13th Annual CCTS Spring Conference
Friday, April 13, 2018 Lexington Convention Center

UK MD/PhD Program Research Day

Oral Presentation

Abstract Title: **Sexual Dimorphism in a Marfan Syndrome Mouse Model**

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Abstract: The effect of sexual dimorphism on aortic pathology in mouse models of Marfan Syndrome has not been defined. Therefore, we determined differences in aortic diameter expansion between sexes in fibrillin-1 hypomorphic (FBN1mgR/mgR) mice. Ascending aortic diameters from male and female FBN1mgR/mgR mice and their wild type littermates were assessed every 4 weeks from 6 to 18 weeks of age by ultrasound. Measurements were taken luminal edge to luminal edge in diastole. Differences in aortic diameters between male and female FBN1mgR/mgR mice were detected at 6 weeks of age. There were no significant diameter differences between sexes of wild type littermates. At 18 weeks of age, differences of aortic diameters between male and female FBN1mgR/mgR mice increased, while there were no significant differences between sexes of wild type littermates. External aortic diameter measured after termination at 18 weeks correlated with in vivo ultrasound measurements. Male FBN1mgR/mgR mice had significantly greater aortic dilation compared to their female littermates. In contrast, aortic diameters were not different between sexes of wild type littermates. In addition to increased aortic diameter, death due to aortic rupture by 18 weeks was more frequent in male FBN1mgR/mgR mice than in female FBN1mgR/mgR mice. FBN1mgR/mgR mice exhibit sexually dimorphic ascending aortic diameters as early as 6 weeks of age. This sex difference increased with age in FBN1mgR/mgR mice, while their wild type littermates do not exhibit significant difference. Subsequent studies using this model of Marfan Syndrome should state the sex of mice.

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UK MD/PhD Program Research Day

Oral Presentation

Abstract Title:	**Neuroprotective strategies following severe controlled cortical impact traumatic brain injury: lipid peroxidation-derived neurotoxic aldehyde scavenging and inhibition of mitochondrial permeability transition**
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Abstract: Traumatic brain injury (TBI) represents a significant health crisis in the United States. Currently there are no neuroprotective FDA-approved pharmacotherapies for TBI. Due to the complex pathophysiology which occurs following TBI, more robust pharmacological approaches must be developed. Mitochondrial dysfunction and the formation of neurotoxic aldehydes contribute extensively to TBI pathology, making them promising therapeutic targets for prevention of cellular death and dysfunction following TBI. The following are evaluated. 1) The neuroprotective effect of cyclosporine A (CsA), on synaptic and non-synaptic mitochondria. Mitochondria are heterogeneous, consisting of both synaptic and non-synaptic populations, which have distinct properties. Our results indicate that compared to non-synaptic mitochondria, synaptic mitochondria sustain greater damage 24h following severe controlled cortical impact injury in young male rats, and are protected to a greater degree by CsA, an FDA-approved immunosuppressant, capable of inhibiting mitochondrial permeability transition. 2) The neuroprotective effects of a 72h subcutaneous continuous infusion of CsA combined with phenelzine (PZ), an FDA-approved monoamine oxidase inhibitor (MAOI) class anti-depressant capable of scavenging neurotoxic aldehydes. Our results indicate that individually CsA or PZ attenuate neurotoxic aldehyde formation, PZ maintains mitochondrial respiratory control ratio and cytoskeletal integrity, but together, PZ and CsA, do not maintain neuroprotective effects. 3) The ability of PZ (aldehyde scavenger and MAOI), to attenuate cognitive dysfunction following TBI compared to hydralazine (aldehyde scavenger) and pargyline (MAOI), in an attempt to further elucidate the role PZ's MAOI mechanism of action has in TBI pathophysiology.

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13th Annual CCTS Spring Conference
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Oral Presentation

Abstract Title:	**Blood-Brain Partition Coefficient Correction Improves Gray-White Matter Contrast in Blood Flow Measurement in Mice**
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Abstract: Introduction: The blood-brain partition coefficient (BBPC) is an important parameter in the quantification of cerebral blood flow (CBF) as measured by arterial spin labeling (ASL) acquisitions. While this tissue-specific parameter is known to vary with age and brain region, particularly in gray vs white matter, the current consensus in the field of ASL is to assume a single constant value of 0.9mL/g for all regions and all subjects.1 In this study we use an accelerated calibrated proton density (ACPD) imaging technique2,3 to measure the BBPC directly, thus enabling a voxel-wise correction for BBPC when quantifying CBF. We then compare the BBPC-corrected CBF maps to standard maps calculated using the assumed constant value to test the hypothesis that BBPC-correction will increase the quality of quantitative CBF images. Methods: Imaging Protocol- Male C57Bl/N mice aged 12 months (n=8) were imaged using a 7T Bruker ClinScan (Bruker Biospin, Ettlingen, Germany) to acquire both ACPD images and pseudo-continuous ASL images. The ACPD images were acquired with a 39mm birdcage transmit/receive coil and the pCASL images were acquired with a four-channel phased-array surface receive coil without disturbing the position of the mouse by means of a custom bed and nose cone. For the ACPD images a series of phantoms with 0, 10, 20, 30, and 40% deuterium oxide in distilled water and doped with gadobutrol (Gadavist, Bayer Healthcare Pharmaceuticals, Whippany NJ, USA, 0.07mM), along with a blood-sample obtained from the facial vein of the mouse were placed inside the volume coil. A series of image stacks were acquired with a phase-spoiled, FLASH-GRE sequence (FOV= 2.8cmx2.8cm, matrix= 256x256, slice thickness= 1mm, number of slices= 10, flip angle= 90°) with a very short TE (3.2ms) and 6 different TR values (125, 187, 250, 500, 1000, 2000ms). The pCASL images were acquired with FOV= 1.8cmx1.3cm, matrix= 128x96, slice thickness= 1mm, number of slices= 6, TE/TR= 20/4000ms, label duration= 1.6s, post-label delay= 0s, averages= 120. Image Analysis- The centermost 2 slices containing the hippocampus were selected for analysis. The brain regions of the ACPD and pCASL images were isolated independently using an automated skull-stripping algorithm and then coregistered. The BBPC map was then calculated voxel-wise by fitting the ACPD series to the mono-exponential recovery curve S= M0*[1-e^(TR/T1)] to yield a map of M0, normalizing to the phantom series, and finally using the equation BBPC= M0,brain/(M0,blood *1.04g/mL).2 Quantitative CBF maps were calculated from the pCASL images according to the equation, where PLD is post-label delay, LD is label duration, T1,blood is the longitudinal relaxation of blood (2.2s at 7T), and ? is label efficiency (0.85). For standard CBF maps the BBPC was assumed to be a constant 0.9mL/g while the corrected maps used the measured BBPC maps to calculate CBF. Regions of interest encompassing the motor and sensory cortex, corpus callosum, and hippocampus were drawn manually on each analyzed slice. BBPC, uncorrected CBF, and corrected CBF values were averaged for each region of interest. Gray-white contrast was determined for each slice as the difference of average CBF values in gray and white matter regions of interest. All analysis was performed with self-written scripts in Matlab (Mathworks, Natick, MA, USA). Results: BBPC maps demonstrate significantly elevated BBPC in the cortical region (µCtx= 0.99±0.04mL/g) relative to the corpus callosum (µCC= 0.93±0.05mL/g, p = 0.008) and the hippocampus (µHc= 0.95±0.04mL/g, p= 0.057) (see Figs. 1&2). The corpus callosum always displayed lower CBF (µuncorrected= 1.44±0.3mL/g/min, µcorrected= 1.51±0.4mL/g/min), than the cortex (µuncorrected= 2.81±0.4mL/g/min, µcorrected= 3.09±0.5mL/g/min, p<0.001) and the hippocampus (µuncorrected= 2.90±0.6mL/g/min, µcorrected= 3.07±0.7mL/g/min, p<0.001) (see Fig. 3), however the uncorrected CBF maps underestimated blood flow in the cortex by 9.3% (95% CI= 5.6-12.9%), the corpus callosum by 4.9% (95% CI= 1.1-8.6%), and the hippocampus by 6.0% (95% CI= 2.5-9.5%) compared to the corrected CBF (see Fig.4). Correcting for regional differences in BBPC thus improves gray-white matter contrast by 15.1% in the cortex (95% CI= 10.1-20.1%) and 7.0% in the hippocampus (95% CI= 2.4%-11.7%). Discussion: In this study we measure significant regional differences in the BBPC of mice. These regional differences translate to errors in CBF quantification when using a global, constant value as is currently the standard in ASL imaging. Those errors are particularly important when studying white matter pathologies in diseases such as multiple sclerosis, leukoaraiosis, and Alzheimer's disease as the gray-white matter contrast can be reduced by as much as 15% by failing to account for the reduced BBPC of white matter relative to gray.

