University Health Service, University of Kentucky
T. Smith, Applied Statistics Lab, University of Kentucky

Abstract: BACKGROUND: Stress affects all college students, however little is known about the differences in stress levels of undergraduates and graduate students, as well as specific coping behaviors used to manage stress. The purpose of this study was to determine stress levels and coping behaviors among college students, considering differences among gender and academic status. METHODS: A random sample of 1,161 students completed an on-line survey designed to describe health behaviors among college students. Students rated their stress level in the last 30 days as none, some, moderate, much, and great deal. Students with no stress were excluded, and much and great deal were collapsed, leaving three categories for comparison. Coping strategies were categorized as healthy or unhealthy. The use of coping strategies for increasing levels of stress was investigated using a Cochran-Armitage test of trend. RESULTS: A total of 1,105 students were used for analysis. Participants were white (85.8%), graduate/professional students (57.5%), and female (58.9%). In the last 30 days, 40% of students indicated much or a great deal of stress, while 36% indicated moderate stress, and 21% some stress. Regardless of gender or student status, food and alcohol were common unhealthy coping strategies, and exercise and sleep were common healthy strategies. Graduate students and females indicated social support as another common healthy strategy, while males indicated hobbies and undergraduates reported pets. CONCLUSION: Considering the high incidence of reported stress, particularly among females and graduate students, intervention strategies should be directed at targeting at-risk groups.

Supported by:
Primary Presenter / e-mail: J. Brown / joanne.brown@uky.edu
Mentor or Senior Author / e-mail: H. Bush / heather.bush@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#183 Abstract Title: Walk Perry County: Establishing Walking Routes in Four Communities

Author(s): J. Williams, Pathfinders of Perry County
K. Knecht, Appalachian Coal Country Team AmeriCorps VISTA, Pathfinders of Perry County

Abstract: Walk Perry County has established and marked four walking routes. Two are in neighborhoods that include low-income housing projects, Walkertown/Highland Heights and East Main Street/Liberty Village. Two routes are in rural communities, Chavies and Buckhorn. The two-mile routes are marked every quarter mile with the distance and the Pathfinders Logo, which is stenciled onto the pavement. Teens from each neighborhood have been instrumental in planning, marking, and promoting the routes. In October, we held a Second Sunday event to celebrate the Liberty Street program, and we will hold another larger event on April 14 to celebrate the entire project. A 2011 study funded by the Robert Wood Johnson Foundation and University of Wisconsin found Perry County ranked 115 out of 120 counties, leading the state in the areas of poor health and premature death. That same study found residents of Perry County have significantly less access to recreational facilities compared to the whole state of Kentucky and the nation. Since then, Kentucky has dropped to rank 119 out of 120. The Ozark Heart Health Project constructed more than 30 walking trails in 8 southeastern Missouri counties in an attempt to reduce the barriers residents face in being physically inactive. The results from their study of community members using the trails showed a significant increase in physical activity. Developing walking routes in 4 Perry County communities and promoting the benefits of their use will not only provide residents with a valuable resource, but will also decrease levels of inactivity in these communities. Walking is an activity that almost anyone can participate in and has many evidence based benefits, such as preventing type 2 diabetes, strengthening the heart, reducing risk of breast and colon cancer, it's good for bones, and alleviating symptoms of depression. During the summer of 2010 Pathfinders conducted a survey in Perry County in which 450 residents were asked if they believed walking and biking paths were important and their likelihood of using such paths if they were available in their communities. Our results show a strong support for walking paths and indicate that if they were available in Perry County, they would be used.

Supported by: 'The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.'

Primary Presenter / e-mail: K. Knecht / karyn@pathperryky.org

Mentor or Senior Author / e-mail: J. Williams / Jenny.Williams@kctcs.edu

#184 Abstract Title: Medical Student Health and Wellness

Author(s): K. Vyas, U of Kentucky College of Medicine
T. Stratton, U of Kentucky College of Medicine
N. Soares, Department of Pediatrics, David Geffen School of Medicine, UCLA

Abstract: Background: Burnout, depression, and anxiety are prevalent among medical students, and they have a higher prevalence of psychological distress when compared to peers. This study explores medical students' perceptions of their own health, and examines these trends across the training continuum. Methods: A cross-sectional electronic survey of first to fourth year medical students at four institutions: University of Kentucky, University of Louisville, Marshall University, and West Virginia University. The 44-item questionnaire included questions on demographics, diet, exercise, sleep, work-life balance, stress, burnout, and awareness and access to support services. Results: A total of 575/1847 electronic forms were received for an overall response rate of 31.1%. First-year ($p = 0.004$) and second-year ($p = 0.001$) students reported significantly higher stress levels than fourth year students. Most students (71.7%) described their current diets as either "healthy" or "very healthy," although fewer first-year students (62.3%) rated the same ($p = 0.02$). Students averaged 6.7 hours of sleep per night and 4.2 hours of exercise per week. The most commonly-cited reasons for not eating healthier foods were related to length of preparation (63.4%) and expense (42.9%). Lack of time was overwhelmingly cited (94.0%) as the most common barrier to getting optimal exercise. Conclusion: Although most medical students perceive their diet, exercise, and sleep habits to be relatively healthy, there was a tendency for first-year students' diet to be significantly more unhealthy and for fourth-year students' perceived stress levels to be significantly lower. There was no difference related to exercise or sleep. This data will guide institutions to improve overall health and wellness education among medical students.

Supported by: The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1RR033173. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Primary Presenter / e-mail: K. Vyas / krishnavyas@uky.edu

Mentor or Senior Author / e-mail: N. Soares / neelsoares@hotmail.com

#185 Abstract Title: **Breathe Easy Perry County Partnership-Media Campaign to Promote Smoke-Free Facililties; Preliminary Findings**

Author(s):
B. Bowling, College of Medicine, U of Kentucky
C. Riker, College of Nursing, U of Kentucky
D. Kronemeyer, College of Medicine, U of Kentucky
J. Akers, College of Social Work, U of Kentucky
K. Watts, College of Social Work, U of Kentucky
L. Napier, Breathe Easy Grassroots Coordinator, Perry Co., KY
M. Slone, College of Social Work, U of Kentucky

Abstract: Rationale: Kentucky continues to have the highest lung cancer rate in the nation and is in the top 10 states for heart disease. Despite progress in local smoke-free policies, rural populations remain disproportionately affected by secondhand smoke (SHS) exposure. Due to the longstanding cultural heritage of tobacco, many rural residents think of SHS as a nuisance rather than a serious health hazard. Goals: 1. Identify effective messaging and develop, disseminate and evaluate media materials. Objectives: 1. Identify three campaign messages that educate and prompt action re smoke-free campaign. 2. Develop ads for various media in consultation with KCSP. 3. Diffuse media messaging throughout Perry County. 4. Conduct focus group(s) to see which messages resonate locally. 5. Prompt 20 people to take action/get involved with smoke-free campaign. Approach: 1. Develop 2- PSA's for radio, 4 ads for WYMT-TV and Hazard Herald newspaper (using research based messages/KSCP). 2. Recruit participants, conduct and survey effectiveness via focus group(s). 3. Disseminate SHS materials in community and recruit members for smoke-free campaign efforts. Analysis: Five media outlets agreed with the movement and offered matching PSA sponsorship. Over 150 business/community leaders held positive opinions re Smoke Free ordinance. Approximately 75 new members have signed on per Facebook, local wellness committee and personal contact. Conclusion: Media campaign has been associated with increased community awareness and participation. Further media evaluation and surveys are pending per focus group(s).

Supported by: NIH Grant, ULITR000117CCTS Seed Grant 'The project described was supported by the National Center for Research Resources and the National Center for Advancing Trnslational Sciences National Institute of Health, through Grant ULITR000117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH'

Primary Presenter / e-mail: L. Napier / lmnapier@harlanonline.net

Mentor or Senior Author / e-mail: M. B Dignon / mbdign2@uky.edu

#186 Abstract Title: **Consumer Perspectives on Electronic Cigarettes: A Content Analysis**

Author(s):
M. G. Mejia, Department of Psychology, U of Kentucky
E. J. Hahn, College of Nursing, U of Kentucky
D. Helme, Department of Communication, U of Kentucky
H. K. Knudsen, Department of Behavioral Science, U of Kentucky
J. L. Studts, Department of Behavioral Science, U of Kentucky

Abstract: Marketing and use of electronic cigarettes (e-cigs) has increased dramatically. To understand consumer perspectives and decision making about using e-cigs, we conducted a content analysis of 97 online reader responses to a newspaper editorial published in Kentucky (July 2012). The editorial addressed the emergence of e-cigs and raised questions concerning their health impact. Adapting a codebook from previous studies examining media coverage of tobacco issues, the investigative team developed a revised codebook with 71 codes addressing 15 general themes, including negative effects of conventional tobacco product use, effectiveness as tobacco cessation or reduction method, and functional health improvements. Comments were then coded by trained graduate students and entered into the database. Responses varied significantly in length with an average of 194.92 (±336.15) words. The most striking aspect of the data was the near universal support for e-cigs, with only 1 of the 97 posts modestly questioning the health benefits of e-cig use. The most commonly mentioned codes included: (1) characterizing the comment's tone as confrontational or in disagreement with the editorial (n=69); (2) referencing other websites (n=27); and (3) comparisons to the risks of smoking conventional tobacco products (harm reduction; n=18). Despite the lack of data supporting the potential for reduced harm, consumers seem highly dedicated to this emerging tobacco product. Consumer perspectives demonstrate substantial enthusiasm for using e-cigs as a harm reduction approach. Combined with data regarding health risks, knowledge of consumer perspectives on e-cigs will be important for informing FDA regulatory efforts and other tobacco control initiatives.

Supported by:

Primary Presenter / e-mail: M. G. Mejia / m.mejia@uky.edu

Mentor or Senior Author / e-mail: J. L. Studts / jlstu2@email.uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#187 Abstract Title: **Investigation into the Timing at which Three Critical Checkpoints of Diagnosis and Intervention in the Treatment of Severe to Profound Congenital Sensorineural Hearing Loss are Met in Appalachian and Non-Appalachian Populations**

Author(s):
Matthew Bush, MD, Department of Otolaryngology, University of Kentucky
Mariel Osetinsky, University of Kentucky College of Medicine
David Fardo, Department of Biostatistics, University of Kentucky
Nancy Schoenberg, Department of Behavioral Science, University of Kentucky
Jennifer Shinn, Director of Audiology, University of Kentucky

Abstract: The ultimate goal of this study is to investigate the time frames during which three key diagnostic and treatment checkpoints, namely diagnosis, amplification with hearing aids, and cochlear implantation, are being met in Appalachian compared to non-Appalachian children with congenital severe-to-profound hearing loss. In this retrospective chart review, data consists of information collected primarily from patient charts at the local nonprofit organization Lexington Hearing and Speech Center, supplemented by information found in patient charts at the University of Kentucky's Department of Otolaryngology. Of all these, specifically examined were the charts of both Appalachian and non-Appalachian patients with congenital severe to profound sensorineural hearing loss who had subsequently undergone cochlear implantation by the time this investigation was conducted. The variables examined in all patient charts for this study were many but include the following: patient's age at which final diagnosis of hearing impairment was obtained, patient's age at which amplification therapy was initiated, patient's age at which the cochlear implantation operation was performed, patient's expressive and receptive language abilities both before and after intervention, and results of connexin 26 genetic testing. A significant difference was demonstrated in the median age of cochlear implantation for non-Appalachian and Appalachian patients with congenital severe-to-profound hearing loss. The non-Appalachian patients received cochlear implantation at 152 weeks of age, whereas Appalachian patients received cochlear implantation at 182 weeks. In examining the role of mandatory newborn hearing screening, subjects were divided into two groups: those born before 2000 when the mandate was made and those born in 2000 or later. In the group of patients born prior to 2000, the average age of implantation was 342 weeks after birth, whereas the average age of implantation for the group of patients born after 2000 was 149 weeks. Our investigation revealed that the Appalachian group fell behind the non-Appalachian group in meeting all three checkpoints. According to median ages, the Appalachian group received cochlear implants later than the non-Appalachian group by 30 weeks (over 7.5 months later). In investigating the success of mandatory newborn hearing screening, the pre-mandate group received implantation 193 weeks later than the post-mandate group (roughly 4 years later).

