

Vitamin D Level Associations with Trauma Patient Outcomes

Bone health plays an important role in overall health, especially in the geriatric patient. Vitamin D levels are often used to assess bone health and predict overall health and outcomes following injury or illness. Vitamin D levels and outcomes have been studied in critically ill ICU patients and in non-critically ill patients, but not in trauma patients. In this study, we examined how bone health, specifically vitamin D levels, correlates with trauma patient outcomes. A retrospective chart review of trauma registry data was performed on 374 geriatric trauma patients treated in 2015 at a rural academic level I trauma center. Patients receiving prior vitamin D supplementation and those taking alternative bone health supplements were excluded. Patients were divided into normal and deficient groups based on a 30ng/ml vitamin D level threshold. A control group was created from patients whose vitamin D levels were unknown. Multiple outcome measures, including morbidity, mortality, discharge disposition, complications, length of ICU stay and number of long bone fractures were compared amongst the groups. Fisher's exact tests and Pearson's chi-squared tests were used to evaluate the data. Of the 374 patients reviewed, 101 (27.01%) had their vitamin D levels measured. 55 (54.46%) patients were found to have deficient levels of vitamin D. A single mortality was seen among the vitamin D deficient patients, compared to zero in the non-deficient patient group ($p=1.00$). 18 (32.73%) deficient patients were noted to have 3 or more comorbidities compared to 16 (34.78%) non-deficient patients ($p=0.84$). Of the vitamin D deficient patients, 15 (27.27%) were discharged without healthcare assistance compared to 17 (16.83%) non-deficient patients. 26 (47.27%) deficient patients were discharged to a skilled nursing facility compared to 11 (10.89%) non-deficient patients. No statistically significant differences were observed in any of the outcome measures studied in this patient population. Vitamin D levels were shown to have little correlation with trauma outcomes in our rural geriatric patient population. No differences in outcomes between patients with and without vitamin D deficiencies were found. However, further studies regarding other aspects of metabolic bone health are necessary to study bone injury recidivism and prevention.

Inflammogenic and Microvascular Effects of Acute Pulmonary Exposure to Titanium Dioxide Nanoparticles

Pulmonary exposure to engineered nanomaterials (ENM) is associated with cardiovascular dysfunction. While these systemic effects have been widely investigated, the majority of research has focused on young adult, healthy, male models: however, with the growth of the nanotechnology industry, the risks to under-represented populations becomes a critical concern. Also, notwithstanding the improvement in the understanding of cardiovascular ENM toxicity, the impact on the uterine circulation is poorly understood. An adequate uterine blood supply is an important determinant of successful implantation of a fertilized ovum and of subsequent fetal development. Disruption of normal physiological function of the uterine macro- and microcirculation may negatively impact the development of the maternal-fetal circulation during mammalian gestation. This may potentially lead to the creation of a hostile gestational environment, causing systemic alterations, that may predispose to adult disease. Therefore, the aim of this study was to assess the inflammogenic and vascular effects of acute pulmonary exposure to titanium dioxide nanoparticles (nano-TiO₂). We hypothesized that acute pulmonary exposure to nano-TiO₂ initiates a systemic inflammatory response and impairs uterine vascular reactivity. Female, virgin, 8-12 weeks, Sprague-Dawley rats were exposed via intratracheal instillation to 200 µg nano-TiO₂ 24 hours prior to vascular assessments. Blood samples were obtained at time 0, 30 minutes, 1 hour, 2 hours and 4 hours following exposure via tail vein puncture for multiplex cytokine analysis. Wire myography was used to evaluate macrovascular active tension generation specifically in the uterine artery. Pressure myography was used to determine vascular reactivity in the radial and basal arteries. Vessels were treated with cumulative concentrations of phenylephrine (PE; 1x10⁻⁹-1x10⁻⁴ M an α-adrenergic agonist), acetylcholine (ACh; 1x10⁻⁹-1x10⁻⁴ M, an endothelium-dependent agonist), and sodium nitroprusside (SNP; 1x10⁻⁹-1x10⁻⁴ M, an endothelium-independent agonist). In radial and basal arterioles endothelium-dependent reactivity was significantly impaired by 27.42±12%, while endothelium-independent dilation (6.73±14%) and α-adrenergic sensitivity (8.22±2%) were not significantly affected. Consistent with previous work, these results highlight the deleterious effects of pulmonary ENM exposure on microvascular endothelial signaling, and confirm the potential of ENM exposure to create a hostile gestational environment. Support: NIH ES015022

Adelman, Avram

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Other, Department of Radiology, Resident

StatIR.com: How a Comprehensive Web-Based Resource Can Maximize Educational and Professional Development For Current and Future Interventional Radiologists.

OBJECTIVE: Our objective was to create a “one stop shop” online resource and training tool for medical students, diagnostic and interventional radiologists in-training, radiologist faculty, and minimally invasive vascular surgeons at a large rural based academic medical center. **MATERIALS AND METHODS:** We performed a comprehensive needs assessment for an online, web-based educational tool for interventional radiology online queries and survey based methodology. We searched google, online databases, and other institutional websites and found that there are extensive online resources for diagnostic radiology but none are currently available for interventional radiology. Our program’s radiology residents and faculty also expressed a need for such an online resource. Therefore, we initiated the process by creating a central hub diagram or ‘business plan’ of the website’s content and organization: visual layout, procedure setup and techniques, guidelines, video simulation with intra-procedural learning, case studies, dictation templates, and additional online resources. Utilizing web programming software, we then developed a beta website following the template as described above, mirroring pre-existing models of web based education. **RESULTS:** Upon completion and implementation of the beta website, access was granted to a select group of medical students, faculty, and residents for immediate feedback in a survey based format; 100% of the respondents found the resource helpful. **CONCLUSION:** A comprehensive web-based resource dedicated to diagnostic and interventional radiology can be a valuable resource for medical students, residents, and staff in professional development, education, and information currency. To our knowledge, this is the first and only of its kind for interventional radiology. Due to the growing popularity of interventional radiology as a subspecialty and now an independent residency, there is ample need and opportunity for expansion and future application of an online educational tool such as StatIR.com.