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UK MD/PhD Program Research Day

Oral Presentation

Abstract Title:	**Contextualizing the Stress Experience of Custodial Grandparents in Central Appalachia**
Author(s):	A. Hansen, College of Medicine, U of Kentucky R. Brown, Department of Sociology, U of Kentucky J. Gambrell, College of Medicine, U of Kentucky N. Schoenberg, College of Medicine, U of Kentucky

Abstract: With escalating rates of parental substance abuse, addiction, and incarceration in the rural U.S. and elsewhere, grandparents increasingly have stepped in to fulfill childrearing responsibilities. The rate of custodial grandparenting has been especially widespread in rural Appalachia, a region with sparse resources. The shift in kinship care reflects the resiliency and utility of extended family structures in Appalachia, but presents new challenges, including increased stress, for grandparent wellbeing. To better understand the stress experience of rural Appalachian grandparents with primary childrearing responsibilities, we conducted twenty-six in-depth interviews. Interviews were transcribed, subject to content analysis, and co-coded with 80% inter-coder reliability using NVivo11. Stress was described as arising from repositioning to parental role and forfeiting the grandparenting role, and from interactions with the parent generation. Physical health and worry about the ability to physically and financially provide for grandchildren were further sources of stress. Despite these sources of stress, grandparents suggested that caregiving was a major protective factor against depression and beneficial for their health and activity levels. Moreover, many grandparents indicated a cultural and historical continuity of grandparenting in a culture that traditionally has emphasized extended family ties and extensive social support.

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UK MD/PhD Program Research Day

Poster Presentation #2

Abstract Title:	**Identifying Novel Therapeutics to Inhibit the Wnt Self-Renewal Pathway in Leukemia Stem Cells**
Author(s):	M. Green, Department of Molecular and Cellular Biochemistry, U of Kentucky C. Liu, Department of Molecular and Cellular Biochemistry, U of Kentucky J. S. Blackburn, Department of Molecular and Cellular Biochemistry, U of Kentucky

Abstract: Although leukemia has a high cure rate, it is plagued by a high relapse rate and 15-20% of pediatric leukemia patients that go into remission will go on to have return of their disease. This relapse rate is likely due to a small population of cells known as leukemia stem cells (LSCs). Current efforts to study LSCs have faced serious limitations which have impeded our understanding of this population of cells. Prior work in our lab has established a zebrafish Myc-induced T-cell acute lymphoblastic leukemia (T-ALL) model that mimics the most aggressive and treatment resistant form of human T-ALL. Using this system, we were able to isolate single LSCs through a novel transplantation strategy. Analysis of growth rates at different limiting dilutions showed significant differences in the rate of self-renewal between different LSCs. Importantly, a subset of LSCs acquired increased self-renewal over time. We were able to generate a library of zebrafish T-ALL with very high self-renewal rates (about 1/10 cells is a LSC) that will be used to study LSC properties more efficiently. We analyzed these primary T-ALLs using RNAseq and single cell qPCR to compare expression profiles of the leukemias with low self-renewal rates to those with high self-renewal rates. This single cell qPCR showed a population of cells that expressed known self-renewal genes and had a very different gene expression profile than the rest of the cells in the population. This population was assumed to be LSCs and several novel genes were identified as markers of these LSCs. From this analysis, the Wnt pathway, more specifically ß-catenin, was identified as an important marker that was enriched in LSCs and not in the rest of the population of leukemia cells. Our collaborator at the University of Kentucky, Dr. Chunming Liu PhD, has designed a panel of 5 different families of Wnt inhibitor compounds which work at various points in the Wnt/B-catenin signaling pathway. We screened several of the Wnt inhibitor compounds in vivo using 6xTCF/LEF:GFP zebrafish which serve as Wnt pathway reporter fish. Several of the Wnt inhibitor compounds showed significantly decreased GFP expression after drug treatment, indicating inhibition of the Wnt pathway in vivo. In the future we plan to create a novel zebrafish model to mark LSCs. We will use 6xTCF/LEF:GFP;Rag2Myc:mCherry zebrafish as an in vivo model of LSCs. We then plan to use these zebrafish to screen our Wnt inhibitor drug compounds to see if they decrease LSC frequency, indicating inhibition of the LSC self-renewal pathway. We hypothesize that inhibitors of the Wnt pathway will inhibit self-renewal of LSCs and force them to differentiate into normal leukemia cells, representing a potential therapeutic strategy for targeting treatment-resistant LSCs.