Supported by:
Primary Presenter / e-mail: M. Osetinsky
Mentor or Senior Author / e-mail:

#188 Abstract Title: **Impact of South Carolina's Prescription Drug Monitoring Program on the use of Benzodiazepines in a Commercially Insured Population**

Author(s):
S. E. Wixson, Institute for Pharmaceutical Outcomes and Policy, U of Kentucky
K. Blumenschein, Pharmacy Practice and Science Department, U of Kentucky
E. S. Brouwer, Pharmacy Practice and Science Department, U of Kentucky
P. R. Freeman, Pharmacy Practice and Science Department, U of Kentucky
J. Talbert, Institute for Pharmaceutical Outcomes and Policy, U of Kentucky

Abstract: Objective: One criticism of prescription drug monitoring programs (PDMPs) is that they exert a 'chilling effect which may compromise access to appropriate therapy. Previous research evaluating the impact of benzodiazepine monitoring reported that benzodiazepine use dramatically decreased (Ross-Degnan et al, 2004). In January of 2008, South Carolina (SC) implemented a PDMP monitoring benzodiazepines. The aim of our study it to examine the impact of the PDMP on benzodiazepine use. Methods: We used a private insurance claims database containing records from January 2007 to December 2009. Continuously eligible SC residents between ages 19-64 were analyzed. Logistic regression models examined the likelihood of filling a benzodiazepine prescription. Control variables included PDMP status (active vs. inactive) and recipient characteristics (age, gender, race, and education). Statistical analysis was conducted in STATA v12.0. Results: 20,260 recipients were included. Regression results showed recipients have higher odds of filling a benzodiazepine prescription when the PDMP is active vs. inactive (CI 1.377-2.023). PDMP implementation was shown to more negatively impact the likelihood of females filling a benzodiazepine prescription compared to males (CI 0.8272-0.9727) and recipients between 50-65 years compared to recipients 19-29 (CI 0.7029 -0.9866). Conclusion: In this population, the implementation of the PDMP did not create a 'chilling effect'; a contrast to previous findings. Our study is limited by the use of a pre/post design with only three years of data from a privately insured population. Further research should focus on additional states and populations to better determine the impact of PDMPs on benzodiazepine use.

Supported by:
Primary Presenter / e-mail: S. E. Wixson / sarah.wixson@uky.edu
Mentor or Senior Author / e-mail: J. Talbert / jeff.talbert@uky.edu

#189 Abstract Title: Clinically Assisted Suicide: Current Status and Trends of Interest to Pharmacists

Author(s): W. M. Black, Student, College of Pharmacy, U of Kentucky
J. L. Fink III, Department of Pharmacy Practice and Science, U of Kentucky

Abstract: Objective: The objective of this legal research project is to review the current status of clinically assisted suicide legislation in the two states where it has been enacted as well as providing an update on developments in a third state where decisions in the state court system have made this lawful. Methods: Legislation enacted in Oregon and Washington to authorize clinically assisted suicide, known in both jurisdictions as the Death with Dignity Act, was reviewed along with relevant regulations to effect the legislative intent. A literature review was also conducted to locate reports and commentaries on these activities. Results: Evolution of the enactments from citizen initiatives to successful legislation is briefly reviewed. Discussion is presented regarding selected issues with the activity in this area: patient eligibility requirements; prescriber requirements; processes for issuing the prescription to obtain the medication; issues surrounding presenting the prescription to the pharmacist; and post-mortem requirements. Data are presented to describe trends with activities in this area. Recent legal developments related to this topic are also discussed. Implications: Pharmacists around the country should be aware of these developments and trends. In addition to the legal issues presented by such activities, pharmacists should consider the ethical dimensions of clinically assisted suicide in order to make an informed decision about their position on this important professional issue.

Supported by: University of Kentucky College of Pharmacy Summer Research Program
Primary Presenter / e-mail: W. M. Black / williamblack@uky.edu
Mentor or Senior Author / e-mail: J. L. Fink III / jfink@uky.edu

#190 Abstract Title: Device Acquired Infections as Vectors for Sepsis in Trauma Patients

Author(s): K. White, College of Medicine, U of Kentucky
A. Bottiggi, Department of Surgery, College of Medicine, U of Kentucky
A. Bernard, Department of Surgery, College of Medicine, U of Kentucky
D. Davenport, Department of Surgery, College of Medicine, U of Kentucky

Abstract: Background: Catheter-associated urinary tract infection (CAUTI) and ventilator-associated pneumonia (VAP) are infections that are considered performance measures. We sought to analyze the incidence, prevalence and risk of CAUTIs, and VAP, in trauma patients, the demographic and injury factors related to CAUTI and VAP and their relative risk of negative outcomes [prolonged length of stay (LOS), sepsis and death]. Methods: Trauma registry data were analyzed (age >18, LOS > 24 hours) from 1/1/07 to 12/31/11, excluding burns. Demographics, injury location, severity, and blunt vs. penetrating were analyzed relative to outcomes along with device-associated infection as defined by the CDC (CAUTI or VAP). Outcomes analyzed included ICU and hospital LOS, sepsis and in-hospital death. We set the significant threshold at $p<0.005$ to allow for multiple comparisons. Multivariable logistic regression was then used to determine contributing factors to sepsis, including device-associated infections. Results: The included population (n=10,755), were 66.6% male, had a mean age of 45.1 years, 91.8% blunt trauma, a median injury severity score (ISS) of 10 and a mean albumin of 2.80 g/dL. Patients developing CAUTI (n= 324, 3.0%, $p<0.005$) were more likely female (59.4%), had higher median ISS (20.5), and were older (56.7 years). Patients with VAP (n=161, 1.5%, $p<0.005$) had higher median ISS (27) and decreased admission albumin (2.51g/dL). Septic patients (n=149, 1.4%, $p<0.005$) had a higher median ISS (24.0), were older (52.3 years), and had a lower admission albumin (2.41g/dL). Sepsis was associated with increased death and prolonged LOS as expected ($p < .005$). In multivariable analysis, independent predictors for sepsis included: CAUTI (odds ratios [OR] 16.15, $p<0.001$), VAP (OR. 6.95 $p<0.001$), ISS (OR 1.05 per unit, $p<0.001$), age (OR 1.02 per year, $p<0.001$) and penetrating, abdominal, pelvic and/or chest injury. Conclusions: Development of CAUTI and VAP significantly increase the risk of sepsis in trauma patients after adjustment for injury type, location, severity, and age. This study suggests the importance of device-associated infections as vectors for sepsis in trauma and highlights the importance of prevention initiatives.

Supported by: PSMRF
Primary Presenter / e-mail: K.D. White / kevin.white@uky.edu
Mentor or Senior Author / e-mail: A.J. Bottiggi / ajbott2@uky.edu

#191 Abstract Title: Adipose-Specific Lipoprotein Lipase Transgenic Mice Are Protected against High Fat Diet-Induced Glucose and Insulin Intolerance by a Unique Mechanism

Author(s):
B.S. Finlin, Department of Internal Medicine, U of Kentucky
G.R. Walton, Department of Internal Medicine, U of Kentucky
B. Zhu, Department of Internal Medicine, U of Kentucky
M. Spencer, Department of Internal Medicine, U of Kentucky
R. Narkevic, Department of Internal Medicine, U of Kentucky
R. Unal, Department of Internal Medicine, U of Kentucky
M. Sunkara, Division of Cardiovascular Medicine, U of Kentucky
A. J. Morris, Division of Cardiovascular Medicine, U of Kentucky
C. A. Peterson, College of Health Sciences, U of Kentucky
P.A. Kern, Department of Internal Medicine, U of Kentucky

Abstract: Lipoprotein lipase (LpL) hydrolyzes the triglyceride core of triglyceride rich lipoproteins, regulating the entry of free fatty acids (FFAs) into metabolically important tissues such as adipose tissue and skeletal muscle. In obesity, a major cause of insulin resistance is the improper deposition of lipid in the liver and skeletal muscle. We hypothesized that increasing adipose tissue LpL would protect mice against diet-induced obesity by partitioning ectopic fat to adipose. We generated transgenic mice that expresses human LPL under the control of the adiponectin promoter (AdipoQ-LpL tg mice), and these mice express the transgene in an adipose specific manner. When the mice were placed on a high fat diet (60% kcal from fat), they displayed improved glucose and insulin tolerance ($P<0.05$, n=6). However, the mechanism does not involve reducing liver or skeletal muscle lipids, which was assessed by mass spectroscopy. Furthermore, the AdipoQ tg mice did not have increased adipose mass as measured by ECHO MRI, and, paradoxically, the adipocyte size was reduced in the Adipo-Q-LpL tg mice ($P<0.05$; n=6). Interestingly, we found that the epidymal fat pads of the AdipoQ-LpL tg mice had increased expression of PPARg and a number of PPARg-regulated genes including CD36, LpL, and adiponectin ($P<0.05$; n=6), but not PPARa- or d- regulated genes. There were also fewer adipose macrophages in the AdipoQ-LpL tg mice ($P<0.05$), and inflammatory gene expression tended to be reduced. Thus, increasing adipose LpL maintains insulin sensitivity by a unique mechanism that involves increasing PPARy and perhaps endogenous PPARy ligands.

Supported by: NIH Awards DK039176, DK71349, AG20941 and the UK Center for Clinical and Translational Science (UL1RR033173)

Primary Presenter / e-mail: B.S. Finlin / bfinlin@uky.edu

Mentor or Senior Author / e-mail: P.A. Kern / philipkern@uky.edu

#192 Abstract Title: PRR as a New Biomarker of Obesity and its Associated Diseases

Author(s):
F.Yiannikouris, Department of Molecular and Biomedical Pharmacology, U of Kentucky
L Cassis, Department of Molecular and Biomedical Pharmacology, U of Kentucky

Abstract: The prorenin/renin receptor (PRR) has been identified recently in human and rat adipose tissue. PRR is a multi-functional protein and can bind renin or its inactive form, prorenin, leading to the cleavage of AGT to form angiotensin I (AngI) which subsequently may influence angiotensin II (AngII) formation. We have recently demonstrated that adipose tissue is a predominant source of elevated circulating concentrations of AngII in obese hypertensive mice. Interestingly, adipocyte AGT deficiency prevented high fat-induced elevations in plasma AngII concentrations and systolic blood pressure. The purpose of this study was to characterize the presence of PRR in adipose tissue of male mice and determine whether obesity regulates adipose PRR expression. Male mice were fed a low fat (LF, 10% kcal as fat) or HF diet (HF, 60 % kcal as fat) for a period of 16 weeks. PRR was expressed abundantly in the adipose tissue of mice. In addition, mRNA abundance of PRR was modestly increased in adipose tissue of HF-fed mice compared to LF-fed mice. These data suggest that PRR may be involved in the production of adipose AngII during the development of obesity. To determine whether adipocyte differentiation regulates PRR abundance, in vitro studies using 3T3L1 cells were performed. Our results showed that PRR is expressed in pre-adipocytes and throughout adipocyte differentiation. Interestingly, the soluble form of PRR (sPRR) was significantly increased during the differentiation of adipocytes reaching a plateau at Day 4 (Day 0: 7069± 230, Day 4: 10498± 81 pg/ml $P<0.05$). Further studies will address whether adipose PRR influences adipose AngII production and the blood pressure and determine the function of sPRR during the development of obesity. In conclusion, our results demonstrated that PRR is abundantly expressed in adipose tissue and is increased during the development of obesity.

Supported by: These studies were supported by the National Heart, Lung, and Blood Institute (HL73085, to Dr Cassis; HL62846, to Dr Daugherty; T32HL091812, to Dr Yiannikouris) and by the National Center for Research Resources (P20RR021954; to Dr Cassis)

Primary Presenter / e-mail: F.Yiannikouris / fbyian2@uky.edu

Mentor or Senior Author / e-mail: L.Cassis / lcassis@uky.edu

#193 Abstract Title: **Dietary DHA Promotes an Anti-oxidant Response in Mice Exposed to environmental Pollutants**

Author(s):
K. Eske, Graduate Center for Nutritional Sciences, U of Kentucky
M. Murphy, Graduate Center for Nutritional Sciences, U of Kentucky
M. Petriello, Graduate Center of Toxicology, U of Kentucky
S.G. Han, Food Science of Animal Resources, Konkuk University, Seoul, Republic of Korea
B. Newsome, Department of Chemistry, U of Kentucky
B. Hennig, Department of Animal and Food Sciences, U of Kentucky

Abstract: Consumption of fish oil is associated with improved coronary health outcomes, but the mechanism of protection is not well understood. Environmental stressors, such as polychlorinated biphenyls (PCBs), contribute to the development of cardiovascular diseases like atherosclerosis. We study the protective benefits of nutrients such as the polyunsaturated omega-3 fatty acids found in fish oil in reducing the inflammatory response to PCBs. To further our understanding of the mechanism by which the omega-3 fatty acid, docosahexaenoic acid (DHA), is protective, we fed C57BL/6 mice diets enriched in DHA (3% DHA/22% safflower oil, % kcal) or a safflower control diet for four weeks before administration of the coplanar PCB 126 via oral gavage at week five. Liver samples were analyzed by microarray and real time-PCR to examine the interactive effects of PCBs and DHA on the nuclear factor (erythroid-derived 2)-like 2 (Nrf-2) anti-oxidant response pathway. Microarray data revealed that animals fed DHA and treated with PCBs had decreased expression of kelch-like ECH-associated protein 1 (KEAP1), a cytosolic inhibitor of Nrf-2 activity. In addition, an increase was observed in the expression of peroxisome proliferator-activated receptor gamma (PPARγ), a positive co-activator of Nrf-2, and its chaperone PPARγ co-activator 1a (PPARγc1a). Real time- PCR analysis revealed increased expression levels of Nrf-2 activated anti-oxidant enzymes, NAD(P)H dehydrogenase (quinone 1) (NQO1) and hemeoxygenase 1 (HO-1) in PCB treated mice on a DHA diet. Together these data suggest that DHA promotes an anti-oxidant response in mice exposed to environmental pollutants such as PCBs.