Ahmed, Masih

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Medicine, Ophthalmology, Clinical Sciences/Epidemiology

The effect of patient selected music on the vital signs of patients undergoing ophthalmic plastic surgery

Purpose: Surgery is known to cause anxiety and distress that can induce physiological alterations affecting the healing and recovery for many patients. Music has been shown to reduce anxiety, to lower heart rate and blood pressure, and to improve satisfaction in patients undergoing cataract surgery. Our study aims to determine the effect of music in the operating room for awake patients undergoing ophthalmic plastic surgery procedures. **Methods:** Patients undergoing various ophthalmic plastic surgery procedures with monitored anesthesia were prospectively randomized to hear either patient-selected music or no music. Exclusion criteria included hearing impairment, hearing aids, or a history of ear surgery. Music was played using a portable speaker system in the operating room. Anxiety and pain were measured using visual analog scale and Self-Evaluation State Trait Anxiety Inventory (STAIT) forms, which were completed before and after surgery. Pain and vital signs before and after surgery were assessed. **Results:** 30 patients underwent ectropion repair, entropion repair, blepharoplasty, ptosis repair, and temporal artery biopsy. The mean age was 65 (range 46-93). 70% (21) were female and 30% (9) were male. 17 patients listened to music while 13 patients did not. Mean arterial pressure decreased post-operatively by 3.64% in the music group but elevated by 7.07% in the control group ($p=0.023$). Pulse rate did not change post operatively within each group, or between groups ($p=0.24$). Respiratory rate decreased in both groups, including significantly in the non-music group ($p=0.017$). There was no significant difference between the two groups. Anxiety score improved from 3.19/10 pre- operatively to 2.08/10 post-operatively in the music group while in the control group, the anxiety score improved from 4.08/10 to 3.67/10, respectively ($p=0.56$). Post-operative pain rating was 3.12/10 in the music group and 4.25/10 in the control group ($p=0.33$). **Conclusions:** This pilot study shows that music can have a positive effect on mean arterial pressure, which may indicate improved anxiolytic effects. Music is a simple intervention that can be used as an alternative or complementary method of reducing discomfort for patients undergoing ophthalmic plastic surgery procedures. On- going data collection can better elucidate the other effects of this intervention.

Ajay Warriar, Pooja

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Other, Biomedical Engineering, Undergraduate

Mitochondrial miRNAs: novel disease-modifying therapeutic targets in Alzheimer's disease

MicroRNAs (miRs) are small non-coding RNAs that act at the post-transcriptional level to regulate the expression of proteins. Mitochondrial miRs have been studied prominently for their crucial involvement in cellular aging, inflammation, and mitochondrial function in neurodegenerative diseases such as Alzheimer's disease (AD). Recent studies from our laboratory and others have identified miR-146a and miR-34a as being overexpressed in specific brain regions of AD patients. We found that an increase of these miRNA levels was highly correlated with a decrease in expression of a set of target mitochondrial proteins: phosphoglycerate kinases 1/2 (PGK1/2), hexose-6-phosphate dehydrogenase (H6PD), NADH dehydrogenase ubiquinone flavoprotein (NDUFV), and ubiquinol-cytochrome c reductase binding protein (UQCRB). The goal of the current study is to determine whether this correlation is maintained when two critical biological variables, sex and age, are manipulated. This study tested target protein levels throughout different age groups (3-24 months) for both sexes of wildtype (WT) and AD transgenic mouse models. miR-146a and 34a target protein levels in the hippocampus were quantified by Western blot and quantitative densitometry analysis. Our results show that hippocampal protein levels for NDUFV and UQCRB are highly dysregulated throughout aging, while H6PD and PGK1/2 exhibit sex differences in both WT and AD transgenic mice. The correlation analysis also showed the target protein H6PD is regulated by miR-146a in the early disease stage while miR-34a takes control over in the later disease stage. These results suggest that age and sex are determining factors in the application of disease-modifying therapeutic targets for AD.

Alhussain, Khalid

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Pharmacy, Pharmaceutical Systems and Policy, Basic Science

Serious Psychological Distress and Emergency Department Use among Adults with Multimorbidity in the United States

Objective: We sought to 1) examine the association between serious psychological distress (SPD) and emergency department (ED) use among adults with multimorbidity in the US and 2) investigate the association between SPD and the reasons for ED use. Methods: A cross-sectional, retrospective, observational study design was conducted using data from the 2014 National Health Interview Survey (NHIS). The study sample consisted of 13,708 US adults with multimorbidity. Chi-square tests were used to examine unadjusted subgroup differences. Multivariable logistic regression models were used to assess the association between SPD and ED use among adults with multimorbidity. Among ED users, adjusted logistic regression models were conducted to examine the association between SPD and the reasons for the ED use in the past 12 months. Results: After controlling for other variables, adults with SPD were more likely to use ED than those without SPD (AOR = 1.73, 95% CI = 1.40, 2.15). Among ED users, we found that adults with SPD were more likely (AOR = 1.43, 95% CI = 1.03, 1.98) to report “the clinic was not open” as the reason for using ED than those without SPD. Conclusion: Combination of SPD and multimorbidity was associated with higher ED use. The inconvenient hours were more likely to be reported by adults with SPD as the reason for their ED use. Management programs addressing SPD among adults with multimorbidity are needed to minimize the risk of ED use.