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UK MD/PhD Program Research Day

Poster Presentation #3

Abstract Title: **Neurotensin Increases AMPK in Estrogen-Dependent Breast Cancer Cells**

Author(s): J. Johnson, Department of Toxicology & Cancer Biology, U of Kentucky
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Abstract: Introduction. Neurotensin (NT) is a thirteen amino acid peptide mainly involved in regulating lipid metabolism and storage. NT can also act through its high-affinity receptor (NTR1) to stimulate the growth and progression of a variety of NTR1-positive cancers. However, very little is known about the underlying NT signaling pathways that stimulate breast cancer growth. The purpose of this study is to elucidate mechanisms by which NT affects breast cancer. Methods. MCF-7 (estrogen-dependent) and MDA-MB-231 (triple negative) are breast cancer cell lines that express NTR1. (i) To assess signaling pathways mediating the effects of NT, both cell lines were treated with NT (0 or 100 nM) in serum-free media for a variety of times; immunoblotting was performed for phosphorylated and total forms of AMP-activated protein kinase (AMPK) and its downstream effector acetyl CoA carboxylase (ACC). (ii) Proliferation and invasion assays were conducted in a variety of different ways. Results. (i) NT induced activation of AMPK and ACC in MCF-7 cells but not in MDA-MB-231 cells. (ii) These changes in AMPK were not linked to any changes in cellular proliferation or invasion. Conclusions. Our findings indicate that NT activates AMPK and its downstream effector in estrogen-dependent breast cancer cells. These effects were minimal in NTR1-expressing triple negative breast cancer cells, suggesting that the molecular classification of the tumor plays an important role in NT signaling. Further delineating the differential effects of NT in specific breast cancer phenotypes has the potential to identify novel therapeutic targets in the treatment of this disease.

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UK MD/PhD Program Research Day

Poster Presentation #5

Abstract Title:	**Divergence of cAMP Signaling Pathways Mediating Augmented Nucleotide Excision Repair and Pigment Induction in Melanocytes**
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Abstract: Loss-of-function melanocortin 1 receptor (MC1R) polymorphisms are common in UV-sensitive fair-skinned individuals and are associated with blunted cAMP second messenger signaling and higher lifetime risk of melanoma because of diminished ability of melanocytes to cope with UV damage. cAMP signaling positions melanocytes to resist UV injury by up-regulating synthesis of UV-blocking eumelanin pigment and by enhancing the repair of UV-induced DNA damage. cAMP enhances melanocyte nucleotide excision repair (NER), the genome maintenance pathway responsible for the removal of mutagenic UV photolesions, through cAMP-activated protein kinase (protein kinase A)-mediated phosphorylation of the ataxia telangiectasia mutated and Rad3 related (ATR) protein on the S435 residue. We investigated the interdependence of cAMP-mediated melanin upregulation and cAMP-enhanced DNA repair in primary human melanocytes and a melanoma cell line. We observed that the ATR-dependent molecular pathway linking cAMP signaling to the NER pathway is independent of MITF activation. Similarly, cAMP-mediated up-regulation of pigment synthesis is independent of ATR, suggesting that the key molecular events driving MC1R-mediated enhancement of genome maintenance (e.g. PKA-mediated phosphorylation of ATR) and MC1R-induced pigment induction (e.g. MITF activation) are distinct.

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UK MD/PhD Program Research Day

Poster Presentation #12

Abstract Title:	**Anti-apolipoprotein A-I Antibody Profile Correlates With Cardiovascular Disease Outcomes**
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Abstract: Apolipoprotein A-I (ApoA-I) is a target of IgG autoantibody induction in patients, but the role of these antibodies has not been fully elucidated. Previous research has characterized anti-ApoA-I IgG antibodies targeting delipidated ApoA-I as a biomarker of cardiovascular progression, but only a moderate association was observed. We hypothesize that free anti-ApoA-I IgG is a single component of the anti-ApoA-I response and characterization of anti-ApoA-I antibody profiles will be more predictive of adverse cardiovascular outcomes. Given the relative concentrations of ApoA-I and anti-ApoA-I antibodies, we examined sera samples from 375 patients with coronary artery disease (CAD) to quantify soluble ApoA-I/IgG immune complexes (ICs). We found a range of ApoA-I/IgG IC concentrations in patients, irrespective of free anti-ApoA-I antibodies. While free antibodies failed to predict outcomes in this CAD cohort, a median Cox regression analysis over 6 years of follow-up determined a hazard ratio of 1.5 (95% CI: 1.03-2.18, p=0.03) for patients with below median ApoA-I/IgG ICs levels after adjusting for 11 traditional cardiovascular risk factors. In comparison, a cohort of healthy subjects exhibited significantly higher ApoA-I/IgG ICs. Pearson correlation analysis between ApoA-I/IgG ICs in the 375 patients with CAD and 25 patient characteristics found that only hypertension showed a significant association with ApoA-I/IgG ICs (r=-0.154, p=0.003). In addition, no significant relationship between ApoA-I/IgG ICs and total ApoA-I concentration (r=-0.0601, p=0.51) or total IgG concentration (r=0.134, p=0.137) was observed. Identification and ongoing characterization of ApoA-I/IgG ICs has the potential to guide clinical diagnosis and intervention strategies in patients with atherosclerotic cardiovascular disease.

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UK MD/PhD Program Research Day

Poster Presentation #17

Abstract Title:	**Characterizing Unique Protein-protein Interactions in Sterol Biosynthetic Enzymes for the Control of Fungal Pathogens**
Author(s):	K.B. Linscott, Department of Molecular and Cellular Biochemistry, College of Medicine, U of Kentucky J. Chappell, Departments of Molecular and Cellular Biochemistry and Pharmaceutical Sciences, U of Kentucky

Abstract: Invasive fungal infections are a significant cause of patient morbidity and mortality, indicating a need for the identification of new therapeutic targets. Squalene synthase is the first committed step in sterol biosynthesis, and while this enzyme plays a critical role in cell growth, the protein architecture is shared among eukaryotes and so is resistant to the design of fungal-specific growth inhibitors. It has been shown that there is a unique component of the fungal carboxy-terminal domain which allows the fungal squalene synthase, not the enzyme from plants or animals, to complement a knockout mutation in yeast. We hypothesize that there is a fungal-specific motif within this domain involved in regulation of the sterol pathway that can be mimicked for the development of an antifungal therapeutic. To identify this motif, we used the yeast Saccharomyces cerevisiae with a squalene synthase knockout mutation and expressed chimeric squalene synthases originating from multiple kingdoms of life. In contrast to previous observations, all enzymes tested were able to partially complement the knockout mutation when the genes were weakly expressed. Induction of non-fungal squalene synthases could not complement the yeast mutation and led to the accumulation of carboxy-sterol intermediates. These results suggest that the motif is involved in mediating an interaction between squalene synthase and the downstream C4-decarboxylase. Restoration of the complete complementation phenotype was mapped to a kingdom-specific 26-amino acid hinge motif, and over-expression of the C-terminal domain containing this hinge motif from a fungal squalene synthase led to growth inhibition of wild-type yeast.