Supported by: Supported by grants from NIEHS, NIH P42ES007380 and the UK AES
Primary Presenter / e-mail: K. Eske / katryn.eske@uky.edu
Mentor or Senior Author / e-mail: B. Hennig / bhennig@uky.edu

#194 Abstract Title: **Exploring the Responsiveness of Osteoblasts to Fluid Pressure Stimulation: A Pilot Study to Examine the Relationship Between Hypercholesterolemia and Osteoporosis**

Author(s):
K.N. Lough, Center for Biomedical Engineering, U of Kentucky
H.Y. Shin, Center for Biomedical Engineering, U of Kentucky

Abstract: Recent studies identified hypercholesterolemia to be a dominant risk factor for osteoporosis but the underlying mechanism is unknown. Interestingly, there is evidence suggesting that osteoporosis is a manifestation of an impaired regulation of osteoblasts (the bone-forming cells) by fluid pressures generated in the bone matrix during mechanical loading. Recently, our laboratory showed that hypercholesterolemia alters the sensitivity of cells to its mechanoenvironment. In this study, we explored the possibility of this relationship extending to bone cells by testing the hypothesis that extracellular cholesterol modifies the osteoblast sensitivity to fluid pressure. For this purpose, we exposed MC3T3 osteoblastic cells to a physiologic pressure regimes characterized by a mean of 40 mmHg, amplitude of 0 to 20 mmHg, and frequency of 1 Hz for 1 hour. Control cells were maintained at 0 (atmospheric) mmHg pressure conditions. As an index of the osteoblast responsiveness to pressure, we quantified F-actin stress fiber formation. Relative to controls, cells exposed to all pressure regimes tested exhibited significantly enhanced stress fiber formation. However, the degree of stress fiber formation exhibited by MC3T3 populations depended on the amplitude of the applied pressure. Notably, incubation of cells with exogenous cholesterol dose-dependently attenuated the pressure effects. Collectively, the results of this pilot study suggests that enhanced cholesterol abundance in the bone cell environment is capable of altering the mechanosensitive activity of the osteoblasts. Moreover, our data serves as a foundation, based on the interstitial pressure-related regulation of the bone matrix, for future efforts in developing clinical approaches to mitigate the negative impacts of hypercholesterolemia on osteoporosis.

Supported by: National Science Foundation-Kentucky EPSCoR Program-Bioengineering Initiative and Research Scholars Program
Primary Presenter / e-mail: K.N. Lough / kristen.lough@uky.edu
Mentor or Senior Author / e-mail: H.Y. Shin / hy.shin@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#195 Abstract Title: Student's Desire for Nutritional Information in Dining Facilities at the University of Kentucky

Author(s): M. Foster, Department of Dietetics and Human Nutrition, U of Kentucky
K.H. Webber, Department of Dietetics and Human Nutrition, U of Kentucky

Abstract: Our hypothesis was that students at the University of Kentucky (UK) want more nutrition information about the foods served in campus dining facilities. Student customers of University Dining Services at both Blazer and Commons dining halls were surveyed in October 2012. The survey contained 18 questions about students' knowledge, attitudes, and behaviors concerning campus dining. All analyses were performed using Windows version 21.0 of the Statistical Package for the Social Sciences (SPSS, Chicago, IL). Correlations were calculated using the Pearson R coefficient. Of 506 students surveyed, 69.8% felt that eating healthy was important to them and 72.7% agreed that more information would be helpful in making healthy choices. The majority (56.7%) of students felt that they could improve their diet if they had more information. However 69.7% of students felt that there was not enough information such as calories about the food served in UK dining facilities. A strong positive response indicating "I try to eat healthy food" was correlated with a strong desire to know the nutrient content of campus food ($R=0.43$, $p<0.001$), but not with a strong feeling that campus food is unhealthy or with confidence in identifying healthy foods on campus. It appears that the availability of nutrition information in UK dining halls is desired and may lead to students to choose healthier diets.

Supported by: The project described was unfunded. The content is solely the responsibility of the authors.
Primary Presenter / e-mail: M. Foster / mdflink@gmail.com
Mentor or Senior Author / e-mail: K. H. Weber / khwebb2@email.uky.edu

#196 Abstract Title: Pioglitazone and Adipose Biology: Immunnohistochemical and automated image anaylises demonstrates a recuction of pro-inflammatory macrophages, Mast cells, and increases in cappilary density.

Author(s): M. L. Spencer, Department of Internal Medicine, U of Kentucky
Akosua Adu, Graduate School of Nutritional Sciences, U of Kentucky
N. Rasouli, Department of Medicine, U of Colorado
C. Peterson, College of Health Sciences, U of Kentucky
P. A. Kern, Department of Internal Medicine, U of Kentucky

Abstract: Pioglitazone is an effective drug for the treatment of type II diabetes, and is a ligand for the nuclear receptor PPARgamma. This drug targets adipose tissue and decreases blood glucose through an increase in insulin sensitivity. Pioglitazone has multiple effects in adipose tissue, including changes in gene expression that would be expected to activate lipid storage, immune cell migration, extra-cellular matrix regulation, and capillary/vascular functions. This study attempted to determine whether many of these changes in gene expression could be verified through immunohistochemical staining and automated image analysis of adipose tissue samples from subjects treated with pioglitazone. Nine subjects with impaired glucose tolerance, but without diabetes, were treated with pioglitazone 45 mg/day for 12 weeks, and adipose tissue biopsies from before and after treatment were examined. All subjects demonstrated an improvement in insulin sensitivity and improved glucose tolerance. Pioglitazone treatment decreased total adipose macrophage number by 25%. When macrophage polarity was examined, M1 macrophages were reduced by 55% whereas M2 (anti-inflammatory) macrophages were increased by 30%, suggesting an overall decrease in adipose tissue inflammation. Mast cells, which are found in adipose and are also associated with obesity and type II diabetes, were decreased from 24 to 13 cells/mm2 ($p = 0.02$). Capillary density as determined by endothelial cell staining was increased from 24 to 32 capillaries/mm2 ($p = 0.04$) after pioglitazone treatment. Pioglitazone treatment increased the size of adipocytes as measured by cross-sectional area by 18% ($p=0.01$). Although there were no changes in total collagen, pioglitazone increased the amount of elastin by 6-fold. Together these data suggest that pioglitazone improves numerous features of adipose dysfunction in insulin resistant subjects, including a reduction in adipose inflammation (macrophages and mast cells, increased vascularity (more capillaries), increased adipocyte lipid storage, and increased elastin. These features would be predicted to make adipose tissue better able to undergo cell expansion to store lipid without triggering cell necrosis and an inflammatory reaction.

Supported by: DK-80327 DK-71349 UL1-RR-033173 (Clinical and Translational Science Award)
Primary Presenter / e-mail: M. L. Spencer / mike.spencer@uky.edu
Mentor or Senior Author / e-mail: P. A. Kern / philipkern@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#197 Abstract Title: Hyperglycemia enhances myeloid cell proliferation and impairs atherosclerosis regression in diabetes

Author(s):
P. R. Nagareddy, Dept. of Medicine, Columbia University, New York and U of Kentucky
A. J. Murphy, Dept. of Medicine, Columbia University, New York
E. A. Fisher, Dept of Medicine, New York University, New York
P. A Kern, Dept of Internal Medicine, University of Kentucky
A. R Tall, Dept. of Medicine, Columbia University, New York
I. J Goldberg, Dept. of Medicine, Columbia University, New York

Abstract: Diabetes is one of the most potent risk factors for coronary heart diseases. Although atherosclerosis is initiated by deposition of cholesterol-rich lipoproteins in the artery wall, the entry of monocytes into the lesion drive the disease progression and/or impair its resolution. We found that hyperglycemia, independently of cholesterol, drives monocytosis in type I diabetic mouse models. Monocytosis was caused by increased proliferation of progenitor cells in the bone marrow but not in spleen. Hyperglycemia-mediated monocytosis was driven by PU.1 and C/EBPa and C/EBPe, the key transcriptional factors involved in myelopoiesis. Lowering plasma glucose with sodium glucose co-transporter inhibitors decreased myelopoiesis and suppressed the expression of lineage commitment markers. Mice or bone marrow cells deficient in S100 calcium binding proteins (S100A8/9) or its receptor, the RAGE (Receptor for Advanced Glycation Endproducts), were protected from diabetes-induced monocytosis in vivo and high glucose conditions in vitro. Enhanced myelopoiesis was not cell-autonomous but mediated by S100A8/9, secreted predominantly by circulating neutrophils and sensed by RAGE on common myeloid progenitors. Binding of S100A8/A9 to RAGE but not to TLR2/4 (Toll Like Receptor) initiated a signaling cascade via NF-κB to induce cytokine release and stimulate proliferation/ differentiation of progenitor cells. Further, in a mouse model of atherosclerotic regression, normalizing plasma glucose reduced lesion area by lowering the number of circulating monocytes as well as their accumulation in the lesion. We propose that hyperglycemia enhances myelopoiesis and that disruption of S100A8/A9-RAGE signaling could be a potential therapeutic strategy in the management of diabetic atherosclerosis.

Supported by: NIH: U01-20 HL087945 & DK095684 - Dual-PI grants to IJG & EAF, P01-HL54591 (IJG) and HL87123, HL107653 (ART) and a Pilot and Feasibility Award from the Diabetes Complications Consortium (DCC to IJG).

Primary Presenter / e-mail: P.R Nagareddy / prna222@uky.edu

Mentor or Senior Author / e-mail: I.J Goldberg and P. A Kern / philipkern@uky.edu

#198 Abstract Title: A Filter that Reduces Aluminum, a Contaminant in Parenteral Nutrition Solutions

Author(s):
R. A. Yokel, Pharmaceutical Sciences Department, U of Kentucky & ALKYMOS, Inc.
W. R. Harris, Dept of Chemistry and Biochemistry, U of Missouri-St. Louis & ALKYMOS, Inc.
C. D. Spilling, Dept of Chemistry and Biochemistry, U of Missouri-St. Louis & ALKYMOS, Inc.
V. P. Abramov, Occam Design, CreoSalus Company, Louisville, KY
J. M. Lone, Occam Design, CreoSalus Company, Louisville, KY
R. J. Kuhn, Pharmacy Practice and Science Department, U of Kentucky & ALKYMOS, Inc.

Abstract: Background: Aluminum is a contaminant of component solutions used to compound parenteral nutrition solutions. Aluminum has no beneficial effects to the human and can produce cognitive impairment, metabolic bone disease, and may contribute to cholestasis. Neonates are the population at greatest risk for aluminum toxicity. Calcium Gluconate Injection, USP, contributes ~ 85% of the aluminum in parenteral nutrition solutions. Typical parenteral nutrition solutions deliver 17 to 24 mcg Al/kg/day to patients, well above the 4 to 5 mcg/kg/day considered non-toxic in the FDA's labeling requirement regulation that addresses aluminum in large and small volume parenterals. Objective: To reduce aluminum delivered to neonates via total parenteral nutrition to a non-toxic level. Methods: We designed and extensively tested a flow-through filter containing an immobilized chelator that complexes aluminum from calcium gluconate as it flows through the filter. The filter, a vial containing a partial vacuum that receives the filtered solution, and an aseptic environment comprise everything needed. Results: At a flow rate of ~ 1 ml/min more than 90% of the aluminum is removed from calcium gluconate. This is calculated to reduce aluminum delivered to > 1 kg infants to < 5 mcg/kg/day. Conclusions: A point-of-use self-contained aluminum-complexing filter has been created that reduces aluminum delivered in total parenteral nutrition solutions by ~ 75%, resulting in daily aluminum delivery below the level considered toxic to all but the smallest (< 1 kg) infants.

Supported by: Thrasher Research Fund, KSEF-06-SBIR-059, KSEF-148-504-09-107, KSTC-06-COMM-006, KSTC #147-406-99, NIH 1R41HD055009, KSTC-184-512-08-041, NIH 2R42HD055009-2, KSTC-184-512-11-106.

Primary Presenter / e-mail: R. A. Yokel / ryokel@email.uky.edu

Mentor or Senior Author / e-mail: R. A. Yokel / ryokel@email.uky.edu

#199 Abstract Title: **Inhibition of TSP1-mediated TGF-β activation reverses adipose tissue fibrosis but does not affect metabolic dysfunction in high-fat fed mice**

Author(s):
R. G. Walton, Department of Internal Medicine, U of Kentucky
L. Muniappan, Department of Internal Medicine, U of Kentucky
M. Spencer, Department of Internal Medicine, U of Kentucky
A. Adu, Graduate Center for Nutritional Sciences, U of Kentucky
B. S. Finlin, Department of Internal Medicine, U of Kentucky
C. A. Peterson, College of Health Sciences, U of Kentucky
P. A. Kern, Department of Internal Medicine, U of Kentucky

Abstract: Our group and others have shown that adipose tissue fibrosis is associated with metabolic dysfunction. Thrombospondin (TSP1) expression is increased with insulin resistance, and TSP1 activates TGF-β. We hypothesized that inhibition of TSP1 mediated TGF-β activation would ameliorate high fat diet-induced metabolic dysfunction in BL/6 mice. LSKL peptide specifically inhibits TGF- β activation by TSP-1. Mice were placed on high fat diet for four-weeks and then given LSKL (1 mg/kg body weight, osmotic mini-pump, 5-6 weeks) or scramble peptide and maintained on a high fat diet. LSKL treatment decreased TGF- β signaling since phospho-SMAD2/3 immunostaining was reduced by 65% (n=6/group; $p<0.05$) in inguinal subcutaneous fat (SQF). SQF inflammation was also reduced following LSKL treatment, evidenced by a 34% and 41% decrease in F4/80 mRNA and F4/80 immunostaining, respectively ($p<0.05$). Importantly, SQF fibrosis determined by Sirius red staining was strikingly decreased by 67% in LSKL treated mice ($p<0.01$), with a concomitant 24% decrease in ColIV mRNA ($p<0.05$). However, no differences were observed in food intake, body weight, weight gain, body composition, fasting glucose, or glucose tolerance using an IP GTT. In a follow-up study, we delivered a higher dose of LSKL (45 mg/kg body weight, i.p. injection) or scramble peptide for 14 weeks, beginning at onset of high fat feeding. No differences were observed in activity, food intake, body weight, weight gain, fasting glucose, glucose tolerance, or insulin tolerance. However, we observed a trend toward increased lean mass in LSKL-treated mice. These results indicate that TSP1 is a significant activator of TGF- β in WAT in diet-induced obesity and that blocking TSP1-mediated TGF-β activation reversed high fat diet-induced adipose tissue fibrosis. However, improvement in adipose inflammation and fibrosis did not affect insulin or glucose tolerance.