Aljammal, Rawaa

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Pharmacy, Pharmaceutics, Basic Science

Permeability changes and effect of chemotherapy in brain adjacent to tumor in an experimental model of metastatic brain tumor from breast cancer

Permeability changes and effect of chemotherapy in brain adjacent to tumor in an experimental model of metastatic brain tumor from breast cancer. Afroz S Mohammad, Chris E Adkins, Rawaa Aljammal, Jesssie Griffith, Rajender Mittapalli, Paul R Lockman Background: Brain tumors vasculature is more compromised and leaky than that of normal brain. But only little is known about the permeability changes and damage due to chemotherapy in brain adjacent to tumor (BAT). We defined BAT basing on oxygen diffusion studies and studied permeation changes in BAT using quantitative fluorescent microscopy and effect of chemotherapy on BAT was determined by staining for activated astrocytes and DNA damage in BAT. Methods: Metastatic brain tumor cells(MDA-MB-231Br) were injected into left ventricle of female NuNu mice. Once metastases were allowed to grow for 28 days, the animals were injected Texas-Red-625Da(TR) , allowed it to circulate for 10 minutes and the concentration of TR was determined in BAT using quantitative fluorescent microscopy. The effect of chemotherapy in BAT was determined by staining for activated astrocytes and DNA damage after treatment with different chemotherapies in mice bearing metastases. Results: We observed 2- 40 fold increase in TR permeability in metastatic tumor over normal brain. We also found that permeability of the TR is highly heterogeneous both within and between the tumors(normal brain Kin TR: 1.2×10^{-5}). TR concentrations in BAT(100 μ m from tumor edge) is consistently 40% of the tumor but significantly higher than that of normal brain. We also observed animals treated with chemotherapy (vinorelbine(10mg/kg), erubilin(1.5mg/kg and docetaxel(10mg/kg)) showed activated astrocytes in BAT. Conclusions: Our data shows increased tracer accumulation in BAT and activated astrocytes in BAT in animals treated with chemotherapy. This data suggests the distribution of chemotherapeutic agents around metastatic lesions.

Allen, Jessica

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Medicine, Neurobiology and Anatomy, Basic Science

CORO1B amplification and overexpression increases lethality and drives tumor invasiveness in 11q13 amplified HNSCC

Head and neck squamous cell carcinoma (HNSCC) is a highly invasive cancer with an overall 5-year survival rate of 40%. The poor survival of HNSCC patients is due to invasive locoregional destruction of craniofacial tissues and cervical lymph node metastasis. The chromosome 11q13 region is amplified in approximately 25% of all HNSCC cases and is associated with decreased patient survival and increased lymph node involvement. The central 11q13 region encodes the genes CCND1 (cyclin D1) and CTTN (cortactin), known drivers of tumor growth and invasion. CORO1B (coronin 1B) flanks the 11q13 core and is amplified in 7-14% of all HNSCC, but how CORO1B amplification and overexpression contributes to HNSCC is unknown. Coronin 1B governs cell motility in fibroblasts by negatively regulating the ability of cortactin to stabilize the actin cytoskeleton during mesenchymal cell migration. The objective of this study is to determine the impact of coronin 1B amplification and protein overexpression on HNSCC patient outcome by utilizing a combination of bioinformatics, cytogenetics, quantitative histology, and functional cellular assays. The overall hypothesis is that coronin 1B amplification and overexpression accelerate HNSCC patient decline by enhancing tumor cell migration and invasion. Kaplan-Meier and Cox-hazard ratio analyses of two independent patient cohorts indicates that CORO1B amplification significantly reduces overall survival. Automated quantitative analysis (AQUA) of coronin 1B expression in HNSCC tissue microarrays indicates that coronin 1B overexpression reduces median survival of HNSCC patients from 81 to 29 months. RNAi-mediated knockdown of coronin 1B in HNSCC cell lines decreases invadopodia formation and extracellular matrix degradation. Tumor spheroids lacking coronin 1B expression display decreased 3D invasion in native collagen I. Collectively these results suggest that elevated coronin 1B expression levels in HNSCC correlate with poor patient outcome, and coronin 1B expression is essential for HNSCC invasion. Coronin 1B amplification and expression status may therefore define a novel aggressive subset of locoregional involved HNSCC warranting enhanced clinical intervention.

Andreini, Derek

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Medicine, Orthopedics, Basic Science

Recovery of *Staphylococcus aureus* Small Colony Variants

Small colony variants (SCV) are morphological variations of *Staphylococcus aureus* (*S. aureus*) that persist within host cells and have been linked to persistent, recurrent, and antibiotic resistant infections. Recently, they are starting to gain attention as they are being more heavily reported in cases dealing with device implantations, skin infections, osteomyelitis, and cystic fibrosis. Due to their odd biochemical characteristics, they are difficult to isolate, diagnose, and treat making them a challenge to physicians. The purpose of this study was to isolate SCVs of *S. aureus* in infected osteoblasts at different time points. A clinical strain of *S. aureus* obtained from Ruby Memorial Hospital, Morgantown, WV was co-cultured with osteoblasts (500:1 ratio) for 4, 8, 16 and 24 hours. Extra-cellular bacteria was eliminated with lysostaphin and the intra-cellular bacteria was harvested after lysing the osteoblasts and plated on sheep blood agar, sheep blood agar plates with gentamicin (2.5µg/mL), chocolate agar, and chocolate agar plates with gentamicin (5 µg/mL). The plates were incubated at 37°C for 72 hours and the colonies of SCV phenotype were enumerated using Acolyte Colony Counter. On the blood agar plates the numbers of SCV recorded were 2.00E3, 4.5E3, 1.23E5, 1.66E6 for 4, 8, 16, and 24 hour incubation times, respectively. On the Sheep blood agar with gentamicin plate the numbers of SCV recorded were 0.00, 7.00E3, 1.38E5, 1.91E6 for 4, 8, 16, 24 hour incubation times, respectively. On the chocolate agar plates the numbers of SCV recorded were 0.00, 6.67E3, 1.63E5, 1.89E6 for 4, 8, 16, 24 hour incubation times, respectively. On the chocolate agar with gentamicin the numbers of SCV recorded were 0.00, 1.5E3, 1.12E5, and 1.70E6. SCV increased in number as the incubation time increased from 4 hours to 24 hours suggesting that *S. aureus* could undergo phenotypic changes and transform into SCV in as little as 4 hours of incubation time. If left untreated the SCV of *S. aureus* may continue to thrive intracellularly and could become the major culprit of recurrent infections.