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Poster Presentation #22

Abstract Title: **Epithelial-Specific P85? KO Enhances Crypt Resilience to Radiation Injury**

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Abstract: While high-dose radiation remains an effective treatment for aggressive cancers, it also exerts stress on physiologically high cycling cells, including intestinal epithelial cells (IEC), where it causes significant toxicity (diarrhea, bleeding, etc). Here we examine the role of PI3-Kinase (PI3K) signaling in promoting epithelial repair after radiation injury. To interrogate the role of IEC PI3K in radiation injury, we utilized VillinCre-p85fl//fl (p85KO) and VillinCre-p85+/+ subjected to high dose (12Gy) radiation. IEC Western blot (WB) data of p85KO mice at baseline revealed a complete ablation of p85?, with subsequent increases in p-AktSer473 along with p-PTEN, p-GSK3?Ser9, as well as anti-apoptotic protein survivin compared to WT controls, suggesting a deregulation of PI3K machinery. RT-PCR studies performed at baseline revealed increases in TA-enriched Wnt target genes, Axin2 (56%) and c-myc (39%) and reserve intestinal stem cell (ISC) markers HopX (33%), and Bmi1 (20%), at the expense of the active cycling Lgr5+ stem cells (-25%). Histopathologic sections highlight a distinct shift in the zone of proliferation with more than a 2-fold increase in BrdU+ cells at the reserve stem cell position 4 compared to controls. Following lethal radiation dosage, p85KO mice exhibited a 20% increase in survival as compared to wildtype (WT) littermates along with increased crypt survival (29% change). In p85KO mice, radiation induced lower levels of PUMA and cleaved caspase 3 compared to WT controls. Our data suggest PI3K signaling enhances recovery from radiation injury through expansion of reserve ISC populations capable of re-creating proliferative Lgr5+ ISC and accelerating crypt recovery.

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UK MD/PhD Program Research Day

Poster Presentation #25

Abstract Title:	**Small Molecule Isotope Resolved Formula Enumerator (SMIRFE): a tool for truly untargeted metabolomics analysis of metabolites represented in Fourier transform mass spectra**
Author(s):	J. M. Mitchell, Department of Molecular and Cellular Biochemistry, Markey Cancer Center, Center for Environment and Systems Biochemistry, Resource Center for Stable Isotope Resolved Metabolomics, U of Kentucky R. M. Flight, Markey Cancer Center, Center for Environment and Systems Biochemistry, Resource Center for Stable Isotope Resolved Metabolomics, U of Kentucky H. N. B. Moseley, Department of Molecular and Cellular Biochemistry, Markey Cancer Center, Center for Environment and Systems Biochemistry, Resource Center for Stable Isotope Resolved Metabolomics, U of Kentucky

Abstract: Fourier-transform mass-spectrometry (FTMS) is often utilized in the detection of small molecules derived from biological samples. What is directly detected in the FTMS spectra are peaks for related sets of isotopologues or molecules that differ only in their isotopic composition for various adducted and charged species corresponding to specific molecules present in a biological sample or introduced by contamination. The sheer complexity of what is detected along with a variety of analytically-introduced variance, error, and artifacts have hindered the systematic analysis of the complex patterns of detected peaks with respect to isotopic content. We have implemented a novel algorithm SMIRFE that detects small biomolecules less than 2000 daltons at a desired statistical confidence and determines their specific elemental molecular formula (EMF) using detected cliques of related isotopologue peaks with compatible isotope-resolved molecular formulae (IMFs). The current implementation efficiently searches a roughly 200 quintillion (2x1020) IMF space for each peak's m/z, but larger IMF spaces are searchable. We validated the assignment performance using verified assignments from a FTMS spectrum of a biological sample treated with ethylchloroformate, a chemoselection agent. SMIRFE provides both high accuracy for untargeted assignment for verified metabolite cliques and unambiguous IMF assignment for over half of the detected peaks in analyzed peak lists. Furthermore, SMIRFE provides E-value estimates of assignment accuracy, which no other available metabolite assignment tool provides. Also, SMIRFE has none of the limitations of current methods that can only detect known metabolites in a database. Thus, this new method enables a truly untargeted metabolomics analysis.

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UK MD/PhD Program Research Day

Poster Presentation #26

Abstract Title:	**Defining an Electronic Phenotype for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis in an Electronic Health Record Paired with a DNA BioBank Facilitates Genetic Discovery**
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Abstract: Stevens-Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN) is the most severe T-cell mediated adverse drug reaction (ADR), associated with mortalities of 30% or higher and significant short and long-term complications. Strong class I HLA-B associations have been defined for SJS/TEN for several drugs, which offer a potential preventive screening strategy, but associations for most drugs and populations remain undefined. Vanderbilt University Medical Center's (VUMC's) DNA repository BioVU, paired with the Synthetic Derivative (SD), its de-identified electronic health record system, offers a platform for developing a robust electronic phenotype for SJS/TEN to facilitate the discovery of genetic associations with this condition. Using ICD9/10 codes, keywords, and time restraints, we developed an electronic phenotype in the SD that identified patients who had been treated for SJS/TEN at VUMC. This electronic phenotype was extremely sensitive, identifying 35/36 (97%) of Bactrim-induced and 25/28 (89%) of Phenytoin-induced SJS/TEN cases in the SD. Of the cases we identified, 25 had DNA samples in BioVU available for genotyping. We genotyped the HLA-B genes of these cases and found that their alleles clustered around alleles with known shared peptide-binding specificities, namely the superfamilies of B7 and B44. Our methodology here provides a framework for developing electronic phenotypes of SJS/TEN that can be validated across other large electronic health record databases.