Supported by: UL1RR033173 (P.A.K.); DK 71349 (C.A.P. and P.A.K.); The project described was supported by the National Center for Advancing Translational Sciences, UL1RR033173 (P.A.K.) and The National Institute of Diabetes and Digestive and Kidney Diseases, DK 71349 (C.A.P. and P.A.K.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH

Primary Presenter / e-mail: R. G. Walton / r.grace.walton@uky.edu

Mentor or Senior Author / e-mail: P.A. Kern / philipkern@uky.edu

#200 Abstract Title: **The Effects of Season-Long Vitamin D Supplementation on Collegiate Swimmers and Divers**

Author(s):
R. M. Lewis, Division of Clinical Nutrition, U of Kentucky
M. Redzic, Division of Clinical Nutrition, U of Kentucky
D. T. Thomas, Division of Clinical Nutrition, U of Kentucky

Abstract: The purpose of this 6-month randomized placebo controlled trial was to determine the effect of season-long (September-March) vitamin D supplementation on changes in vitamin D status (measured as 25(OH)D), body composition, inflammation, frequency of illness and injury. Thirty-two male and female athletes were randomized to 4000IU vitamin D (n=19) or placebo (n=13). 25(OH)D, bone turnover markers (NTx and BSAP), and inflammatory cytokines (TNF-alpha, IL-6, and IL1-β) were measured at baseline, midpoint, and endpoint. Body composition was assessed by DXA. Injury and illness data were collected. All athletes had sufficient 25(OH)D (>32ng/mL) at baseline (mean: 57ng/mL). At midpoint and endpoint, 13% and 16% of the total sample had 25(OH)D <32ng/mL, respectively. 25(OH)D was not positively correlated with bone mineral density (BMD) in the total body, proximal dual femur, or lumbar spine. In men, total ($p=0.04$) and trunk ($p=0.04$), mineral-free lean mass (MFL) were positively correlated with 25(OH)D concentration. In women, right femoral neck BMD ($p=0.02$) was positively correlated with 25(OH)D. 25(OH)D did not correlate with changes in bone turnover markers or inflammatory cytokines. Illness (n=1) and injury (n=13) were not related to 25(OH)D; however, 77% of injuries coincided with decreases in 25(OH)D. Our data suggests that 4000 IU vitamin D supplementation is an inexpensive intervention that effectively increased 25(OH)D, which was positively correlated to bone measures in the proximal dual femur and MFL. Future studies with larger sample sizes and improved supplement compliance are needed to expand our understanding of the effects of vitamin D supplementation in an athletic sample.

Supported by: The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1RR033173. The content is solely the responsibility of the authors and does not necessarily represent official views of the NIH.

Primary Presenter / e-mail: R. M. Lewis / rmlewi4@g.uky.edu

Mentor or Senior Author / e-mail: D. T. Thomas / david.t.thomas@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#201 Abstract Title: Association of BMI, Leptin and markers of inflammation in the first trimester.

Author(s):
R. Pollack, Department of Obstetrics and Gynecology, University of Kentucky
S. Mast, Department of Obstetrics and Gynecology, University of Kentucky
K. Ashford, School of Nursing, University of Kentucky
J. O'Brien, Department of Obstetrics and Gynecology, University of Kentucky

Abstract: Background: Leptin is increased in obesity, and plays an immunoregulatory role. We assessed the first trimester associations between BMI and inflammatory markers and Leptin as they may help elucidate early pathophysiology related to adverse pregnancy outcomes. Methods: This is a secondary analysis from a prospective multicenter study. Women over 16 years of age with singleton gestations, and no pre-existing diabetes were recruited in the first trimester. Serum concentrations of Leptin, IL-1a and b, IL-6, IL-8, IL-10, CRP, TNF-alpha, and MMP-8 were determined by Luminex or ELISA. Statistical analysis using paired t-test, and univariate and multivariate regression models were performed. Results: We analyzed samples from 128 women. The mean age was 26.4yrs (18-41), the mean BMI was 28.3 (15.8-58.3). BMI was significantly associated with Leptin (p=.0001) and CRP (p=.0003). BMI as a categorical variable with obese versus non-obese showed similar associations. All other biomarker associations with BMI were non-significant. Increasing Leptin concentrations were significantly associated with CRP (p=.004), and MMP-8 (p=.028). Using multiple regression analysis and controlling for BMI there was not a significant association between CRP and Leptin. However, with different BMI cutoffs (>30, >35, >40) we noted that with BMI >40 Leptin was independently associated with CRP. Discussion: Obesity is a pro-inflammatory state. BMI in the first trimester is significantly associated with CRP and Leptin. After controlling for BMI the association between CRP and Leptin was only noted at very high BMI levels. Further studies are needed to relate these biomarkers to adverse outcomes seen with obesity in pregnancy.

Supported by: NIH BIRCWH, Grant # K12DA14040, and Center for the Biologic Basis of Oral/Systemic Disease, NIH/NIGMS 8P20GM103538-09 (PI) - Kristin Ashford, PhD. University of Kentucky Center for Clinical and Translational Sciences - National Center for Advancing Translational Sciences, UL1TR000117

Primary Presenter / e-mail: R.I. Pollack / riep222@uky.edu

Mentor or Senior Author / e-mail: J.M. O'Brien / jmob224@uky.edu

#202 Abstract Title: Serum Amyloid A Shifts from HDL to Pro-atherogenic Lipoproteins in Obese Diabetic Subjects

Author(s):
V.L. King, Department of Internal Medicine, BBDOC, Saha CVRC, U of Kentucky
P. Wilson, Department of Internal Medicine, U of Kentucky
P.A. Kern, Department of Internal Medicine, BBDOC, U of Kentucky
L.R. Tannock, Department of Internal Medicine, BBDOC, Saha CVRC, U of Kentucky

Abstract: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in developed nations. The retention of atherogenic lipoproteins by vascular proteoglycans initiates atherosclerosis development. Numerous studies have demonstrated that factors which increase lipoprotein-proteoglycan interactions are associated with increased CVD. Serum Amyloid A (SAA) is an acute phase reactant that is persistently elevated in chronic inflammatory conditions associated with increased rates of CVD such as diabetes, metabolic syndrome (MetS) and rheumatoid arthritis. We recently demonstrated that over-expression of SAA increases atherosclerosis development in mice. However, the mechanisms by which SAA increases atherosclerosis remain unclear. In the healthy state SAA is exclusively associated with HDL. However, in a murine model of obesity/ insulin resistance we found SAA in association with apolipoprotein (apo)B-containing lipoproteins, and we have recently validated this observation in human studies. Our data demonstrate that the association of SAA with apoB-containing lipoproteins is enhanced in subjects with insulin resistance and is dynamic, with SAA shifting from HDL to apoB-containing lipoproteins post-prandially. To determine if the presence of SAA affects the binding of apoB-containing lipoprotein (VLDL and LDL) to proteoglycans we preformed proteoglycan binding assays with native human VLVL and LDL with or without exogenously added SAA. The presence of SAA augmented VLDL and LDL binding to proteoglycans. These data suggest that the redistribution of SAA to apoB containing lipoproteins enhances the retention of these lipoproteins in the vascular wall thus promoting the development of atherosclerosis in MetS and diabetes.

Supported by: NIH Award: COBRE RR021954 (VLK) and pilot funding from UK Center for Clinical and Translational Science UL1TR000117 (VLK)

Primary Presenter / e-mail: V.L. King / vicky.king@uky.edu

Mentor or Senior Author / e-mail: V.L. King / vicky.king@uky.edu

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#203 Abstract Title: Lifestyle Predictors of Childhood Obesity in Eastern Kentucky

Author(s): M.L. Smith, College of Medicine, University of Kentucky
K.A. Winkler, College of Medicine, University of Kentucky

Abstract: Background: In the U.S., 17% of children and adolescents are obese.1 Rates are higher among low-income households and in rural areas.2, 3 Eighty five of Kentucky's 120 counties are rural. Most of these counties are in eastern Kentucky.4 Childhood obesity is widely researched however there are few studies about obesity-related behaviors in rural areas, specifically eastern Kentucky.5 Methods: A cross-sectional study was conducted on a sample of families in eastern Kentucky. Parents completed an anonymous survey regarding family activities and nutritional habits. Comparisons of obese and non-obese families were made based on BMIs of children. A BMI above the 95th percentile was considered obese. Chi square test and Fisher's Exact test were used to examine the association between the explanatory variables and an outcome variable (obese family or non-obese family). Results: Of the 96 distributed surveys, 65 were sufficiently completed. 57% of families were defined as obese. Parents of non-obese children were more likely to play board games (p=0.0232) and read with their children (p=0.034). A correlation existed between obesity and exercise (p=0.029). There was no statistically significant relationship between childhood obesity and playing video games, watching television, fruit/vegetable consumption, or beverage choices. Conclusion: Childhood obesity rates were higher than the national average.1 Although we expected sedentary activity to be higher and exercise lower among obese families, the results were almost completely opposite of this. The relationship between reading, board games and obesity was surprising and to our knowledge is not described elsewhere in the literature.

Supported by: The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant 8UL1TR000117-02. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH REDCap Citation Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Kentucky.

Primary Presenter / e-mail: M.L. Smith, K.A. Winkler / kawink2@uky.edu

Mentor or Senior Author / e-mail: P. Arnett / paula.arnett@uky.edu

#204 Abstract Title: Inpatient Pain Management Analysis at a Rural Hospital in Eastern Kentucky

Author(s): C. Norgren, College of Medicine, U of Kentucky
C. Starnes, Department of Statistics, U of Kentucky
C. Shely, Department of Pharmacy, St. Claire Regional Medical Center

Abstract: BACKGROUND: A Press Ganey survey from 2012 reveals that St. Claire Regional (SCR) Medical Center in Morehead, KY has low patient satisfaction scores for inpatient pain management as compared to national and statewide averages. By conducting an in-depth chart review, we hope to identify key factors that will help us improve the quality of patient care. METHODS: 55 patients who were admitted to SCR between July 1, 2012 – September 30, 2012 and who had one or more pain medicines ordered (Hydromorphone, Morphine, Oxycodone and/or Hydrocodone) were selected at random for review. Data collected from heir medical records included age, sex, pain source/character, admitting service, location in the hospital, allergies, home pain medications, hospital pain medications, pain scores, acceptable level of pain, length of stay, and any relevant notes about their stay. Data was then organized into patient profile plots, bar graphs, and descriptive statistics tables. RESULTS: Patients were less likely to receive adjunctive non-opioid pain medicines on the internal medicine service. There was no significant difference in the distribution of those receiving non-opioid medicines based on other services, location in the hospital, pain source or character, or whether they had home opioid pain medicines. Acceptable level of pain was not recorded in 40% of patients. CONCLUSION: Pain control may be affected by frequency of pain assessments, use of adjunctive non-opioid medicines, and patient specific factors such as opioid tolerance. Further analysis of pain scores as related to medicine regimens such as dose, route of administration, and schedule is warranted.

Supported by:

Primary Presenter / e-mail: C. Norgren / crystalnorgren@gmail.com

Mentor or Senior Author / e-mail: C. Shely / catherine.Shely@st-claire.org

CCTS Poster Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

#205 Abstract Title: Use and Knowledge of 5 Non-pharmacologic Treatments for Low Back Pain

Author(s): K. Johnson, Rural Physician Leadership Program, College of Medicine, U of Kentucky
L. Jackson, Rural Physician Leadership Program, College of Medicine, U of Kentucky
C. Starnes, Biostatistics, Epidemiology, and Research Design, CCTS, U of Kentucky

Abstract: Background: Narcotic usage in Eastern KY is among the highest in the nation, devastating communities. Five non-pharmacologic treatments have been proven effective in treating chronic pain. Our research is an attempt to understand the limiting factor(s) keeping Primary Care Providers (PCP) from using these alternative treatments for low back pain. Methods: We administered a survey to primary care providers to assess their usage, knowledge, and perception of usefulness and availability of these alternative treatments for low back pain. Primary care providers targeted included Nurse Practitioners, Physicians Assistants and Physicians working in Family or Internal Medicine who practice outpatient medicine in Eastern KY. Our research utilized Fisher's Exact test and Spearman correlation. Statistical significance was calculated with p-values < 0.05. Results: We received 29 complete surveys. Of the five therapies included in the survey, Spinal Manipulation, Progressive Relaxation, and Yoga provided the most significant findings. There was a statistically significant relationship between knowledge and use of these therapies, and a positive correlation between knowledge and the provider's perceived usefulness for them. We also identified a relationship between provider's use and perceived usefulness of these three therapies; as well as a relationship between use and availability of treatment for Massage and Yoga was identified. Conclusion: Our research shows improving a provider's knowledge through increased education about Spinal Manipulation, Progressive Relaxation, and Yoga, could lead to increase use of, perceived usefulness would increase, which could lead to an increase use of these treatments as an alternative first step to controlling chronic back pain than narcotic prescribing.

