Appalachian Health Summit
Oral Presentation Abstracts
7th Annual CCTS Spring Conference
March 29, 2012

CTS Presentations: Bench to Bedside

Abstract Title: **Noninvasive Optical Evaluation of Spontaneous Low Frequency Oscillations in Cerebral Blood Flow and Oxygenation**

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Abstract:
Background: The phase shift between the low frequency (~0.1 Hz) oscillations (LFOs) of arterial blood pressure (ABP) and cerebral blood flow (CBF) velocity in large cerebral arteries has been used to assess cerebral autoregulation (CA), but no one has directly evaluated the CA in microvasculature. In this study, we explore using near-infrared diffuse optical technologies to simultaneously detect the LFOs of CBF and cerebral oxygenation (i.e., oxy-, deoxy-, and total- hemoglobin concentrations: [HbO2], [Hb], THC) in microvasculature. Methods: Fifteen healthy subjects participated in this study. The cerebral hemodynamics and ABP were noninvasively measured by a novel hybrid optical instrument and a finger plethysmography under three physiological conditions, sequentially: at rest, 70° head up tilting (HUT), and enforced breathing at 0.1 Hz. The measurements under each condition lasted for 10 minutes. The valid LFO signals were judged by the coherences (> 0.4) between the ABP and each of the hemodynamic parameters, respectively. Results: The successful rates to obtain the valid LFOs of CBF, [HbO2], [Hb], and THC under three conditions are listed as follows respectively: 83%, 70%, 53%, and 73% at rest; 100%, 100%, 80%, and 100% during HUT; and 93%, 97%, 87%, and 100% during enforced breathing. Conclusions: The CBF, [HbO2] and THC are reliable parameters in detecting LFOs and HUT is the most robust and stable protocol for quantifying the phase shifts of hemodynamic LFOs. Future study will investigate LFOs in patients with cerebral vascular diseases and evaluate their CAs via the quantification of LFO phase shifts.

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CTS Presentations: Bench to Bedside

Abstract Title: **AKT and AR Signaling Cooperate to Mediate Cell Survival in Advanced Prostate Cancer**

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Abstract:

The PI3K/AKT and AR-driven ETS signaling pathways are often concurrently activated and cooperate to promote prostate cancer progression. The objective of this study is to determine the mechanisms of AKT and AR cooperation in prostate cancer growth and whether inhibition of both AKT and AR signaling is an effective approach to therapy. Selective inhibitors of AKT and AR, a variety of molecular techniques and tissue culture and in vivo xenograft models were used to determine the effects of AKT and AR inhibition, alone or in combination, on AKT or AR pathway activity, cell proliferation and survival, and tumor growth in advanced prostate cancer models with AKT activation, alone or in the context of co-activation of AR/ETS signaling. We showed that AKT inhibition alone effectively suppressed growth of AKT-activated prostate cancer only in AR-negative tumors. In contrast, prostate tumors with coexistent activation of the AR/ETS signaling pathway were resistant to AKT inhibition. In such tumors, inhibition of either AKT or AR alone was insufficient to induce apoptosis or to inhibit tumor growth. However, combined inhibition of both AKT and AR synergistically induced apoptosis and effectively repressed tumor growth in vivo. Notably, we identified that AKT and AR signaling cooperated to regulate expression of the anti-apoptotic protein survivin. Reduction of survivin expression by RNA interference markedly inhibited cell proliferation and caused cell death in prostate tumors. These data demonstrate that both AKT and AR signaling pathways are required for cell survival by convergent regulation of survivin expression. Inhibition of both pathways, therefore, is a useful therapeutic strategy for advanced prostate cancer.