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UK MD/PhD Program Research Day

Poster Presentation #30

Abstract Title: **?-Catenin Regulation of Skelatal Muscle Hypertrophy**

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Abstract: Purpose: Cytoplasmic free ?-catenin is tightly regulated as a downstream effector in the canonical Wnt signaling cascade, which is capable of implementing a cellular growth program during development and regeneration. A second and equally important function of ?-catenin involves linking the cell cytoskeleton with the transmembrane protein, cadherin, which binds to its counterpart in a neighboring cell, thereby forming stable intercellular connections known as adherens junctions. Previous studies suggest that Wnt signaling is intimately involved in the regulation myogenesis and muscle repair, and that ?-catenin may be a key contributor to hypertrophic growth in adult skeletal muscle. Methods: We generated an adult muscle-specific mouse model of tamoxifen-induced ?-catenin inactivation only in mature myofibers and not in satellite cells. We used a surgical model, synergist ablation, to induce mechanical overload on the plantaris muscle and cause robust hypertrophy within one week. Results: Loss of ?-catenin led to significantly blunted myofiber hypertrophy and a concomitant increase in satellite cell proliferation. Conclusion: ?-catenin and its interaction with cadherins on the myofiber side may be a necessary component of myofibers' mechanotransduction signals that controls satellite cell entry into the "Galert" phase and prepare resident stem cells for regeneration.

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UK MD/PhD Program Research Day

Poster Presentation #34

Abstract Title:	**An Epigenetic Approach for the Modulation of Amyloid Precursor Protein (APP) Processing in Alzheimer's Disease**
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Abstract: Alzheimer's disease (AD) is a multifactorial ailment for which current therapeutics remain insufficient to broadly address the underlying pathophysiology. Because epigenetic gene regulation can affect multiple gene and protein pathways, including those involved in AD, we hypothesized that a single epigenetic modulating drug would simultaneously affect the expression of a number of AD-related gene targets. Using an AD cell model over-expressing APP with the Swedish mutation (HEK/APPsw), we screened our in-house library of epigenetic drugs to identify non-toxic small molecules that significantly reduced ?-amyloid (A?). Candidate compounds were confirmed with A? ELISA. Then, using real time quantitative polymerase chain reaction (RT-qPCR) and western blots, we analyzed the effects of the small molecules on AD-relevant gene and protein expression. We identified a small molecule histone deacetylase inhibitor, M344, that is non-toxic, reduces A?, and alters the expression of multiple AD-related genes. Of note, M344 decreases amyloidogenic ?-secretase (BACE) gene expression. Additionally, M344 increases the expression of BDNF, a-secretase (ADAM10), MINT2, FE65, and other AD-relevant genes. M344 also increases sAPPa and CTFa metabolite production, both cleavage products of ADAM10, concordant with increased ADAM10 gene expression. M344 also increases levels of immature APP, supporting an effect on APP trafficking, concurrent with the observed increase in MINT2 and FE65, both shown to increase immature APP. Using an epigenetic approach, we show that it is possible to use a single drug compound to simultaneously affect the expression of key AD and neuroprotective genes.

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UK MD/PhD Program Research Day

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UK MD/PhD Program Research Day

Poster Presentation #35

Abstract Title:	**Novel Applications of MRI Techniques in the Detection of Neuronal Dysfunction before Tangle Pathology in Tau Transgenic Mice**
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Abstract: Background: Tauopathic patients have significant cognitive decline accompanied by severe, irreversible brain atrophy. Neuronal dysfunction is thought to occur years before diagnosis. A major obstacle in the treatment of tauopathies is that current diagnostic tools are ineffective at detecting pre-pathological changes. We previously developed a MEMRI (manganese-enhanced magnetic resonance imaging) protocol coupled with R1-mapping to measure the extent of neuronal dysfunction that occurs before appearance of cognitive deficits and tau pathology associated with the rTg4510 tau model. In this study, we performed MEMRI with mangafodipir, an FDA-approved contrast. Methods: We used MEMRI to measure neuronal dysfunction in rTg4510 mice tau transgenic mice at 2 months (no pathology/cognitive deficits), and 3 months (presymptomatic pre-tangle pathology detectable). We measured MEMRI R1 changes before (baseline) and after (time-course) injecting mangafodipir (50mg/kg) intraperitoneally. We focused on the superior cortex and hippocampal sub-regions. Results: We found mangafodipir to be an effective contrast for MEMRI of mouse brains. Optimal enhancement of the cortex and hippocampus occurs 12-24 hours post-injection. Functional changes were detectable in transgenic mice at two months. Conclusions: This study builds upon our previous work showing that MEMRI (with MnCl2) reveals important functional differences between tau transgenic and non-transgenic mice. Here we found that mangafodipir is at least as effective as MnCl2 in performing MEMRI, detecting differences at an earlier time point. Mangafodipir exhibits less toxicity than MnCl2 due to structural similarity to EDTA (used to treat manganese toxicity), making mangafodipir a target for translation of MEMRI for tauopathy into human subjects.

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UK MD/PhD Program Research Day

Poster Presentation #36

Abstract Title:	**CLARITY for 3-D In Vivo Imaging of the Neurovascular Unit**
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Abstract: CLARITY is a newly developed tissue clearing method used for the transformation of biological tissue into a tissue-hydrogel hybrid, enabling highly detailed images of the brain's cellular structure. Historically, imaging studies have been limited to small regions of the brain or do not allow for staining of relevant proteins or genes. CLARITY uses an acrylamide hydrogel to maintain the structural organization of proteins and nucleic acids and surfactant-assisted delipidation to render the tissue permeable to immunostaining and suitable for detailed microscopic analysis. For our studies, we used the X-CLARITY™ System from Logos Biosystems. Male CD-1 mice were anesthetized; the thorax was opened; and an infusion needle was placed into the left cardiac ventricle to perfuse the brain with PBS and paraformaldehyde. Whole brain was collected and fixed in paraformaldehyde. After washing with PBS, brains were either processed as a whole or sliced into sections. Brain tissue was placed in hydrogel solution and hybridized utilizing the X-CLARITY™ Polymerization System. Once hybridized, lipids from the tissue were removed through electrophoresis with ionic detergents using the X-CLARITY™ Tissue Clearing System. After clearing, the neurovasculature was stained with collagen IV primary antibody followed by incubation with Cy3-conjugated secondary antibody. In addition, we cleared the brains of mice with YFP-labeled neurons. Cleared brain tissue was imaged using a Nikon A1R inverted confocal microscope. We are currently using CLARITY with single- and two-photon microscopy imaging to examine the spatial relationship between cells of the neurovascular unit in animal models of neurodegenerative and neurological disorders.