Supported by: Statistical Analysis was provided by C. Starnes, Biostatistics, Epidemiology, and Research Design; Center for Clinical and Translational Science; U of Kentucky

Primary Presenter / e-mail: K. Johnson / kgwh222@uky.edu

Mentor or Senior Author / e-mail: P. Arnett / paula.arnett@uky.edu

#206 Abstract Title: Naltrexone Induces Opioid Withdrawal After Cutaneous Inflammation: Contribution of the Nucleus Accumbens and the Anterior Cingulate Cortex

Author(s): J.C. Morales-Medina, Department of Physiology, U of Kentucky
G. Corder, Department of Physiology, U of Kentucky
B.K. Taylor, Department of Physiology, U of Kentucky

Abstract: Opioid receptor antagonists such as naltrexone (NTX) precipitate withdrawal in morphine-dependent animals and humans. Our recent data suggest that cutaneous inflammation with complete Freud's adjuvant (CFA) induces a state of endogenous opioid dependence. When administered 21 days after CFA, after initial signs of hyperalgesia had resolved, we found that either systemic (3mg/Kg) or Intracerebroventricular (ICV; 1 µg) administration of NTX induced reinstatement of pain as well as withdrawal behaviors including enhanced rearing and increased locomotion. We next investigated the effects of a selective µ antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH2 (CTOP). We found that ICV CTOP (300 µg) reinstated tactile hypersensitivity and elicited withdrawal behaviors. To determine the site of action of ICV NTX, we evaluated the expression of the immediate-early gene Fos, a marker of cell activation in CFA-treated animals 2 hours after administration of NTX. We focused on brain regions involved in the control of persistent pain, opioid analgesia and/or opioid dependence, including the nucleus Accumbens (NAcc), the Locus coeruleus (LC), the anterior cingulate cortex (ACC), the ventral tegmental area (VTA), the basolateral amygdala (BLA) and the rostral ventral medulla (RVM). When administered 21 d after CFA, NTX decreased Fos expression within the NAcc and ACC of CFA treated animals by more than two-fold. NTX had no effect on the RVM or controls animals. We suggest that peripheral inflammation induces endogenous opioid dependence at the NAcc and ACC by reducing inhibitory outputs from the NAcc and ACC, leading to the behavioral expression of opioid withdrawal.

Supported by: NIH to Bradley Taylor

Primary Presenter / e-mail: J.C. Morales-Medina / julio.morales-medina@uky.edu

Mentor or Senior Author / e-mail: B.K. Taylor / brad.taylor@uky.edu

#207 Abstract Title: **Recent KAN Study Demonstrates Successful Translational Science Team Building**

Author(s):
K. Stewart, Community Faculty, Department of Family and Community Medicine, U of Kentucky
N. Munk, Department of Family and Community Medicine, U of Kentucky
M. Love G. Bruckner, Department of Health Sciences, U of Kentucky
K. Pearce, Department of Family and Community Medicine, U of Kentucky
W.G. Elder, Department of Family and Community Medicine, U of Kentucky

Abstract: The UK Department of Family and Community Medicine's (DFCM) Kentucky Pain Referral and Outcomes Studies (KYPROS) group is examining complementary approaches for primary care patients with chronic low back pain (CLBP). KYPROS built a translational research team for an NIH supported study that involves academic and community professionals. Utilizing a base network of community licensed massage therapists (LMTs) established through prior NIH support, KYPROS continued to build its research team to include 26 community LMTs as study personnel. This approach enabled novel effectiveness (real-world application) rather than efficacy methodology. One-hundred-four CLBP patients consented to participate in the clinical massage therapy (CMT) study arm. Participants had 12 weeks to receive up to 10, one-hour treatments. Institutional study personnel consented participants and gathered baseline data after which, community LMTs handled CMT intervention scheduling, administration, and documentation. To prepare and support community LMTs in their roles as study personnel, training, supervision, and guidance was provided by DFCM faculty, staff, and Community Faculty members. LMTs were assigned an average of 4 participants and completed an average of 68% of their total potential treatments. LMT compliance to rigorous methodology was successful with 97% of the documentation submitted for the 759 administered CMT treatments. As a community LMT appointed as UK Community Faculty, and having participated in COM fellowship training activities and courses, and as a contributor to DFCM NIH funded applications, the presenter is herself as an example of successful translational science team building.

Supported by: NIH/NCCAM Grant # 1R21AT004544-01A2 awarded to the Department of Family and Community Medicine at the University of Kentucky for the study CAM Referral and Outcomes: Chronic Low Back Pain in Urban and Rural Primary Care.

Primary Presenter / e-mail: K. Stewart / KEStewartLMT@aol.com

Mentor or Senior Author / e-mail: W.G. Elder / welder@uky.edu

#208 Abstract Title: **Clinical Predictors of Fatigability and Maximum Voluntary Isometric Contraction (MVIC) in a Cohort of Patients with Idiopathic Inflammatory Myopathies**

Author(s):
L.C. Cleary, U of Kentucky College of Medicine
B.Y. Hanaoka, Department of Internal Medicine, U of Kentucky
D. Long, U of Kentucky C.P. Starnes, U of Kentucky
J. Duan, U of Kentucky
Q. Fan, U of Kentucky
C.A. Peterson, U of Kentucky
L.J. Crofford, Department of Internal Medicine, U of Kentucky

Abstract: Background: Many patients with IIMs exibit chronic muscle weakness and functional disability despite treatment. In polymyositis/ dermatomyositis (PM/DM), male sex, higher prednisone dosage and older age have been associated with muscle weakness and functional disability.[1,2] Sporadic inclusion body myositis (sIBM) itself is associated with major end-stage disability.[3] The ACR functional status (ACRFS) criteria have been used as a core measure of the consequences of impairment in IIM.[4] However, its association with known or suspected risk factors of disability warrants further investigation. Objectives: To determine predictors of current/ worst ever ACRFS with known or suspected risk factors of disability and muscle weakness in patients with IIM. Methods: Data were obtained from chart reviews of IIM and overlap myositis (OM) cases seen in the Rheumatology and Neurology Clinics at the University of Kentucky from May/06 until July/12. Current and worst ever ACRFS, demographic and clinical characteristics were abstracted from medical records. One-way ANOVA and Fisher's exact/ Chi-square tests were used to compare groups on continuous/ categorical variables, respectively. Ordinal logistic regression was applied to estimate the effects of IIM type, age, sex and disease duration from diagnosis on current and worst ever ACRFS. Results: 90 patients with IIM and OM were included: 38 PM, 29 DM, 12 IBM and 11 OM. When patient ages were divided into tertiles, sIBM patients were significantly older (p= 0.03). Females predominated in the PM, DM and OM groups. In sIBM, females were slightly outnumbered. Mean duration of disease from diagnosis was highest in sIBM (73 mo) compared to PM (39 mo), DM (18 mo) and OM (35 mo) (p=0.01). sIBM was more likely to be associated with presence of some degree of disability at the last time of assessment (91%), compared to all other groups combined (73%) (p=0.001). In the multivariable analysis, poorer current ACRFS and worst ever ACRFS were independently associated with higher age, and higher age and longer disease duration, respectively, controlling for all other variables. Conclusions: The demographic and clinical characteristics of our cohort are consistent with previous reports. As expected, sIBM was associated with increased odds of disability. In the multivariate analysis, higher age and disease duration were identified as independent risk factors for disability.

Supported by: This study was supported by the Arthritis Foundation, the Center for Clinical and Translational Science (CCTS) at the University of Kentucky, the University of Kentucky College of Medicine Clinical Scholars Program and Research Data Capture (REDCap). The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Primary Presenter / e-mail: L.C. Cleary / laura.cleary@uky.edu

Mentor or Senior Author / e-mail: B.Y. Hanaoka / byhanaoka@uky.edu

#209 Abstract Title: The effects of daily physical work on the trunk stiffness and risk of low back pain

Author(s):
M. Vazirian, Center for Biomedical Engineering, U of Kentucky
B. Kock, Center for Biomedical Engineering, U of Kentucky
A. Agarwal, Center for Biomedical Engineering, U of Kentucky
B. Bazrgari, Center for Biomedical Engineering, U of Kentucky

Abstract: Low back disorders (LBDs) have been found to be significantly associated with heavy physical work. Providing the important role of trunk mechanics in LBD, it is important to find out how physical activity affects trunk mechanical properties. Ten healthy individuals participated after completing a consent procedure. Four of them (i.e., high physical activity (HPA), 22 (3) years, 185 (3) cm, 90 (9) kg) were members of the University's Ultimate Frisbee team and were tested before and after a daylong tournament, the other six (i.e., low physical activity (LPA), 26 (5) years, 178 (4) cm, 78 (9) kg) were students and staff and were tested at the beginning and the end of their work day. All participants were also tested the following morning to evaluate recovery. During each session, participants completed two tests: 1) maximum voluntary trunk exertion (MVE) tests, 2) flexion-relaxation tests during which they were passively moved into a flexed trunk position and were kept in such posture for about four minutes. MVEs decreased significantly (P = 0.00291) in the HPA group and did not fully recover by the following morning. The magnitude of initial trunk resistance to passive flexion as well as its relaxation after four minutes increased significantly (P = 0.43228) after the exposure in the HPA group. Both active and passive trunk tissues contribute to trunk stiffness and an incomplete recovery may adversely affects spine stability and the risk of LBD.

Supported by: This publication was supported by CDC-NIOSH grant number R21OH010195.
Primary Presenter / e-mail: M. Vazirian / milad.vazirian@uky.edu
Mentor or Senior Author / e-mail: B. Bazrgari / babak.bazrgari@uky.edu

#210 Abstract Title: Selective elimination of noradrenergic locus coeruleus (LC) neurons alleviates chronic orofacial pain.

Author(s):
R. Kaushal, Department of Physiology, U of Kentucky
L. Zhang, Department of Physiology, U of Kentucky
A. Jamal, Department of Physiology, U of Kentucky
B.K. Taylor, Department of Physiology, U of Kentucky
K.N. Westlund, Department of Physiology, U of Kentucky

Abstract: Trigeminal neuralgia (TN) is an excruciating and debilitating form of clinical orofacial pain. Noradrenergic locus coeruleus (LC, pontine A6 neurons) is involved in bidirectional modulation of pain. Multiple studies indicate that LC activity is increased during noxious stimulation and following inflammation or nerve damage. Predominantly known for its role in the feedback inhibition of pain, emerging studies also indicate a contribution of the LC in pain facilitation. For example, lesions of the LC significantly reduce tonic behavioral responses to intraplantar formalin injection, prevent autotomy, and reduce hypersensitivity associated with peripheral nerve injury. In this study we hypothesized that noradrenergic (LC) neurons contribute to the facilitation of chronic pain in TN. We used a rat model of TN involving infraorbital nerve chronic constriction injury (ION-CCI) which produces mechanical hypersensitivity as assessed by a reduction in von Frey threshold. Administration of anti-dopamine-β-hydroxylase saporin (anti-DβH-saporin) toxin was performed for selective elimination of noradrenergic LC neurons or IgG saporin (nonspecific) as the control either by intracerebroventricular (i.c.v space 2) or by bilateral spinal trigeminal nucleus (STN) injections. Under minimal restraint, rats received either no stimulation or repeated stimulation with a 100gm von Frey hair applied directly to the maxillary branch. Withdrawal threshold (tactile allodynia) from von Frey fiber stimulation to the face was not changed as compared to baseline in animals subjected to sham surgery; this was true in both saporin and anti-DβH-saporin groups. However, i.c.v. anti-DβH-saporin significantly increased withdrawal threshold animals with ION-CCI as compared to IgG saporin controls. More selective destruction of the LC-trigeminal pathway with bilateral STN anti-DβH-saporin injection also alleviated behavioral signs of chronic orofacial hyperalgesia. Elimination of noradrenergic LC neurons was confirmed by complete loss of tyrosine hydroxylase (TH) immunoreactivity in anti-DβH-saporin injected animals. Compared to unstimulated controls, mechanical stimulation increased immunoreactive phosphorylated extracellular cell-regulated protein kinase (pERK), a marker of neuronal activity, in the LC and STN. Nerve injury also increased expression of a neuronal injury and stress marker, activating transcription factor 3 (ATF3), in trigeminal ganglia neurons. Together, these results indicate that noradrenergic locus coeruleus neurons facilitate chronic orofacial neuropathic pain.