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CTS Presentations: Bench to Bedside

Abstract Title: **The Evaluation of An Optimized Sigma Receptor Ligand: Effects Against Methamphetamine**

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Abstract:
Methamphetamine interacts with sigma receptors at physiological relevant concentrations suggesting a potential site for pharmacologic intervention. In the present study, a previously studied sigma receptor ligand, CM156, was optimized for metabolic stability and the lead analog was evaluated against the behavioral effects of methamphetamine. Radioligand binding studies demonstrated seven of the nine CM156 analogs maintained high nanomolar affinity at sigma-1 receptors while eight of the compounds retained high nanomolar affinity at sigma-2 receptors. In addition, the lead analog AZ66, had preferential affinity for sigma receptors compared to 64 non-sigma sites and a significantly longer half life than its predecessor, CM156, both in vitro and in vivo. Pretreatment of male, Swiss Webster mice with intraperitoneal or oral dosing of AZ66 significantly attenuated the acute locomotor stimulatory effects of methamphetamine. Additionally, AZ66 significantly reduced the expression and development of behavioral sensitization induced by repeated methamphetamine administration. Taken together with earlier studies, the data indicate that sigma receptors can be targeted to mitigate the acute and subchronic behavioral effects of methamphetamine.

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CTS Presentations: Bench to Bedside

Abstract Title: **Identification of phosphodiesterase-4 (PDE4) subtypes in the regulation of ethanol intake**

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Abstract:

Cyclic AMP (cAMP)-protein kinase A (PKA) signaling has been implicated in regulating alcohol consumption. Our previous studies showed that inhibitors of phosphodiesterase-4 (PDE4) increased cAMP in the brain and decreased ethanol intake in the two-bottle choice test in mice. However, since there are no selective inhibitors of individual PDE4 subtypes (PDE4A-D), it is not known which PDE4 subtype(s) is (are) involved. Using mice deficient in PDE4A, PDE4B, or PDE4D, the major PDE4 subtypes in the brain, we determined the contributions of individual PDE4 subtypes to ethanol intake and preference. Mice deficient in either PDE4A or PDE4B displayed decreases in ethanol (7-12%) intake and ethanol preference by more than 50% relative to wild-type controls in the two-bottle choice test. They also exhibited decreases in ethanol intake in the ethanol (9%) drinking-in-the-dark paradigm. In contrast, mice deficient in PDE4D did not show similar effects on ethanol drinking. Sucrose (2% and 4%) intake was also decreased in mice deficient in PDE4A or PDE4B relative to WT controls, but quinine intake was not changed between the genotypes. These results suggest that PDE4A and PDE4B are important PDE4 subtypes in the regulation of ethanol consumption. Selective inhibitors of PDE4A or PDE4B may be used for treatment of alcohol dependence (This work was supported by research grants from NIH R21 AA020042 and WVU RFDG).

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CTS Presentations: Bedside to Community

Abstract Title: **Family Health History and Epigenetics in Rural Appalachian Communities: The West Virginia Community Genetics Forum**

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Abstract:

Background: Research is uncovering more knowledge that lifestyle and environmental factors change gene expression. However, communities have limited knowledge of epigenetics, particularly in rural areas. This project seeks to establish a model of community engagement by increasing rural communities' knowledge about epigenetics to motivate health behavior change. Methods: The WVU Prevention Research Center (PRC) and their Community Partnership Board (CPB) collaborated on all aspects of this study. Partners conducted town hall forums in three rural WV communities. Information was collected via surveys and open discussions of family health history. We assessed knowledge surrounding genetics/genomics, and the transfer of knowledge to friends and family. Results: We identified methods for engaging communities in genomic education and central beliefs surrounding the ability to change individual health outcomes. Family health stories may be an effective tool for targeting education in these populations. Communities provided guidance for engaging health care providers in future discussions. Conclusions: Rural communities often have a fatalistic view of health and disease. Educating communities on family health history and how lifestyle can modify gene expression may motivate and empower behavior change at individual, family, and community levels. Community driven health promotion and translational research projects will be targeted in future statewide, regional, and national initiatives.

Supported by: This project was supported by the National Human Genome Research Institute through an intramural Contract #HHSN268201100321P to T.L. Barr and the West Virginia Prevention Research Center.