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UK MD/PhD Program Research Day

Poster Presentation #37

Abstract Title:	**Differential Susceptibility of Large-Scale Brain Networks to White Matter Alterations in Aging**
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Abstract: Introduction: Older adults experience significant alterations in white matter (WM) structure during aging. Most studies examining these measures have focused on whole brain or single tract-focused approaches to quantify these alterations. However, it is unclear how these alterations differentially affect various large scale brain networks, such as the default mode network (DMN), dorsal attention network (DAN), or fronto-parietal control network (FPCN). In this study, we investigated the differential effects of WM alterations within and between these large-scale brain networks. Methods: 66 cognitively normal older adults (ages 60-92) underwent diffusion tensor imaging (DTI) and FLAIR imaging. Probabilistic tractography was performed to generate group templates of WM pathways within each network (DMN, DAN, FPCN) and between each network (i.e. DMN to DAN). WM hyper-intensities (WMHs) were identified in FLAIR images using an automated approach. Fractional anisotropy (FA) and WMH volume were measured within each WM template. Repeated-measures ANOVA was performed to examine whether there was a significant WM template × age interaction for either FA or WMH volume. Results: There was a significant WM template × age interaction for WMH volume ($F_{5,60} = 3.35$, $p = .01$) but not for FA ($F_{5,60} = 1.36$, $p = .25$). Follow-up analyses demonstrated that the following pattern for the strength of positive correlations between age and WMH volume: DAN > FPCN = DAN to FPCN > DMN to FPCN = DMN to DAN = DMN. In contrast, FA values across all WM templates were negatively associated with age to a similar degree. Conclusions: WMH volume, but not WM microstructure, is differentially affected across large-scale brain networks in aging. The DAN and FPCN appear to show greater WMH volume with increasing age, while the DMN shows the least. Future work should investigate whether the differential susceptibility of these networks to accumulating WMHs is associated with cognition.

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Poster Presentation #39

Abstract Title:	**Neuroprotective strategies following severe controlled cortical impact traumatic brain injury: lipid peroxidation-derived neurotoxic aldehyde scavenging and inhibition of mitochondrial permeability transition**
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Abstract: Traumatic brain injury (TBI) represents a significant health crisis in the United States. Currently there are no neuroprotective FDA-approved pharmacotherapies for TBI. Due to the complex pathophysiology which occurs following TBI, more robust pharmacological approaches must be developed. Mitochondrial dysfunction and the formation of neurotoxic aldehydes contribute extensively to TBI pathology, making them promising therapeutic targets for prevention of cellular death and dysfunction following TBI. The following are evaluated. 1) The neuroprotective effect of cyclosporine A (CsA), on synaptic and non-synaptic mitochondria. Mitochondria are heterogeneous, consisting of both synaptic and non-synaptic populations, which have distinct properties. Our results indicate that compared to non-synaptic mitochondria, synaptic mitochondria sustain greater damage 24h following severe controlled cortical impact injury in young male rats, and are protected to a greater degree by CsA, an FDA-approved immunosuppressant, capable of inhibiting mitochondrial permeability transition. 2) The neuroprotective effects of a 72h subcutaneous continuous infusion of CsA combined with phenelzine (PZ), an FDA-approved monoamine oxidase inhibitor (MAOI) class anti-depressant capable of scavenging neurotoxic aldehydes. Our results indicate that individually CsA or PZ attenuate neurotoxic aldehyde formation, PZ maintains mitochondrial respiratory control ratio and cytoskeletal integrity, but together, PZ and CsA, do not maintain neuroprotective effects. 3) The ability of PZ (aldehyde scavenger and MAOI), to attenuate cognitive dysfunction following TBI compared to hydralazine (aldehyde scavenger) and pargyline (MAOI), in an attempt to further elucidate the role PZ's MAOI mechanism of action has in TBI pathophysiology.

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Poster Presentation #42

Abstract Title: **Reading aloud improves working memory related frontal theta oscillations in older adults**

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Abstract: We previously reported that two different cognitive interventions (reading aloud and origami practice) improved memory performance in cognitively normal older adults. Both tasks exercise working memory, and successful working memory manipulation has been associated with increased frontal theta power as detected by EEG. Here we test the hypothesis that these tasks increased theta power during the intervention to improve working memory performance. We randomly assigned 36 cognitively-normal participants over age 65 to a reading, an origami, or placebo group over the course of eight weeks. Pre- and post-intervention EEG signals were collected as participants performed the Bluegrass Short-Term (BeST) memory task. Changes in theta power in frontal-lobe and parietal-lobe leads were analyzed and compared to performance on the BeST task and neuropsychology tests. Participants in the reading group showed increases in theta power in the left frontal ($0.009uV^2$, $p=0.028$), right frontal ($0.008uV^2$, $p=0.028$), left parietal ($0.005uV^2$, $p=0.017$), and right parietal ($0.008uV^2$, $p=0.013$) leads, while participants in the origami group did not. Participants in the control group showed an increase in the left frontal lead ($0.005uV^2$, $p=0.041$). Of note, theta power changes in bilateral frontal sites were associated with FCSRT (Frontal Left $b=175$, $p=0.05$, Frontal Right $b=245$, $p=0.009$) but not MOCA scores. Our results suggest that reading intervention may have enhanced performance on cognitive tasks by increasing working memory performance mediated by theta waves in the frontal lobe. Future analyses will examine post-intervention alpha and gamma changes to see how they mediate improved cognitive functioning from reading aloud or origami practice.

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Poster Presentation #45

Abstract Title: **Elucidating Subtypes and Risk Factors of Brain Arteriolosclerosis**

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Abstract: Cerebrovascular pathologies are often seen in aged brains. Here, we focus on brain arteriolosclerosis (B-ASC), i.e., degenerative thickening of cerebral arterioles. We recently reported that severe B-ASC pathology is associated with global cognitive status (PMID 26738751). To study risk factors of B-ASC, we analyzed 2,390 cases with clinical and neuropathological autopsy data from the National Alzheimer's Coordinating Center. Cases were analyzed according to age at death (< 80 years and ? 80 years) using logistic regression modeling. Gender was associated with B-ASC pathology in both age at death groups after controlling for covariates including age at death, and conventional vascular risk factors: hypertension, diabetes, smoking, and hypercholesterolemia. In a subset of cases with genetic information (n = 925), the ABCC9 gene variant (rs704180), previously associated with hippocampal sclerosis, was also associated with B-ASC pathology in the ? 80 year-old group. To address in finer detail the heterogeneous arteriolar morphologies that could be classified as B-ASC, we analyzed 74 cases from the University of Kentucky Alzheimer's Disease Center (UKADC) and UK Pathology Department. Within this convenience sample, the median age at death was 56.5 years with a range of 20 – 96 years. One of the subtypes of B-ASC pathology in this cohort consisted of arteriolar profiles with multiple internal lumens, which we refer to as multi-lumen vessels (MLVs, which generally have ? 3 lumens in a single vascular profile). In this sample, 62.1% (n = 46) of cases had ? 5 MLVs per brain section, as operationalized using CD34 immunohistochemistry in the frontal neocortex (Brodmann area 9). Interestingly, MLV densities increased with advanced age of death ($r = 0.51$; $p < 0.0001$). We conclude that B-ASC is a complex pathologic phenotype in advanced age with both genetic and clinical risk factors, as well as morphologic subtypes, that require further study.