Supported by: Acknowledgements. Include BKT K02DA19656 and R01NS62306 University of Kentucky President's Research Fund (KNW) Dean of the College of Medicine (KNW)
Primary Presenter / e-mail: R. Kaushal / r.kaushal@uky.edu
Mentor or Senior Author / e-mail: K.N. Westlund / kwhigh2@uky.edu

#211 Abstract Title: Chronic constriction injury of the infraorbital nerve produces anxiety-like behaviors in the rat

Author(s): R.H.Kline IV, Department of Pysiology, U of Kentucky
R. Kashual, Department of Physiology, U of Kentucy
A. Jamal, Department of Anesthesiology, U of Kentucky
K.N. Westlund, Department of Physiology, U of Kentucky

Abstract: Chronic pain is associated with the development of affective disorders. Clinical orofacial pain can be difficult to treat therefore patients suffering from chronic orofacial pain may have a higher risk for developing a pain-related mood disorder. In the present study, we used an infraorbital nerve constriction model of neuropathic pain (ION CCI) to assess time-dependent changes potentially reflecting the affective-motivational dimensions of pain. ION CCI treated animals were tested for anxiety-like behaviors using an open field activity monitor and a modified dark-light preference task. Orofacial Von Frey filament testing showed mechanical hypersensitivity began 14-21 days after ION CCI while reductions in open field and dark-light preference activities were seen at day 28. To further evaluate the effects of ION CCI-induced anxiety-related behaviors, the effects of the anti-neuropathic pain drug gabapentin (GBP) were determined with the dark-light preference task seven weeks after injury. ION CCI enhanced the aversive quality of the bright light and was completely reversed after low dose (GBP 15mg/kg s.c.). Results from the present study demonstrate, 1) orofacial mechanical hypersensitivity precedes anxiety-related behavior by two weeks, 2) open field and dark-light preference testing detect orofacial pain-induced anxiety-related behavior and 3) ION CCI-induced anxiety-like behavior is reversed with gabapentin. In conclusion, this study establishes a direct connection between orofacial neuropathic pain and affective disorders in the present model. This study also highlights the utility of the open field activity monitor and dark-light preference task for screening candidate drugs for the management of chronic orofacial pain.

Supported by: NIH
Primary Presenter / e-mail: R.H. Kline IV / robert.kline@uky.edu
Mentor or Senior Author / e-mail: K.N. Westlund / karin.high@uky.edu

#212 Abstract Title: Mechanisms For Long-term Endogenous Control of Inflammatory Hyperalgesia By Spinal Neuropeptide Y

Author(s): W. Fu, Department of Physiology, U of Kentucky
B. Solway, Department of Physiology, U of Kentucky
G. Corder, Department of Physiology, U of Kentucky
R. Donahue, Department of Physiology, U of Kentucky
B. Taylor, Department of Physiology, U of Kentucky

Abstract: Despite the dramatic up-regulation of neuropeptide Y (NPY) in the dorsal horn of the mammalian spinal cord following inflammation, we know very little about its intrinsic ability to regulate the transmission of sensory signals. We found that doxycycline-induced conditional in vivo (Npy(tet/tet)) knockdown of NPY produced rapid, reversible, and repeatable increases in the intensity and duration of tactile and thermal hypersensitivity following midplantar injection of CFA. Remarkably, when allowed to resolve for several weeks, behavioral hypersensitivity could be reinstated with intrathecal administration of Y1 receptor antagonist BIBO3304 in a dose-dependent manner. However, the reinstatement of hypernociception could be reversed with intrathecal administration of TRPV1 antagonist, AMG9810. What's more, using microdialysis, we found that application of NPY to the spinal cord significantly reduced the capsaicin-evoked increase of SP-like immunoreactivity in microdialysate. In addition, Triple-label immunohistochemistry suggested co-expression of Y1, SP, and TRPV1 in lamina II of the dorsal horn. Taken together, NPY and Y1 receptors appear to be part of an endogenous braking mechanism whereby mammals naturally recover from the hyperalgesia associated with inflammation. The endogenous NPY-Y1 anti-hyperalgesic system can be targeted to TRPV1 to inhibit nociceptive neurotransmitter (such as SP) release from presynaptic terminals of primary afferent neurons in the superficial dorsal horn, and ultimately mask the inflammatory latent nociception. Furthermore, the reinstatement of hypernociception induced by intrathecal BIBO could also be reversed by intrathecal TRPA1 antagonist HC030031 and NMDA receptor antagonist MK801, indicating spinal TRPA1 and NMDA receptor are also downstream targets of spinal NPY- Y1 inhibitory signaling.

Supported by: NIH award: R01NS45954
Primary Presenter / e-mail: W. Fu / wfu222@uky.edu
Mentor or Senior Author / e-mail: B. Taylor / bkta222@uky.edu

#213 Abstract Title: Survey Says Patients are in Pain: An Analysis of HCHAPS Pain Scores

Author(s): W.S. Wilkie, Pharmacy Services, U of Kentucky
J. Smith, College of Medicine, U of Kentucky
K. Deep, Department of Internal Medicine, U of Kentucky
G. Davis, Pharmacy Services, U of Kentucky

Abstract: In 2006, the Centers for Medicare and Medicaid Services began publicly reporting Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) results. With the passage of the Affordable Care Act in 2010, Medicare reimbursement is now tied to patient satisfaction. Satisfaction with pain management is one of the core questions in the HCAHPS survey. Thus, improvement of pain management practice is a high priority especially for UK Chandler Hospital whose scores fall below the national average. It is our belief that pain control is more difficult in the subpopulation of patients who are at risk for opioid tolerance. Consequently, their satisfaction in relation to pain control will negatively impact the HCAHPS survey. Ultimately, this study could reveal areas for improvement in our pain management practice.This retrospective observation study will analyze patients' response to a satisfaction survey for patients admitted to the Internal Medicine (IM) service at UK Chandler Hospital between May 1, 2011 and September 30, 2012. Inclusion criteria include adults greater than 18 years of age and exclusion criteria include patients transferred to the IM service from other hospital services, patients transferred from outside hospital with a length of stay greater than 48 hours, and patients who had a hospital length of stay at UK less than 24 hours. Variables measure will include patient satisfaction, prior opioid exposure, history of drug abuse, past medical history, underlying cause of pain, duration of pain, pain assessment scores and pain medication orders.

Supported by:
Primary Presenter / e-mail: W. S. Wilkie / scott.wilkie@uky.edu
Mentor or Senior Author / e-mail: G. Davis / gadavi00@uky.edu

#214 Abstract Title: Epigenetic Regulation of Eotaxin Expression in Human Retinal Pigment Epithelium

Author(s): A.K. Berner, Department of Ophthalmology and Visual Sciences, U of Kentucky
D. Lou, Department of Ophthalmology and Visual Sciences, U of Kentucky
K. Mohan, Department of Ophthalmology and Visual Sciences, U of Kentucky
C.H. Jackson, Department of Ophthalmology and Visual Sciences, U of Kentucky
J.L. Brown, Department of Ophthalmology and Visual Sciences, U of Kentucky
J. Ambati, Department of Ophthalmology and Visual Sciences, U of Kentucky
M.E. Kleinman, Department of Ophthalmology and Visual Sciences, U of Kentucky

Abstract: Purpose: Age-related macular degeneration (AMD) is a most common cause of irreversible blindness in developed countries. Previous reports have identified increased eotaxin expression in retinal pigment epithelium (RPE) in both dry and neovascular AMD. New insights into epigenetic derangements and chromatin remodeling have garnered great interest as a potent biologic regulatory system. Histone deacetylases (HDAC) are part of this epigenetic regulatory system and serve as a unique control of the chromatin remodeling process. HDACs have become a novel target for the epigenetic regulation of critical pathways in aging and neurodegenerative diseases including AMD. Here, we show that eotaxin expression is regulated by HDAC-1 and demonstrate binding of HDAC-1 to the promoter region of eotaxin-3. Methods: Primary human RPE (hRPE) isolates (n=3, single donor, Lonza) were treated with class I/II HDAC inhibitors (valproic Acid (VPA), trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA) as well as a class III HDAC inhibitor, nicotinamide (NIC). Eotaxin 1/2/3 expression levels were measured at 24 hours via real-time PCR. HDAC1 binding of the eotaxin-3 promoter was confirmed using chromatin immunoprecipitation with appropriate target and control antibodies (SimpleChIP®, Cell Signaling) followed by PCR. Results: Exposure of primary hRPE isolates to class I/II HDAC inhibitors uniformly led to upregulation of eotaxin-3 ($P<0.05$) at 24 hours compared to vehicle alone or class III HDAC inhibition. While TSA led to elevated pan-eotaxin expression, VPA and SAHA resulted in specifically increased eotaxin-3 mRNA. At 48 hours, supernatant from VPA treated hRPE cells revealed an approximately 20% upregulation of eotaxin-3 protein compared to vehicle ($P<0.05$). ChIP demonstrated that HDAC-1 binds to the eotaxin-3 promoter in genomic DNA isolated from human RPE. Conclusion: We observed HDAC-1 regulation of eotaxin-3 gene with multiple class I/II inhibitors causing increased expression in primary hRPE isolates. Ongoing studies in our laboratory are focused on whether epigenetic derangements that occur with aging may cause increased expression of pro-inflammatory gene cassettes in AMD via HDAC-1 modulation.

Supported by: National Eye Institute K08EY021757 Research to Prevent Blindness Career Development Award Foundation Fighting Blindness Career Development Award University of Kentucky College of Medicine Physician Scientist Award
Primary Presenter / e-mail: A.K. Berner / Andre.Berner@uky.edu
Mentor or Senior Author / e-mail: M.E. Kleinman / Mark.Kleinman@uky.edu

#215 Abstract Title: Identifying Molecular Mechanisms Underlying SNP-related BIN1 Splice Variants

Author(s):
C. Van Sanford, College of Medicine, U of Kentucky
J. F. Simpson, Department of Physiology, Sanders-Brown Center on Aging, U of Kentucky
S. Peterson, School of Medicine, University of Louisville
S. Estus, Department of Physiology, Sanders-Brown Center on Aging, U of Kentucky

Abstract: Recent Genome-Wide Association Studies have identified a series of single nucleotide polymorphisms (SNP)s that are associated with Alzheimer's disease. Several of these SNPs are near or within the gene Myc box-dependent-interacting protein (BIN1). We looked at two AD-associated SNPs in BIN1; one, rs1060743 ("SNP1"), is located in exon 6 of BIN1, and the other, rs7561528 ("SNP2"), is located in the BIN1 promoter region and is more strongly correlated with AD. PCR of 60 brain cDNA samples visualized on acrylamide gels suggested a possible association between SNP1 and skipping of exon 7. To investigate this possibility more rigorously, we used real-time PCR and found a positive correlation between the major SNP 1 allele (T) and exon 7 skipping. The functional significance of these changes is unclear at this time; however, the BIN1 protein encoded by BIN1 mRNA missing exon 7 (or "delta-7" BIN1 mRNA) is missing 31 amino acids from the BIN1-amphiphysin-Rvs167 domain which has been previously identified as critical to BIN1 function. To quantitatively measure the effects of SNP 1 on exon 7 splicing, we used ion torrent RNA-SEQ to gather sequence data from brain cDNA samples that were heterozygous for SNP 1. We then extracted allelic expression imbalance (AEI) ratios for SNP 1 in each sample by comparing the number of delta-7 BIN1 sequences containing the minor SNP1 allele (C) to the number containing the major SNP1 allele (T). Five of the 20 samples showed significant AEI for SNP 1. In all five of these cases, there were more delta-7 sequences containing the minor SNP 1 allele than delta-7 sequences containing the major allele. We used fluorescent dideoxynucleotide sequencing to identify other BIN1 SNPs that may have influenced the AEI in these five samples, and identified two possible candidates: rs934826 and rs67327804, both of which were more frequently heterozygous in the five "significant AEI" samples than in the 15 "non-AEI" samples. We plan to use minigene constructs to investigate the specific effects of these SNPs on BIN1 exon 7 splicing in SNP1 heterozygotes. Results of this ongoing work will be presented.

Supported by: NIH award: P01-AG030128 and UK CCTS Professional Student Mentored Research Fellowship
Primary Presenter / e-mail: C. Van Sanford / cvansanford@uky.edu
Mentor or Senior Author / e-mail: S. Estus / steve.estus@uky.edu

#216 Abstract Title: A Murine Model of Acute Pancreatitis Exhibiting Age-Dependent Mortality, Inflammation, and Thrombosis

Author(s):
D. Okamura Department of Surgery and Markey Cancer Center, U of Kentucky
M. E. Starr, Department of Surgery and Markey Cancer Center, U of Kentucky
E. Y. Lee, Department of Pathology, U of Kentucky
A. J. Stromberg, Department of Statistics, U of Kentucky
B. M. Evers, Department of Surgery and Markey Cancer Center, U of Kentucky
H. Saito, Departments of Surgery and Physiology and Markey Cancer Center, U of Kentucky

Abstract: BACKGROUND: Acute pancreatitis is a common inflammatory disease affecting >200,000 people annually in the US. Although the severity and mortality rates of AP are significantly elevated in the elderly population, the underlying mechanisms for this age-dependent vulnerability is largely unknown mainly due to a lack of appropriate animal models. OBJECTIVE: In the present study, we used a murine model of AP and identified pathophysiologies that are distinctive of the aged with AP. METHODS: AP was induced in young (4-5 months), middle-aged (12-13 months), and aged (23-25 months) C57BL/6 mice by repeated injection of caerulein, a homologue of the gastrointestinal hormone cholecystokinin. RESULTS: Approximately 10% of aged mice died during AP while young and middle-aged mice showed no mortality. Although both young and aged mice exhibited early signs of edema and inflammation in the pancreas, kidney, and lung, young mice showed signs of recovery within 24 h while aged mice exhibited increasingly severe tissue damage and cell death. There was a significant age-dependent increase in pancreatic neutrophil activation and systemic inflammation as assessed by pancreatic myeloperoxidase and plasma interleukin-6 concentration, respectively. Importantly, aged but not young mice with AP showed significantly elevated thrombosis in the lung and kidney as well as a marked increase in plasma concentration of plasminogen activator inhibitor-1, a primary inhibitor of the fibrinolytic system. CONCLUSIONS: These results demonstrate that aging is associated with increased severity of AP characterized by augmented and prolonged pancreatic inflammation and also increased cell death and thrombosis in multiple extra-pancreatic organs.