Facial Imagery BMI Algorithm correlates with Normal and Overweight Measured BMI but Lacks Accurate Representation in Obese or Underweight Extremes

Efficient procedures to determine health status are in high demand in today's generation. Body Mass Index (BMI) is a global method for determining an individual's health status. This research exploration is aimed to identify if a facial image (photograph) can identify participant's BMI correctly. Sample of 1,210 young adults with a facial image and objective height and weight were used for analysis. Facial BMI (fBMI) was measured through an algorithm formulated to identify points on each face located in L.Wen and G-D. Guo, in *Image and Vision Computing*, Vol. 31, Issue 5, pages 392-400, 2013. Given the detected facial landmarks, some distances and ratios can be computed, which are used as the features to characterize the facial fatness. Then a regression function is learned to represent the relation between facial measures and the BMI values. The learned function can then be used to compute the BMI for each test face image. Measured BMI (mBMI) was calculated by weight in kilograms divided by height in meters squared. Correlation analysis of fBMI to mBMI showed significant correlation between BMIs in the normal and overweight categories ($p < .0001$). Further analysis indicated the measure to be less efficacious in underweight and obese participants. Matched pairs data for each individual, there was a range of 14.73-49.74 for mBMI and a narrowed spread for fBMI (range = 16.29-28.85) indicating that fBMI detected participant BMI 0.4212 less than mBMI ($p < .0004$). BMI categories used included: less than 18.5 BMI (0), 18.5-24.9 (1), 25.0-29.9 (2), and equal to or above 30 (3). mBMI had representation of categories across 0-3 BMI (mBMI category N, 0=70, 1=728, 2=303, and 3=109), while fBMI representation included just 0-2 (fBMI category N, 0=10, 1=991, 2=209). This shows less sensitivity of the algorithm to underweight and obese individuals. Contingency table analysis indicted 109 participants in the 3rd category of mBMI were placed into a lower category for fBMI. Agreement test for symmetry shows significant disagreement 95% CI [0.0618,0.1446] ($p < .0001$). Facial imagery identification of health status is a useful measure in human research however; more sensitive measures to identify underweight and obese individuals are warranted.

Barr, Jamie

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Medicine, Cancer Cell Biology, Basic Science

Regulation of the Long Noncoding RNA Onco-LncRNA-3 by the HPV Oncoproteins

The objective of this study is to identify long non-coding RNAs (lncRNAs) that are altered in early stages of high-risk human papillomavirus (HPV)-16 infection as well as show persistent importance in the induction of carcinogenesis. Dysregulation of lncRNAs occurs in most human cancers, however, there are only a few studies showing dysregulation of specific lncRNAs in HPV-related cancers. It is well known that one of the main factors contributing to HPV-related carcinogenesis is the expression of high-risk HPV E6 viral oncoprotein and its interaction with several human proteins, such as the tumor suppressor p53. It is hypothesized that HPV-16E6 changes the expression of host lncRNAs to regulate downstream processes important in the induction of carcinogenesis. To test this hypothesis, we stably express high-risk HPV-16E6 in primary human keratinocytes (HEKa) and conducted high-throughput RNA sequencing analysis to identify HPV-16E6-mediated changes in lncRNAs expression. Our preliminary data show over 500 lncRNAs up- or down- regulated by greater than 2-fold with the expression of HPV-16E6 compared to control, and specifically onco-lncRNA-3 up-regulation with HPV-16E6 expression. The Cancer Genome Atlas (TCGA) shows higher expression of onco-lncRNA-3 in cervical cancer patients compared to normal, as well as a correlation of poor overall survival with high expression of onco-lncRNA-3. We observe similar expression patterns of onco-lncRNA-3 when comparing primary cervical keratinocytes (HCK) to HPV+ cervical cancer cell lines and to HPV+ HNSCC cell lines, as well as HCK transfected with HPV-16 genome (JAMM-16) compared to uninfected HCK. Preliminary data using HCK stably expressing HPV-16E6 alone, 16E7 alone, or co-expressing HPV-16E6/16E7 allows us to speculate that onco-lncRNA-3 is primarily regulated by E6. Currently, we are determining mechanism of action of onco-lncRNA-3 contributing to cancer by conducting knockdown and rescue experiments followed by behavior assays (e.g. invasion, migration, and proliferation). The significance of this project is that it will identify and show the importance of lncRNAs in HPV-related cancers as well as provide insights for novel mechanism by which high-risk HPV infection contributes to cervical and HNSCC carcinogenesis. In addition, it could reveal diagnostic biomarkers to identify patients who will likely progress to cervical intraepithelial neoplasia (CIN) stages.

Beard, Stephanie

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Medicine, Obstetrics and Gynecology, Masters

Curcumin inhibits the biofilm formation and also dislodges the preformed biofilm of *Gardnerella vaginalis* by blocking extracellular DNA (eDNA): Implication in antibiotic resistant/recurring Bacterial Vaginosis

Bacterial Vaginosis (BV) is one of the most common vaginal infections with serious consequences in woman's sexual and reproductive health. Its prevalence in US women ranges from 22-50%, with antibiotic resistance/recurrence in 30-60% of these women after antibiotic treatment. This has been attributed to the biofilm formation. *Gardnerella vaginalis* (GV) is a dominant causative microbe involved in BV. Curcumin, commonly known as diferuloylmethane, has immense biological properties including anti-inflammatory and anticancer. The objective of this study was to investigate the ability of curcumin to inhibit the biofilm formation and to dislodge the preformed biofilm by GV. We hypothesize that curcumin will inhibit and dislodge the biofilm. For inhibitory experiments, GV was grown in BHI medium supplemented with 0.3% starch and glucose to an exponential growth phase and then cultured overnight into 96 well plates to develop biofilm, without and with various concentrations of curcumin. For dislodging experiments, the biofilm was developed overnight and then treated with various concentrations of curcumin for 24 hr. The biofilms were quantified using the assay involving crystal violet staining and measuring the absorbance at 650nm using an ELISA plate reader. The eDNA was extracted from the supernatants using a mixture of phenol:chloroform:isoamyl alcohol (25:24:1), precipitated with 100% ethanol, and the absorbance measured at 260nm. Curcumin inhibited the biofilm development as well as dislodged the preformed biofilm in a concentration-dependent manner. At concentrations >1-20ug/ml, it completely inhibited the biofilm development ($p < 0.05$ to < 0.001) depending upon the bacteria concentration. The dislodging experiments required a higher concentration with >80ug/ml completely dislodging the preformed biofilm within 24hr. The eDNA secretion coincided with the kinetics of biofilm formation. The inhibitory/dislodging effects of curcumin seems to be mediated via inhibition of eDNA secretion. In conclusion, our data indicates that curcumin can not only inhibit the biofilm formation but can also dislodge the preformed biofilm. These findings will have significant application in the management of antibiotic resistance/recurring BV which is a major problem in the Obs/Gyn clinics at this time.