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UK MD/PhD Program Research Day

Poster Presentation #46

Abstract Title:	**Identifying Predictive Fluid Biomarkers for White Matter Hyperintensities (WMH) and Cognitive Impairment in Vascular Cognitive Impairment and Dementia (VCID)**
Author(s):	T. L. Sudduth, Sanders-Brown Center on Aging, U of Kentucky Z. S. Winder, Department of Physiology, U of Kentucky D. M. Wilcock, Department of Physiology, U of Kentucky

Abstract: Vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia and often occurs co-morbidly with Alzheimer's disease (AD). Currently diagnosis for VCID is limited to clinical signs of cognitive impairment partnered with vascular injury seen most often as white matter hyperintensities (WMH) on MRI neuroimaging. There is a growing need in the research and clinical communities to develop an earlier and more accurate diagnosis of VCID. This project seeks to identify fluid biomarkers in CSF and blood collections, which can help to act as early markers for VCID. Our preliminary data looked primarily at the cross-sectional results of CSF and blood samples collected from patients in our MCI-CVD (Mild Cognitive Impairment-Cerebrovascular Disease) cohort using MSD V-PLEX assays to measure levels of 4 possible biomarkers (TNF?, IL-12, PIGF, VEGF-D) along with other inflammatory and angiogenic proteins. The future plans for this project will look towards determining the correlation of these biomarkers to longitudinal clinical progression as well as pathologic changes as seen with neuroimaging. In addition we hope to make use of machine learning to help us better predict a diagnosis of VCID with the fluid biomarkers seen in our CSF and blood samples.

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Poster Presentation #47

Abstract Title:	**APOE, Metabolism and Cognitive Function: An Assessment via Indirect Calorimetry**
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Abstract: The gene Apolipoprotein E (APOE) encodes for three isoforms in the human population (E2, E3, and E4), and the E4 isoform – carried by approximately 1/5 of the population – is the strongest genetic risk factor for late onset Alzheimer's Disease (AD). Both AD and E4 have been associated with impaired brain metabolism. Our preliminary data show that aged mice expressing human E4, and not E3, demonstrate a metabolic "shift" reflected as a preference for lipids vs carbohydrates as a fuel source. We hypothesize that similar apoE differences are present in cognitively normal individuals, and therefore aim to translate these findings to human subjects. We believe an E4-directed shift away from carbohydrate utilization may represent a critical step in the progression of cognitive decline, and thus a potential novel biomarker for AD risk. To test our hypotheses, we aim to measure metabolic rate and respiratory quotient (RQ) using indirect calorimetry (IC). Real-time metabolic measures will be assessed in individuals with various APOE genotypes – both at rest and during a cognitive and dietary challenge. Interpretation of RQ will be aided by measuring adiposity, blood glucose, and urinary urea nitrogen. Initial feasibility studies show measurable increases in RQ during a cognitive challenge, as well as a trend toward increased resting energy expenditure. Additionally, an acute dietary challenge resulted in a steady increase in RQ following ingestion. We hope to expand our methods to measure elderly subjects (cognitively normal, mild cognitive impairment and AD), as well as potential collaborative efforts in other areas of neuroscience.

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Poster Presentation #50

Abstract Title:	**Cooking classes and dietary change in rural Appalachia**
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Abstract: Introduction: In rural Appalachia, rates of diet-linked diseases including hypertension, diabetes, cardiovascular disease, and cancer are all significantly higher than in other regions of the nation. Suboptimal dietary intake stems from a web of individual, interpersonal, social, and structural factors including taste preferences, peer influences, cultural patterns, food cost and access. Methods: When local residents identified lack of cooking skills as a significant barrier to healthy eating, we developed a multi-component, community-engaged dietary intervention that included six weekly cooking classes held in community centers. Questionnaires were administered at baseline, 3-weeks post intervention and 3-months post intervention to assess participants' barriers to healthy eating, food purchasing practices, cooking skills and adherence to nutritional guidance. We used a pre-test, repeated measures follow-up design with one group. Friedman's tests and Wilcoxon signed rank tests were used to compare participants' responses across time. Results: Eighty-five adults, ages 15-75, who regularly cooked for children participated in this study. Nearly half (43%) of participants indicated their household income was below $10,000. Results demonstrated statistically significant improvements in dietary behavior, including fewer barriers to eating healthfully, decreased consumption of fast food and unhealthy snacks, and increased use of nutritional information. Most improvements were sustained or even enhanced three months after class completion. Discussion: Acquisition of cooking skills and experience was associated not only with improved dietary attitudes and behavior, but also with decreased barriers to eating healthfully. Impressive in any population, these findings are particularly promising given participants' low-income levels and the modest sample size.

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Poster Presentation #56

Abstract Title:	**Progress towards developing zebrafish models to study the link between SoxC transcription factors and CHARGE syndrome**
Author(s):	L. A. Krueger, Department of Biology, U of Kentucky A.C. Morris, Department of Biology, U of Kentucky

Abstract: CHARGE syndrome (coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear abnormalities) is a complex congenital genetic disorder resulting in severe defects in multiple organ systems with an occurrence of 1:8,000-10,000 live births. Mutations in chromodomain helicase binding protein 7 (CHD7) and defects in neural crest cell development and migration have been implicated in the pathogenesis of CHARGE syndrome, however the mechanisms underlying the ocular birth defects observed in CHARGE patients have not been identified. Our laboratory studies the development of the vertebrate visual system using zebrafish (Danio rerio). Previous work from our lab has shown that knockdown of Sox11, a member of the SoxC family of transcription factors, in zebrafish results in microphthalmia, coloboma, brain, trunk, and heart defects, all phenotypes observed in CHARGE syndrome. Furthermore, a duplication of Sox11 has been identified in a patient clinically diagnosed with CHARGE syndrome, and CHD7 has been shown to directly interact with Sox11 and Sox4 in neural stem cells. Taken together, these data strongly suggest that loss of SoxC expression contributes to the ocular and other phenotypes observed in Chd7-associated CHARGE syndrome. In this study, we begin to further investigate the role that Sox11 plays in the phenotypes seen in CHARGE syndrome by generating Sox11-mutant zebrafish using the CRISPR-Cas system. These experiments will provide a better understanding of the potential role of Sox11 in the pathogenesis of CHARGE syndrome.