Supported by: NIH Award: R01AG025908, R01AG039732, and R36AG038547
Primary Presenter / e-mail: D. Okamura / marlene.starr@uky.edu
Mentor or Senior Author / e-mail: H. Saito / hiroshi.saito@uky.edu

#217 Abstract Title: **Degeneration of Cochlear Outer Hair Cells in the Mouse Model of Non-Syndromic Deafness, DFNB3.**

Author(s):
D. Syam, Department of Physiology, U of Kentucky
A. J. Alexander, Department of Physiology, U of Kentucky
A. C. Velez-Ortega, Department of Physiology, U of Kentucky
G. P. Sinha, Department of Physiology, U of Kentucky
G. I. Frolenkov, Department of Physiology, U of Kentucky

Abstract: In the US, approximately one in thousand newborns is deaf or develops profound hearing loss in early childhood. There are many identified genes, which mutations result in congenital nonsyndromic deafness. One of these genes (MYO15) encodes unconventional myosin XVa. Mutations in myosin XVa are responsible for congenital profound deafness, DFNB3 in humans and deafness and vestibular defects in Shaker-2 (Sh2) mice. Murine myosin XVa (Myo15a) is localized at the tips of mechanosensory stereocilia in the inner ear hair cells. In the organ of Corti, these sensory cells form one row of inner and three rows of outer hair cells (OHCs). The molecular identity of channels responsible for mechano-electrical transduction (MET) in the mammalian hair cells is yet unknown, but number of evidence indicate that these channels are also located at the tips of stereocilia. In wild type hair cells, the mechanical movement of stereocilia is transduced into an electrical signal when current flows through the MET channels into the cell and depolarizes it. Myo15a interacts with the actin core of stereocilia and is important in the maintaining their structure. However, its role in the mechanotransduction process is not fully understood. In Sh2 mice, a missense mutation, (260G>A), makes the motor domain of Myo15a dysfunctional and leads to profound deafness. Both inner and outer hair cells of homozygous Sh2/Sh2 mice have abnormally short stereocilia. However, Sh2/Sh2 OHCs start to degenerate after the first few days of postnatal development. We hypothesize that structural abnormalities due to the dysfunctional Myo15a result in redistribution of mechanical forces applied to the MET channels, which remain open, resulting in a standing current that continuously flows into the hair cell. This may result in a continuous influx of calcium that leads to disassembly and degeneration of stereocillia. Whole cell patch-clamp technique was used to record standing currents in OHCs of Sh2/+ and Sh2/Sh2 mice at different ages. MET channel-dependent component of the standing current was determined by bath application of dihydrostreptomycin (DHSM), a known blocker of the MET channels. Preliminary results show that MET-dependent component of the standing current is larger in Sh2/Sh2 OHCs than in control, normally functioning Sh2/+ OHCs. The patch-clamp recording data were supported by scanning electron microscopy (SEM) imaging that demonstrated concomitant degeneration of stereocilia with age. Thus, continuous influxes of calcium into the OHCs may be responsible for their degeneration in patients with DFNB3 deafness.

Supported by: Supported by NIDCD/NIH (R01DC008861).
Primary Presenter / e-mail: D. Syam / diana.syam@uky.edu
Mentor or Senior Author / e-mail: G.I. Frolenkov / gregory.frolenkov@uky.edu

#218 Abstract Title: **CD8+ Immune T Cells Remove Tissue Cysts of Toxoplasma gondii from the Brain by Recognizing Both the Parasite Genotype-Specific Antigens and Common Antigens Expressed in Different Genotypes**

Author(s):
E. Ochiai, Microbiology, Immunology and Molecular Genetics, U of Kentucky College of Medicine
S. Qila, Microbiology, Immunology and Molecular Genetics, U of Kentucky College of Medicine
S. Perkins, Microbiology, Immunology and Molecular Genetics, U of Kentucky College of Medicine
Y. Suzuki, Microbiology, Immunology and Molecular Genetics, U of Kentucky College of Medicine

Abstract: T. gondii establishes a chronic infection by forming tissue cysts preferentially in the brain. This chronic infection is one of the most common parasitic infections worldwide. Our recent study revealed that CD8+ immune T cells of BALB/c mice genetically resistant to the infection have a potent activity to remove tissue cysts from the brain through their perforin-mediated activity. To address the parasite antigens important for this T cell-mediated immune process, we examined whether the T cells remove the tissue cysts by specifically recognizing genotypes of the parasite. SCID mice were infected with the ME49 strain (type II) and treated with sulfadiazine to establish chronic infection. The animals then received CD8+ immune T cells from wild-type animals infected with either the ME49 or CEP (type III) strain. One week after the cell transfer, cyst numbers were markedly fewer in the mice that had received the T cells from either ME49- or CEP-infected donors when compared to control animals that had received no T cells. Cyst numbers in mice that had received normal T cells did not differ from those of the control animals. When compared between the groups that had received the T cells from ME49-infected and CEP-infected donors, cyst numbers were significantly fewer in the former than the latter. Greater levels of cerebral expression of perforin were observed in the recipients in association with larger decreases in cyst numbers. These results indicate that CD8+ immune T cells can recognize T. gondii antigens commonly expressed in the cyst stage of the different genotypes of the parasite and remove them from the brains of infected host. Genotype-specific recognition of the cysts by the T cells also contributes to their anti-cyst activity to a lesser extent.

Supported by: Supported in part by grants from NIH (AI095032, AI078756, and AI077887) and The Stanley Medical Research Institute (#08R-2047).
Primary Presenter / e-mail: E. Ochiai / eri.ochiai2@uky.edu
Mentor or Senior Author / e-mail: Y. Suzuki / yasu.suzuki@uky.edu

#219 Abstract Title: Mechanisms for Age-Dependent Coagulation after CLP-Induced Sepsis in Mice

Author(s): H. Saito, Departments of Surgery and Physiology and Markey Cancer Center, U of Kentucky
M. E. Starr, Department of Surgery and Markey Cancer Center, U of Kentucky
H. Takahashi, Department of Surgery and Markey Cancer Center, U of Kentucky
B. M. Evers, Department of Surgery and Markey Cancer Center, U of Kentucky
D. Okamura Department of Surgery and Markey Cancer Center, U of Kentucky

Abstract: Background: Activation of coagulation and inhibition of fibrinolysis are important mechanisms in the pathogenesis of sepsis. We previously reported that increased mortality of aged mice during endotoxemia is partly due to enhanced coagulation, caused by age-dependent retardation of anti-coagulant protein C (PC) pathway activation. Objective: The purpose of this study was to investigate mechanisms for age-dependent coagulation during cecal ligation and puncture (CLP)-induced sepsis. Methods: Intra-abdominal peritonitis was induced by CLP using either 21 or 16 gauge (G) needles on young (4-6 months) and aged (23-25 months) male C57BL/6 mice. Coagulation was assessed by measuring fibrin formation. Plasma d-dimer and plasminogen activator inhibitor type-1 (PAI-1) were measured to evaluate fibrinolysis. Activated protein C (aPC) levels were used to evaluate activation of the PC pathway. Degree of inflammation was assessed by plasma IL-6 levels. Results: Compared to young mice, aged mice showed significantly increased mortality, coagulation and inflammation after 21G-CLP. Young mice with 16G-CLP showed a mortality rate and inflammation levels equivalent to aged mice with 21G-CLP; however, fibrin formation in the lung and kidney was prominent only in aged mice. Levels of pulmonary tissue factor, plasma d-dimer and plasma PAI-1 were equivalent in young (16G) and aged (21G) mice. Plasma aPC levels were elevated after CLP in young (16G and 21G) mice but remained low in aged (21G) mice. Conclusions: Disseminated intravascular coagulation during CLP-induced sepsis is enhanced in an age-dependent fashion and likely due to reduced anti-coagulant PC pathway function in the aged; fibrinolysis seems largely unaffected by aging.

Supported by: NIH Award: R01AG025908, R01AG039732, and R36AG038547
Primary Presenter / e-mail: H Saito / hiroshi.saito@uky.edu
Mentor or Senior Author / e-mail: H Saito / hiroshi.saito@uky.edu

#220 Abstract Title: IgG Antibodies Recognize Unique Toxoplasma gondii Antigens in Association with Active Proliferation of Tachyzoites in the Brain During the Chronic Stage of Infection

Author(s): J. Mullins, U of Kentucky
J. Hester, U of Kentucky
Q. Sa, U of Kentucky
L. Payne, Virginia Polytechnic Institute and State University
C. Mercier, U Joseph Fourier
M.F. Cesbron-Delauw, U Joseph Fourier
Y. Suzuki, U of Kentucky and Virginia Polytechnic Institute and State University

Abstract: Our recent study revealed that the anti-T. gondii antibody titer profile of mice with active cerebral proliferation of tachyzoites (reactivation of infection) during the chronic stage of infection resembles those of individuals with certain diseases including cryptogenic epilepsy. To develop a better serological method to detect reactivation of the infection, we examined whether IgG antibodies recognize different parasite antigens in the hosts with and without cerebral tachyzoite growth during the chronic stage of infection. For this purpose, two groups of CBA/J mice, which display continuous tachyzoite growth in their brains during the later stage of infection, were infected, and one group received treatment with sulfadiazine to prevent tachyzoite proliferation during the chronic stage of infection. T. gondii antigens recognized by the IgG antibodies from these two groups of mice were compared using immunoblotting following separation of tachyzoite antigens by two-dimensional gel electrophoresis. Several antigens, including the microneme protein MIC2, the cyst matrix protein MAG1, the dense granule proteins GRA4, and GRA7, were commonly recognized by IgG antibodies from both groups of mice. There were multiple antigens recognized mostly by IgG antibodies of only one group of mice, either with or without cerebral tachyzoite growth. The antigens recognized only by or mostly by the antibodies of mice with cerebral tachyzoite growth include MIC6, the rhoptry protein ROP1, GRA2, one heat shock protein HSP90, one (putative) heat shock protein HSP70, and the myosin heavy chain. The antigen recognition pattern of IgG antibodies of mice with acute acquired infection differed from those described above. These results indicate that IgG antibody levels increase only to selected and unique T. gondii antigens in association with cerebral tachyzoite proliferation in immunocompetent hosts with chronic infection.

Supported by: This work was supported by a grant (#08R-2047) from The Stanley Medical Research Institute, and in part by grants from the National Institutes of Health (AI078756, AI095032, and AI077887).
Primary Presenter / e-mail: J. Mullins / jeremi.mullins@uky.edu
Mentor or Senior Author / e-mail: Y. Suzuki / yasu.suzuki@uky.edu

#221 Abstract Title: **Inhibition of Class I/II Histone Deacetylases Results in Degeneration of the Retinal Pigment Epithelium**

Author(s):
K. Mohan, Department of Ophththalmology and Visual Sciences, U of Kentucky
A.K. Berner, Department of Ophththalmology and Visual Sciences, U of Kentucky
D. Lou, Department of Ophththalmology and Visual Sciences, U of Kentucky
J. Abney, Department of Ophththalmology and Visual Sciences, U of Kentucky
J. Ambati, Department of Ophththalmology and Visual Sciences, U of Kentucky
M.E. Kleinman, Department of Ophththalmology and Visual Sciences, U of Kentucky

Abstract: Purpose: Histone deacetylase complexes (HDACs) influence diverse regulatory pathways that effect cell death and survival. Although HDAC inhibitors are currently being tested for neuroprotection, including in the retina, our knowledge of the complex immune regulatory functions of HDACs is surprisingly lacking. Here, we have tested several widely used HDAC chemical inhibitors and present preliminary data suggestive of pro-inflammatory and degenerative effects to the RPE/choroid in mice following such HDAC inhibition. Methods: Wild type C57BL/6 mice received intravitreal injections of valproic acid (VPA, 1µg), trichostatin A (TSA, 0.1 µg) or suberoylanilide hydroxamic acid (SAHA, 1µg) (n=3 eyes per group) or DMSO as a negative control. Color fundus and fluorescein angiography images were acquired (Topcon 50-IX) at 3 and 7 days after injection. Eyes were then harvested and prepared as RPE/choroid flatmounts for Zo-1 immunostaining and analysis (Leica SP5). Mice were also sacrificed at 24 hours after injection for RNA isolation from RPE/choroid. RNA was prepared for real time PCR (RT-PCR; ABI 7900HT) assay to quantify cytokine expression. Results: Intravitreal injections of TSA, SAHA, and VPA resulted in RPE degeneration while DMSO did not, as observed by fundus photography and confirmed with Zo-1 immunostaining. RT-PCR analysis revealed an increased expression of eotaxin-2 in RPE/choroid of mice injected with HDAC inhibitors, as compared to vehicle. Conclusion: Chemical inhibition of HDACs using TSA, VPA, and SAHA results in RPE degeneration and increased eotaxin-2 expression in an animal model.