A High Percentage of Kisspeptin and GnRH Neurons are Colocalized with Neuronal Nitric Oxide Synthase in Prepubertal Female Sheep

The neural mechanisms underlying the initiation of puberty are not well understood. While the neuropeptide kisspeptin is critical for puberty onset, other neural inputs likely play a role as well. Nitric oxide (NO) stimulates gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) release in rats, and deletion of neuronal nitric oxide synthase (nNOS) causes infertility in mice. This study examined the relationship between either kisspeptin or GnRH and nNOS neurons in prepubertal female sheep. Hypothalamic tissue from prepubertal ewes that were either ovariectomized (OVX; n=6) or were ovariectomized and received estradiol (OVX+E; n=6) was used. Dual-label immunofluorescence was used to determine the percent colocalization between nNOS and kisspeptin and nNOS and GnRH. Confocal microscopy was used to determine numbers of either kisspeptin or GnRH close-contacts onto 10 nNOS neurons/ewe in the arcuate nucleus (ARC) and preoptic area (POA) for kisspeptin and in the POA only for GnRH. In the POA of OVX+E ewes, only $5.4 \pm 1.1\%$ of nNOS neurons contained kisspeptin. The number of kisspeptin contacts per nNOS neuron was also low (0.10 ± 0.03). In contrast, $78.9 \pm 4.9\%$ of POA kisspeptin neurons contained nNOS in OVX+E ewes. In the ARC, E-treatment decreased the percentage of nNOS neurons containing kisspeptin (from $42.8 \pm 5.2\%$ to $21.6 \pm 3.3\%$) and tended to reduce the number of kisspeptin contacts onto nNOS neurons (from 3.2 ± 0.6 to 0.5 ± 0.1). In the ARC, there was no effect of E with $98.2 \pm 0.7\%$ of kisspeptin neurons containing nNOS. In the POA, $4.7 \pm 1.1\%$ of nNOS neurons contained GnRH with no observed effect of E. No GnRH close-contacts were observed onto nNOS neurons, and E did not affect the relatively high percentage of GnRH neurons containing nNOS ($78.5 \pm 3.7\%$). These data establish a neuroanatomical relationship between nNOS and kisspeptin which, particularly in the ARC, may be important for controlling GnRH secretion. Estradiol may also influence kisspeptin input to these neurons. Combined with findings of GnRH/nNOS coexpression, we suggest NO may influence GnRH secretion both directly and indirectly, via kisspeptin, in prepubertal female sheep.

Bell, Christopher

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Medicine, Orthopedics, Basic Science

Unique antimicrobial peptide promise for clinical infection treatment

Staphylococcus aureus (*S. aureus*), one of the most prevalent inpatient bacteria, may invade non-professional phagocytes (e.g. osteoblasts, epithelial cells) to set up an intracellular population which is protected from host defenses. Few of the conventional antibiotics available can penetrate human cells to go after the intracellular populations which leaves clinicians with a serious problem. The aim of this study was to test the killing efficacy of peptide HHC-36 against *S. aureus* within human osteoblast cells. This study used a unique design to determine the parameters best suited to kill the highest % of the intracellular population with sparing the greatest % of host cells. We initially established the killing efficacy vs osteoblast viability at a neutral pH, favorable to the peptide. It was determined that a 200 M concentration yielded 100% killing and ~65% osteoblast viability. Adjusting the pH parameters to better resemble that of the human of the cell, it took a markedly higher concentration (500 M) to achieve approx. the same % killing with approx. 55% osteoblast viability. Next, we determined the effect of time on the % killing and osteoblast viability. At 1 hour incubation with a 500 M solution, the % killing was approx. 95%, while the osteoblast viability was approx. 80%. After only increasing the time parameter to 4 hours, the % killing improved to 100% while the osteoblast viability was decreased to approx. 50%. Comparison with conventional antibiotics such as rifampin, vancomycin and gentamicin, showed that only rifampin was comparable with % killing, while HHC-36 yielded a much better osteoblast viability. This study showed that media and time play an important role in the killing efficacy and osteoblast viability when treated with HHC-36. Through these trials it was determined that HHC-36 had a greater efficacy than conventional antibiotics in % killing while also showing an improved osteoblast cell viability. We concluded that a higher concentration with a shorter incubation time would be more suited for the battle against intracellular *S. aureus*. In future research, we hope to further establish the link between incubation, concentration and efficacy, while limiting the impact on host cells.

Bevere, Justin

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Medicine, Microbiology, Immunology, and Cell Biology, Undergraduate

LolB Regulates Membrane Stress, Virulence, and Alginate Overproduction in *Pseudomonas aeruginosa*.