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UK MD/PhD Program Research Day

Poster Presentation #66

Abstract Title:	**Dendritic cells influence the altered neonatal CD8 T cell immunodominance hierarchy during influenza virus infection**
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Abstract: Neonates are more susceptible to influenza virus infection than adults, resulting in increased morbidity and mortality as well as delayed clearance of the virus. Previous work has indicated that decreased T cell and dendritic cell function underlies some of this vulnerability. We sought to understand CD8 T cell specificity and immunodominance during neonatal influenza infection as well as how any differences from the adult hierarchy might impact immunodominance and protection in subsequent infections. We found that neonatal C57BL/6 mice display an altered CD8 T cell immunodominance hierarchy, preferentially responding to an epitope in the influenza protein PA rather than the co-dominant adult response to NP and PA. Additionally, upon secondary infection, mice first infected as pups display inconsistent immunodominance and suffer increased morbidity compared to mice infected previously as adults. Finally, transfer of influenza infected adult dendritic cells to pups resulted in increased T cell activation and enhanced viral clearance as well as a slight induction of NP specific CD8 T cells. Taken together, these data suggest that infection early in life alters the specificity of memory responses to that pathogen and that dendritic cells may play a role in mediating this process. Additionally, vaccines targeting T cells should consider epitope usage and age specific dendritic cell physiology if the intended patient population includes infants as well as adults.

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UK MD/PhD Program Research Day

Poster Presentation #67

Abstract Title:	**Inhibition of human metapneumovirus binding to heparan sulfate blocks infection in human lung cells and airway tissues**
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Abstract: Human metapneumovirus (HMPV), a recently discovered paramyxovirus, infects nearly 100% of the world population and causes severe respiratory disease in infants, the elderly, and immunocompromised patients. We previously showed that HMPV binds heparan sulfate proteoglycans (HSPGs) and that HMPV binding requires only the viral fusion (F) protein. To characterize the features of this interaction critical for HMPV binding and the role of this interaction in infection in relevant models, we utilized sulfated polysaccharides, HS mimetics and occluding compounds. Iota-carrageenan had potent anti-HMPV activity by inhibiting binding to lung cells mediated by the F protein. Furthermore, analysis of a minilibrary of variably sulfated derivatives of Escherichia coli K5 polysaccharide mimicking HS structure revealed that the highly O-sulfated K5 polysaccharides inhibited HMPV infection, identifying a potential feature of HS critical for HMPV binding. The peptide dendrimer SB105-A10, which binds HS, reduced binding and infection in an F-dependent manner, suggesting occlusion of HS at the target cell surface is sufficient to prevent infection. HMPV infection was also inhibited by these compounds during apical infection of polarized airway tissues, suggesting these interactions take place during HMPV infection in a physiologically relevant model. These results reveal key features of the interaction between HMPV and HS, supporting the hypothesis that apical HS in the airway serves as a binding factor during infection, and HS modulating compounds may serve as a platform for potential antiviral development.

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Poster Presentation #82

Abstract Title:	**The Bayesian Method for Confounding as Applied to Personality and Substance Use Data to Estimate Average Causal Effect**
Author(s):	L. Su, College of Medicine, U of Kentucky C. Wang, Department of Biostatistics, U of Kentucky C. Lee, Department of Psychology, U of Kentucky R. Milich, Department of Psychology, U of Kentucky D. Lynam, Department of Psychology, Purdue U

Abstract: Purpose: To investigate possible correlations between substance use and personality trait measurements in students attending the University of Kentucky using the Bayesian Adjustment for Confounding. Methods: The analysis was done in the statistical analysis software R using the Bayesian Adjustment for Confounding as developed by Dr. Chi Wang et al. The resulting model related the personality trait measures with substance use while accounting for a multitude of confounders. Data/Results: There were 449 individuals in the data. The dataset contained 10 different personality measurements from two different models. These variables were the exposure variables. The four outcome variables used were frequency of alcohol use, frequency of marijuana use, frequency of tobacco use, and audit total score, a measure of how harmful the subject's alcohol use is. 37 confounders were also included in the model, including sex, race, age, and quite a few variables involving the subject's friends' usage and opinions of alcohol, marijuana, and stimulants. This resulted in evaluating 40 associations/relationships, each relating one exposure variable to one outcome variable. The results showed which confounders were selected often in each model. The average causal effect (ACE) was also calculated from the models, providing a measurement of the actual level of causation between the two variables. Conclusions: Overall, the Bayesian Adjustment for Confounding is a method useful for eliminating confounders in observational studies and establishing causation with more certainty. The relationship that showed the highest positive effect was between positive urgency and audit total score. The relationship showing the most negative effect was between conscientiousness and audit total score. An example of a relationship with no effect was between marijuana use frequency and extraversion. Through the BAC method, the direct effects of personality traits on substance use can be accurately estimated.

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Poster Presentation #84

Abstract Title:	**RNA-seq and Histological Characterization of Human Peripheral Nerve Tissue Used in Brain Grafts for the Treatment of Parkinson's Disease**
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Abstract: Currently two clinical trials (NCT01833364 and NCT02369003) are underway which feature the implantation of a peripheral nerve autograft to the brain (targeted to the Substantia Nigra) in combination with Deep Brain Stimulation (DBS) for the treatment of patients with Parkinson's disease. As of 1/8/2018, 46 patients have received a graft. This nerve tissue is harvested from the sural nerve, a cutaneous sensory nerve located in the lateral ankle, from patients undergoing DBS surgery. The tissue receives a conditioning injury -in situ two weeks prior to grafting. This study aims to characterize the effect of this conditioning. Two sural nerve tissue samples (pre-conditioned and post-conditioned) per patient were collected from six patients during DBS surgeries 14 days apart. RNA sequencing (RNA-seq) was used to measure absolute and relative levels of gene transcripts in the pre-conditioned and post-conditioned nerve tissue. These findings were supplemented by histology of the nerve tissue. The results of these experiments show: 1) Consistent similarity within the pre-conditioned and post-conditioned group transcriptomes 2) Consistent changes between the pre-conditioned and post-conditioned group transcriptomes 3) Increased transcript levels related to nerve repair, growth factor production, and immune cell migration pathways 4) Decreased transcript levels related to myelin production pathways, consistent with the repair Schwann cell phenotype. All results are statistically significant ($p < 0.05$ and $q < 0.05$). These findings suggest that the nerve graft tissue implanted in human patients has a pro-regenerative phenotype which has the potential to alter the course of neurodegeneration in the brain.

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