Supported by: National Eye Institute award: K08EY021757 Research to Prevent Blindness Career Development Award Foundation Fighting Blindness Career Development Award University of Kentucky College of Medicine Physician Scientist Award

Primary Presenter / e-mail: K. Mohan / mo.hak@uky.edu
Mentor or Senior Author / e-mail: M.E. Kleinman / mark.kleinman@uky.edu

#222 Abstract Title: **Validating the Use of HL60-Derived Neutrophilic Cells to Examine Cathepsin B Release Dynamics Under Shear Stress Exposure**

Author(s):
M. L. Akenhead, Center for Biomedical Engineering, U of Kentucky
X. Zhang, Center for Biomedical Engineering, U of Kentucky
N. M. Horrall, Center for Biomedical Engineering, U of Kentucky
H. Y. Shin, Center for Biomedical Engineering, U of Kentucky

Abstract: Shear stress-sensitive cleavage of CD18 cell-cell adhesion molecules off the human neutrophil surface is part of a control mechanism to minimize inflammation in the blood under non-pathogenic conditions. Recently, cathepsin B (catB) has been identified as a key protease involved in CD18 cleavage, but it is unclear how shear regulates the release of this protease. To address this, we plan to overexpress a catB-GFP construct in neutrophils and track its extracellular release. Transfection of human neutrophils, however, is not feasible due to their short lifespan (<24 hours) outside the body. As an alternative, we tested the possibility of using HL60-derived neutrophilic cells as a transfectable culture model, capable of exhibiting a shear-induced CD18 cleavage response comparable to human neutrophils. To accomplish this, HL60 cells were treated with 1.25% DMSO for 5 days to induce a neutrophilic phenotype prior to 5 dyne/cm2 shear stress exposure for 10 minutes. Based on flow cytometric analyses, sheared cells exhibited reduced expression of CD18 and CD11a, but not CD11b. Moreover, E64, a catB inhibitor, attenuated the shear-induced CD18 and CD11a cleavage responses of cells. Based on our results, HL60 neutrophilic cells exhibit preferential shear-induced cleavage of CD11a over CD11b isotypes, which differs from that of human neutrophils. Primary neutrophils have been shown to exhibit preferential cleavage of CD11b over CD11a isotypes. Despite this difference, our results indicate that the CD18 cleavage response to shear is a characteristic of the neutrophil phenotype. As such, HL60-derived neutrophilic cells may be a suitable transfection model for exploring shear-related catB release.

Supported by: National Science Foundation IGERT, 'Engineered Bioactive Interfaces' (PI: Kim Anderson, PhD, Department of Chemical Engineering)

Primary Presenter / e-mail: M. L. Akenhead / mak227@g.uky.edu
Mentor or Senior Author / e-mail: H. Y. Shin / hy.shin@uky.edu

#223 Abstract Title: **Dietary Restriction and Surgical Removal of Adipose Tissue Reduce Age-Dependent Intolerance to Inflammatory Stress**

Author(s):
M. E. Starr, Department of Surgery and Markey Cancer Center, U of Kentucky
B. M. Evers, Department of Surgery and Markey Cancer Center, U of Kentucky
H. Saito, Departments of Surgery and Physiology and Markey Cancer Center, U of Kentucky

Abstract: BACKGROUND: Despite increased risk of mortality from sepsis in older patients, the underlying mechanisms for this age-related predisposition remain largely unknown. Our previous studies using a murine endotoxemia (LPS) model of sepsis showed that augmented inflammation and thrombosis in the aged is associated with increased mortality (Blood 2010). We also reported that adipose tissue is a major source of pro-inflammatory and pro-coagulant factors during endotoxemia and that these factors are more abundantly produced in aged compared to young mice (Aging Cell 2013). OBJECTIVE: To test the hypothesis that loss of fat in middle-aged (12-months) and aged (22-24-months) mice would remove the major source of many pro-inflammatory and pro-coagulant factors and thus, improve age-associated sensitivity to endotoxemia. METHODS: Two methods were utilized to reduce fat mass: short-term 40% dietary restriction (DR) and surgical removal of fat. Mice were injected with LPS and monitored for survival or sacrificed for tissue harvesting. RNA was isolated from fat for qRT-PCR. Plasma was analyzed by ELISA. RESULTS: Short-term DR in middle-aged mice resulted in significantly lower levels of circulating cytokines (IL-6 and IL-1β) and adipose-tissue derived pro-inflammatory (IL-6) and pro-coagulant (TF, PAI-1, PAI-2, Thbs-1) factors during endotoxemia. Short-term DR in aged mice did not improve pathophysiology during endotoxemia. Surgical adipose tissue removal improved survival by 20-40% in aged mice after injection with a lethal dose of LPS. CONCLUSIONS: Reduction in the quantity of adipose tissue through DR reduces susceptibility to endotoxemia in middle-age, however, in old age the beneficial effects of short-term DR are lost.

Supported by: NIH Awards: R01AG025908, R01AG039732, and R36AG038547
Primary Presenter / e-mail: M.E. Starr / marlene.starr@uky.edu
Mentor or Senior Author / e-mail: H. Saito / hiroshi.saito@uky.edu

#224 Abstract Title: **A Combination Approach In a Canine Model of Aging: Effects of Immunotherapy and Behavioral Enrichment**

Author(s):
P. R. Davis, Sanders-Brown Center on Aging, Molecular and Biomedical Pharmacology, U of Kentucky
G. Giannini, Lovelace Respiratory Research Institute, Albuquerque, NM
X. Wang, Sanders-Brown Center on Aging, Molecular and Biomedical Pharmacology, U of Kentucky
T. Beckett, Sanders-Brown Center on Aging, Biochemistry, U of Kentucky
T. Platt, Sanders-Brown Center on Aging, Biochemistry, U of Kentucky
M. P. Murphy, Sanders-Brown Center on Aging, Biochemistry, U of Kentucky
E. G. Barrett, Lovelace Respiratory Research Institute, Albuquerque, NM
A. L. S. Dowling, Sanders-Brown Center on Aging, Molecular and Biomedical Pharmacology, U of Kentucky
E. Head, Sanders-Brown Center on Aging, Molecular and Biomedical Pharmacology, U of Kentucky

Abstract: Alzheimer's disease (AD) is characterized by cognitive decline and a hallmark neuropathology, senile plaques (SPs) and neurofibrillary tangles. SPs contain β-amyloid (Aβ), cleaved from the amyloid precursor protein (APP). Several therapeutic strategies being developed focus on reducing the production or deposition of Aβ. The canine model is useful for testing potential therapeutic agents. Canines produce APP with 98% homology to human APP, develop Aβ neuropathology, and cognitively decline with age. Active immunization with fibrillar Aβ1-42 (IMM) for 2 years in aged canines has shown to significantly decrease brain Aβ and maintained executive function, while other measures of cognition remained unchanged. However, behavioral enrichment (BEH) improved cognition without reducing brain Aβ. We hypothesized that IMM combined with BEH would provide larger cognitive benefits and further reduce neuropathology, as compared to controls or IMM and BEH alone. Forty aged beagles (10.5-13.6 y) were divided into four groups: controls (Alum adjuvant only), fibrillar Aβ1-42 + Alum, BEH with Alum, and combination treatment (IMM+BEH). Animals were treated for 18 months. Fibrillar Aβ1-42 antibody titers in serum and Aβ levels in cerebral spinal fluid (CSF) were measured by ELISA. By 6 months, anti-Aβ1-42 IgG responses in IMM groups increased significantly ($F(2,64)=3.24$ $p=0.046$) as compared to non-IMM groups, and were maintained. No effects on CSF Aβ1-42, Aβ1-40, or total Aβ were observed. On a test of spatial attention (landmark task), BEH dogs performed significantly better than IMM dogs ($t(16)=2.7$ $p=0.016$). Additional measures of cognition are being analyzed, as are changes in brain Aβ, extent of neurogenesis, and growth factor levels.

Supported by: NIH/NIA AG031764
Primary Presenter / e-mail: P. R. Davis / pau.davis@uky.edu
Mentor or Senior Author / e-mail: E. Head / Elizabeth.Head@uky.edu

#225 Abstract Title: **IL-2 Produced by CD8+ Immune T cells Can Play an Autocrine Enhancing Role in Their IFN-γ Production Independently from Their Proliferation in the Secondary Response To an Intracellular Pathogen**

Author(s):
Q. Sa, Microbiology, Immunology and Molecular Genetics, U of Kentucky College of Medicine
J. Woodward, Microbiology, Immunology and Molecular Genetics, U of Kentucky College of Medicine
Y. Suzuki, Microbiology, Immunology and Molecular Genetics, U of Kentucky College of Medicine

Abstract: CD8+ T cells and IFN-g are important for protection against various intracellular pathogens. Chronic infection with Toxoplasma gondii induces a potent resistance to re-infection, and IFN-g production by CD8+ T cells is crucial for the resistance. Here we examined the role of IL-2 in IFN-g production by CD8+ immune T cells in their secondary responses using T. gondii-specific CD8+ T cell hybridomas and splenic CD8+ immune T cells from chronically infected mice. The majority of CD8+ T cell hybridomas produced large amounts of IFN-g only when a low amount (0.5 ng/ml) of exogenous IL-2 was provided in combination with T. gondii antigens. Inhibition of cell proliferation by mitomycin C (MMC) did not affect the enhancing effect of IL-2 on the IFN-g production, and significant increases in transcription factor T-bet expression were associated with the IL-2-mediated IFN-g amplification. Splenic CD8+ immune T cells produced similar low levels of IL-2 in the secondary response to T. gondii, and a blocking of IL-2 signaling by anti-IL-2Ra antibody or inhibitors of JAK1 and JAK3 significantly reduced IFN-g production of the T cells. This IL-2-mediated upregulation of IFN-g production was observed in MMC-treated CD8+ immune T cells, thus independent from their cell division. Therefore, endogenous IL-2 produced by CD8+ immune T cells can play an important autocrine enhancing role on their IFN-g production in the secondary responses to T. gondii, suggesting an importance of induction of CD8+ immune T cells with an appropriate IL-2 production for vaccine development.

Supported by: Supported in part by grants from NIH (R01 AI077887, AI078756, and AI095032) and The Stanley Medical Research Institute (#08R-2047).

Primary Presenter / e-mail: Q. Sa / qsa222@uky.edu
Mentor or Senior Author / e-mail: Y. Suzuki / yasu.suzuki@uky.edu

#226 Abstract Title: **Subset of microRNAs Is Regulated by Peroxisome Proliferator-Activated Receptors/Retinoid X Receptors in Distinct Rat Brain Cells**

Author(s):
W.-X. Wang, Sanders Brown Center on Aging, U of Kentucky
I. Artlushin, Sanders Brown Center on Aging, U of Kentucky
Q. Huang, Sanders Brown Center on Aging, U of Kentucky
B.R. Wilfred, Sanders Brown Center on Aging, U of Kentucky
C.M. Norris, Molecular and Biomedical Pharmacology, Sanders Brown Center on Aging, U of Kentucky
P.T. Nelson, Pathology and Lab Medicine, Sanders Brown Center on Aging, U of Kentucky

Abstract: MicroRNAs (miRNAs) play fundamental roles in biological and pathological processes that include many human diseases such as Alzheimer's disease (AD) and diabetes. Studies on miRNA biology have constituted an active research field, but the regulation of miRNA is not well understood. Peroxisome proliferator-activated receptors (PPARs) and retinoid X receptors are ligand-activated nuclear transcription factors that regulate gene expression. PPAR/RXR transcription complex play critical roles in normal and disease-related biological processes including tissue regeneration, differentiation, lipid and glucose metabolism, and immune response. Activation of PPAR isoforms, especially PPARγ, has been shown to be protective in brain; however, how PPARs confer neuroprotection is not well understood. Earlier clinical trials of AD prevention and treatment using PPARγ activating drugs produced mixed results, perhaps due to the incomplete understanding of PPAR pathways that could well be due to the lack of knowledge on their roles in miRNA regulation. PPAR regulation of miRNA expression in central nervous system (CNS) is an unexplored area. Based on our preliminary studies, we hypothesized that PPARs regulate miRNAs expression in different brain cells (neuron, astrocyte, and microglia) in CNS. Using NanoString miRNA nCounter technology, initial miRNA profiling showed a subset of miRNA is regulated by PPAR/RXR transcription factors. Several miRNAs including miR-20a, miR-22, miR-27a were among the most significantly up-regulated miRNAs in response to PPARγ and RXR agonist treatments. The preliminary data also revealed a distinct pattern of miRNA regulation by PPAR/RXR in neuronal and non-neuronal cells. This project provides a groundbreaking data resource for further understanding the role of miRNA and PPAR/RXR in gene regulations.

Supported by: The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117.

Primary Presenter / e-mail: W.-X. Wang / wwangc@email.uky.edu
Mentor or Senior Author / e-mail: P.T. Nelson / pnels2@email.uky.edu