Pseudomonas aeruginosa is an opportunistic Gram-negative respiratory pathogen. When under attack from the immune system *P. aeruginosa* synthesizes and secretes an exopolysaccharide known as alginate which allows the bacterium to survive. When the membrane is perturbed by stress, alginate production is necessary to protect the bacteria. Outer membrane proteins are synthesized and then shuttled to the membrane. LolB is a chaperone that facilitates insertion of these proteins into the membrane. Here we show that in the absence of lolB, *P. aeruginosa* produces alginate, likely as a result of the stress caused by improper localization of outer membrane proteins. To investigate the effects of lolB mutation on bacterial cell stress, we performed RNAseq analysis with wild type and the lolB mutant. We observed that MucD was activated in the lolB mutant. As expected alginate biosynthetic genes were also activated in the lolB mutant. In addition, we saw systems of genes involved in protein folding and type II secretion. To confirm the data obtained by RNAseq, we cloned a promoter that is active when the strains produce alginate (PalgD). The PalgD promoter was fused with the luxCDABE genes, which when expressed produce bioluminescence. We then expressed protease chaperones in trans (mucD, skp, lolB, lolA, ostA, fkpA, surA) and monitored light production during growth in broth. MucD was able to decrease light production of the PalgD-lux reporter, which indicated that MucD could attenuate the stress caused by the loss of lolB. Contrary, lolA was able to increase light production of the palgD-lux reporter, which indicated that lolA could increase stress caused by the loss of lolB. In the waxworm infection model the lolB mutant was less virulent than that of the wild type. Overall our data suggest that membrane homeostasis is essential for *P. aeruginosa* survival. These data hint that lolB protein chaperone may be an attractive target for antibiotics because it would result in destabilized membranes allowing for killing of the bacteria.

Bevil, Geoffrey

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Pharmacy, SOP, Basic Science

Application of molecular modeling to explain caffeine metabolism by cytochrome P450 1A1.

Caffeine gives a slight stimulatory effect to your central nervous system, whether it's in someone's morning coffee or their favorite carbonated beverage. The molecule, caffeine, is broken down mainly in the liver, but also other tissues, by several enzymes. The enzymes involved are human cytochromes P450, especially P450 1A1 and 1A2. In fact, caffeine is a marker substrate for P450 1A2 activity. However, P450 1A1 and 1A2, share 72% amino acid sequence identity, but often display different substrate specificities and inhibitor susceptibilities. Therefore, the objective of this study was to characterize the metabolism of caffeine by cytochrome P450 1A1 through molecular modeling. The substrate undergoes N-demethylation at several positions: at N1, N3 and N7, producing theobromine, paraxanthine and theophylline, respectively. Molecular modeling simulations were conducted using InsightII/Discover software. Caffeine molecule was docked within a crystal structure of the cytochrome P450 1A1 enzyme, and Affinity module was used to produce various substrate-binding orientations. The 10 lowest energy poses were analyzed in order to explain likely metabolites. Each orientation was evaluated with respect to the distance between a given oxidation site and heme iron, which determines the likelihood of oxidation at a given position, thus giving rise to a specific metabolite. Theobromine was observed to have the lowest energy needed for demethylation at N1 position with 546.314 kcal/mole at a distance of 5.09 Å from the iron of the heme group in cytochrome P450 1A1. Additionally, manual docking of caffeine in various productive binding orientations is also planned.

Bobo, Tierra

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Medicine, microbiology, Basic Science

TGF β 1 suppresses autophagy via DNA methylation in Idiopathic Pulmonary Fibrosis (IPF)

Objective: IPF is characterized by inappropriate wound healing and scarring in the lung leading to a decline in lung function. It is a chronic and progressive lung disease with a high mortality rate and few treatments options for severely affected patients. Transforming growth factor beta (TGF β) is a key cytokine that promotes differentiation of fibroblasts to myofibroblasts at injured sites, which in turn causes an accumulation of extracellular matrix and scarring in the lung. Moreover, Autophagy, an intracellular process for turnover of subcellular components and maintenance of cellular quality-control systems, is impaired in IPF. Interestingly, higher TGF β 1 levels inhibit autophagy degradation in IPF. Our lab has recently discovered that DNA methyltransferases (DNMTs) are overexpressed in IPF lung tissues and lung fibroblasts, yet the specific mechanisms of DNMT upregulation remains unknown. Here, we hypothesize that changes in DNMT's expression via TGF β 1 may contribute to the pathogenesis of IPF. Thus, specific genes involved in autophagy, such as MAP1LC3A and MAP1LC3B, may be altered epigenetically and contribute to the development of IPF. **Results:** We found that TGF β 1 increase DNMT3A and DNMT3B gene expression and activity in normal lung fibroblasts as well as differentiated them to more IPF phenotype as indicated by increased α -SMA expression. LC3 cleavage is decreased in primary IPF fibroblasts compared to normal. We demonstrate that the CpG island in the promoter region of MAP1LC3A and MAP1LC3B genes are hypermethylated in IPF fibroblasts compared to normal. In primary lung tissue samples, we observed a decrease in LC3 cleavage as IPF became more severe suggesting a correlation with DNA methylation and silencing in vivo proposing that autophagy is epigenetically regulated/ repressed in IPF. As predicted, treating IPF lung fibroblast with DNMT inhibitor (5'-aza-2'-deoxycytidine), relieved repression of autophagy genes and increased LC3 cleavage in primary IPF fibroblasts. **Conclusion:** This study demonstrates that there is altered DNA methylation on the promoters of genes that are known to regulate improper cellular accumulation in pulmonary fibrosis and may serve as a novel biomarker or drug target. This knowledge suggests insight in the pathogenesis of not only in IPF, but in fibrosis of other organs.

Boehm, Dylan

58

Medicine, Microbiology, Immunology, and Cell Biology, Basic Science

Characterizing the neutrophil response to *Bordetella pertussis* in the context of acellular and whole cell vaccines.