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CTS Presentations: Bedside to Community

Abstract Title: **A Genome-wide Association Study of Pathologically-confirmed Hippocampal Sclerosis of Aging**

Author(s): D. W. Fardo, Department of Biostatistics, University of Kentucky
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Abstract:

It is becoming evident from autopsy-based research that hippocampal sclerosis (HS) neuropathology is relatively prevalent in older persons and is associated with considerable antemortem clinical dysfunction. HS refers to a specific pattern of neuronal cell loss and astrocytosis in hippocampus and subiculum, independent of Alzheimer's disease (AD) pathology. The extent that genetic or environmental risk factors that influence AD pathology interact strongly with those for HS is as yet unresolved. We and others have recently studied HS using Alzheimer's Disease Center (ADC) data and other datasets. We find that HS occurs in up to 15% of older individuals (especially persons over 90 years of age). We also showed that the presence of HS correlates with significant impact on the severity of antemortem cognitive impairment. Therefore, individuals with HS are more likely to be diagnosed with "dementia" and/or AD because the HS probably contributes to cognitive impairment independently. That said, assessing the cognitive changes attributable to HS pathology is a challenge. For individuals above 85 years of age, it is the norm for brains to harbor multiple types of pathology. A relatively sophisticated approach is thus required in terms of concomitant clinical and pathological factors and various other potential confounders. Candidate gene studies of HS have been published, but there has not been a previously published genome-wide association study (GWAS) of single nucleotide polymorphisms (SNPs) in HS. We present GWAS results comprising ~2.5 million SNPs on ~100 pathology-confirmed HS cases and ~600 HS controls.

Supported by: Alzheimer's Disease Genetics Consortium Special Analysis Grant (5U01AG032984-03)

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CTS Presentations: Bedside to Community

Abstract Title: **Safety and Efficacy of an Automated Protocol in Management of Diabetic Ketoacidosis (DKA)**

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Abstract:
Objective: To determine the efficacy of an automated protocol for management of Diabetic Ketoacidosis (DKA). Methods: Our study is a retrospective chart review of DKA patients managed before and after the automated DKA protocol implementation at a tertiary care hospital. Results: There were 88 patients managed one year prior (control group) and 70 patients managed one year after the implementation of automated DKA protocol (study group). The DKA resolution time was significantly shorter [11.5 (8.1-17.1) hours vs. 8.5 (5.8-12) hours, P = 0.008] and the hypoglycemic events were significantly less [P = 0.042] in the study group compared to the control group. There was no difference in the potassium abnormalities and rate of decline of glucose. On a 1-10 scale survey, the majority of physicians and nurses surveyed rated the protocol as safe (83%) and effective (96%). However 54% of the nurses found the protocol difficult to follow. Conclusions: Our study showed that implementation of an automated protocol reduced the DKA resolution time and hypoglycemic events without compromising electrolyte imbalance, and was associated with improved clinical measures of DKA management.

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CTS Presentations: Bedside to Community

Abstract Title: **Parent-Implemented Training for Autism through Telemedicine (PITA-T)**

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Abstract:
The purpose of the Parent-Implemented Training for Autism through Telemedicine (PITA-T) study is to conduct research on a novel telemedicine model to address service and training barriers associated with rural and low-income families. Hypothesis: This study will test three hypotheses. We anticipate that (1) parents will learn to effectively implement discrete trial teaching (DTT), (2) the skills of children receiving Applied Behavior Analysis (ABA) therapy from parents will improve, and (3) parents will report reductions in their stress levels. Number of subjects: We are still in the experimental phase, and hope to have data for 100 participants at the conclusion of the study. Procedures: We are training parents of young children with Autism Spectrum Disorders (ASD) through written or videotaped instruction to implement ABA therapy in their homes. Parents complete initial assessments at our clinic and are mailed written or videotaped instructional materials for implementing DTT with their child. Parents record themselves implementing DTT in their home on a weekly basis and mail the videos to the research team for evaluation. The team reviews the videos and provides the parents with written or videotaped feedback on their implementation of DTT. Important findings: Preliminary findings from several participants indicate that parents did not correctly implement 80% of the components of DTT following instructions alone, regardless of whether the instructions were in written or video format. Feedback was necessary to improve performance.

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