Bordetella pertussis is the causative agent of pertussis (whooping cough), a respiratory infection leading to a violent cough, which can be fatal in infants. Acellular pertussis vaccines (ACV) replaced whole cell vaccines (WCV) in the US immunization schedule in the early 1990s, pertussis is re-emerging despite 95% vaccine coverage. In this study a bioluminescent neutrophil reporter mouse, NeCre luc, was utilized to determine spatiotemporal recruitment of neutrophils to the sites of infection of vaccinated mice, when challenged with *B. pertussis*. NeCre luc mice immunized with ACV and WCV resulted in increased clearance of bacterial burden compared to naïve mice. Mice in WCV group were morbid at Day 6 post challenge, despite the reduced bacterial burden in the respiratory tract. In vivo live imaging (IVIS) of mice throughout infection revealed increases in neutrophils in WCV immunized mice. When compared to naïve mice, WCV mice had 20-fold increase in luminescence indicated the WCV induces a cellular response mediated by neutrophils to the pathogen, while this accumulation of neutrophils did not occur in ACV immunized mice. The in vivo imaging data was validated and corroborated by flow cytometry of the cell populations of the nasal cavity and the lungs of the mice. We hypothesized that WCV immunized mice would have increased expression of inflammatory factors such as, chemokines and cytokines. The naïve, ACV, and WCV responses to challenge, we performed RNA sequencing of the total lung RNA from each the mice of the experimental groups. Experimental groups were compared to non-challenged control we found over 200 more genes differently regulated by WCV than naïve, or ACV vaccination. Cytokine analysis was performed and clearly corroborated the transcriptome analysis. With the three part approach of IVIS, flow cytometry, and RNAseq, the NeCre luc mice confirmed that neutrophils are highly recruited in WCV immunized mice. While this caused sterilizing immunity, it also resulted in morbidity and mortality which echoes the main safety issues of using crude WCVs. Current studies are underway to determine the correct physiological murine vaccine doses for the ACV and WCV so that we can improve the ACV to promote a cellular response.

Boothe, James

42

Medicine, N/A, Basic Science

Inhibition of the Ras-MAPK pathway induces mesenchymal-to-epithelial transition in mesenchymal breast cancer cells

The vast majority of human cancers arise from epithelial tissues, and the vast majority of deaths from cancer are due to metastasis of the disease. The epithelial-to-mesenchymal transition (EMT) is a process of cellular transcriptional reprogramming that occurs in such normal physiological processes as embryogenesis and wound healing. Many studies have also implicated the EMT as a driver of cancer tumor invasion and metastasis. Thus, inhibition of the EMT or induction of the reverse phenomenon, the mesenchymal-to-epithelial transition (MET), holds promise as an anti-metastatic strategy in clinical cancer treatment. We have previously shown that the zinc finger transcription factor ZEB1 plays a key role in induction of EMT in breast cancer cells; however, the upstream regulation of ZEB1 expression remains poorly understood. To elucidate the regulatory elements of ZEB1 expression, we treated EMT-transited mesenchymal breast cancer cell lines with chemical inhibitors of various biochemical pathways that have been implicated in regulation of EMT; included in our analysis were inhibitors of the TGF-beta, BMP, Ras-MAPK, and PI3K-AKT pathways, as well as CDKs. We demonstrated that inhibition of the Ras-MAPK pathway dramatically decreased expression of ZEB1, inducing a partial MET in the cells as confirmed by decreased expression of the mesenchymal and stem cell marker CD44. Furthermore, inhibition of the G1 phase CDK4/6 by palbociclib prevented phosphorylation of RB protein and similarly led to decreased ZEB1 expression. These results indicate that ZEB1 upregulation is likely mediated by the Ras-MAPK pathway-mediated induction of cyclin D, activation of CDK4/6, phosphorylation of RB, and release of E2F transcription factors. Investigation into the exact mechanism by which inhibition of the Ras-MAPK pathway leads to decreased ZEB1 expression is ongoing. This demonstration of a pharmacological approach for preventing or reversing EMT in breast cancer cells, as well as inhibiting cell cycle progression, presents great promise in the search for an anti-metastatic adjuvant therapy in the treatment of human breast cancer.

Bradford, Shelby

166

Medicine, Microbiology, Immunology, and Cell Biology, Undergraduate

Novel Vectors for Inducible Protein Expression & Secretion in Gram Negative Bacteria

Protein acquisition from bacteria usually requires lysing the cells, followed by a series of purification steps to remove cellular debris and unwanted contaminants. This process can be lengthy, costly, and not always fully efficient. That is why this project aimed to design a plasmid construct to secrete proteins of interest to circumvent the need to lyse cells for protein purification. OsmY is the most highly secreted protein in *E. coli*. Therefore, the construct designed in this study consists of a protein fusion between *osmY*, which encodes a signal peptide for secretion of proteins in *E. coli*, the sequence of the gene of interest, and a 6xHis-Tag for identification and purification. The fusion protein also includes protease cleavage sites so the OsmY and the 6xHis-Tag can be removed from the protein of interest during purification, and a carbenicillin gene for selection after transformation. Expression of the fusion protein is controlled by an IPTG inducible promoter (Plac) and a T7 promoter. The backbone was linearized using HindIII-HF and EcoRI-HF to insert *osmY*. In this model, the gene encoding FpvA, an iron-acquisition receptor from *Pseudomonas aeruginosa*, was inserted behind *osmY* using HindIII-HF and NcoI. To prove the efficacy of this concept, this fusion plasmid was transformed into TOP10 *E. coli*, and the protein was expressed using IPTG induction. Next, this plasmid was transformed into ClearColi, a LPS deficient strain of *E. coli* which encodes an IPTG-inducible T7 polymerase on its chromosome. This strain will allow for stronger induction of gene expression and endotoxin-free purification of the protein of interest. Once the protein is expressed and purified, it will be tested as a vaccine antigen against *P. aeruginosa* in a murine model of acute pneumonia, where the whole protein's immunogenicity will be compared to that of peptides from FpvA. Furthermore, this construct will be able to be used in many other molecular applications in which protein expression and purification is desired

Brandebura, Ashley

62

Medicine, Biochemistry and Molecular Biology, Basic Science

Single Cell RNA-Sequencing of a Developing Neural Circuit

The calyx of Held (CH) is the largest nerve terminal in the mammalian central nervous system. The large size of this terminal, rapid period of growth (24-72 hours) and well-defined endpoint of mono-innervation, along with the mostly homogeneous population of postsynaptic neurons in the medial nucleus of the trapezoid body (MNTB), make this brain region an ideal model system to study the molecular mechanisms of neural circuit formation. Our lab previously published an extensive microarray study characterizing gene level changes within the MNTB across the development of this neural circuit. Several canonical and non-canonical signaling pathways were represented, but the cell types of origin of relevant genes were not determined. The purpose of this study is to utilize single cell RNA-Sequencing to characterize gene level changes in a cell-type-specific manner. The initial goal of the first round of experiments was to uncover key signaling pathways which orchestrate rapid growth of the CH terminal and which cell types are associated with these pathways. The En1 Cre was crossed to a TdTomato reporter line to fluorescently label neurons. MNTB microdissections were performed at postnatal day (P3) during the height of CH growth. The tissue was enzymatically digested to form a single cell suspension and these cells were loaded into the Fluidigm C1 Integrated Fluidic Circuit (IFC) chip for single cell capture and processing for single cell RNA-Sequencing. Imaging of the cell capture sites allows for an initial characterization of TdTomato+ neurons or TdTomato- nonneuronal cells and the subsequent analysis of the sequencing data allows for clustering of individual cell types into distinct groups based on differences in gene expression. The majority of libraries had greater than 70% genome alignment. The number of detected genes was saturated at read depth of 2.5 million mapped reads per cell. We detected 5,000 to 6000 genes in most of the single cell libraries that met or exceeded this read depth threshold. In conclusion, the single cell capture approach allows for cell-type-specific sequencing in the developing MNTB. This work has implications for the study of disorders involving abnormal neural circuit formation, including autism and schizophrenia.

Stroke is a fatty word! The crosstalk between the brain and adipose: Implications for Stroke

The risk of stroke increases by 70% in obese people. Visceral adipose tissue (VAT) is a key regulator of inflammation, which can lead to an increase in oxidative stress. The vicious cycle of VAT inflammation and oxidative stress is released into the systemic circulation, which may affect stroke outcome. We hypothesize that the VAT inflammatory responses negatively affect the brain microvasculature and increases stroke severity. Obese (OZR) and lean (LZR) Zucker rats were exposed to a 60-minute transient middle cerebral artery occlusion (tMCAO). The ipsilateral middle cerebral artery (MCA) was isolated and hung in a pressurized microvessel myobath. To determine the effect of post-stroke VAT on MCA function, the MCA was incubated with 50 mg of VAT for 30 minutes and then exposed to increasing doses of acetylcholine. In general, dilation responses in OZR MCAs were decreased 40% vs. LZRs. 24 hours after stroke, both LZR and OZR MCA dilation was decreased (53% and 64%, respectively). MCA dilation was further decreased 14 days post-stroke in OZR (146%) but not in LZRs. At this time point, loss of cerebral microvascular density (via IHC) was seen in OZR (40%) and to a lesser extent in LZR (15%). Healthy MCAs incubated with 24 hr post-stroke LZR VAT had a decrease in dilation response (24%) but this decrease was recovered at 14 days post-stroke. When healthy MCAs were incubated with OZR non-stroke VAT, reactivity decreased by 20%. 24hr post-stroke OZR VAT decreased dilation by 37% and 14 day post-stroke OZR VAT attenuated dilation further to 53%. VAT exudate showed that OZR VAT produced significantly higher concentrations of pro-inflammatory markers at 24 hrs and 14 days post-stroke but LZRs had a pro-inflammatory response only at 24 hrs. By this time, anti-inflammatory markers were elevated in LZR VAT but not in OZR VAT. These data suggest that the effect of stroke on MCA function is mediated in part by VAT inflammation. Our results also suggest that LZR VAT is recovered 14 days post-stroke but OZR VAT actually gets worse as time progresses post-stroke.

Effects of Electronic Cigarette Vapor on Body Mass, Food Intake, and Body Composition

Nicotine and cigarette smoking promotes weight loss and suppresses appetite. Since 2007, the use of electronic cigarettes (E-cig) has increased dramatically in the US, however there are still few studies that examine the long-term consequences of e-vapor, particularly in the context of appetite regulation/weight management. This study compares the effects of cigarette smoke and E-cig vapor on food intake, body weight, and body composition in mice. We hypothesized that E-cigs would elicit similar changes on body mass, adiposity, and food intake as conventional cigarettes (i.e. 3R4F reference cigarette). Female C57BL/6 mice were exposed to filtered room air (n=15), mainstream smoke from 3R4F reference cigarette (n=15), or cappuccino E-cig vapor (n=15) for a total of 8-months. In this report, we show assessments in body mass, food intake, and body composition following daily exposure (4 h/d, 5d/wk) for up to 6 months. Food and water were administered ad libitum. 3R4F, E-cig and control mice increased body mass by 15%, 30%, and 31%, respectively, over 6 months. 3R4F mice had 15 and 16% lower body mass (24.9 ± 0.55 g, $p < 0.01$) compared to E-cig (28.2 ± 0.77 g) and controls (27.7 ± 0.72 g), respectively. 3R4F exposed mice also exhibited reduced total body fat (2.74 ± 0.25 g, $p < 0.01$) compared to E-cig (4.10 ± 0.42 g) and controls (4.18 ± 0.40 g). E-cig mice food consumption was significantly increased compared to 3R4F (12.4 ± 0.8 vs 9.5 ± 0.7 g/day, respectively; $p < 0.05$) but not significantly different compared to controls (12.4 ± 0.8 vs 10.5 ± 0.8 g/day, respectively, $p = 0.12$). Likewise, kcal food consumption over 3-days was greater in E-cig compared to 3R4F and control mice (50.7 ± 2.3 vs 42.7 ± 0.8 and 45.2 ± 0.9 kcal, respectively; $p < 0.01$). Unlike conventional cigarettes, we found that our E-cig exposed mice did not elicit reductions in total body or adipose mass. This suggests the effects of E-cig may not be the same as that occurring with traditional tobacco cigarettes, or that the exposure to nicotine and/or other chemicals in the E-cig liquid elicits a different response on appetite or feeding behavior. Further studies are needed to evaluate the effect that flavorings and/or the compounds produced in E-cig vapor exert on metabolism and the hypothalamic appetite neurosystems.

Brownmiller, Tayvia

65

Medicine, WVU Cancer Institute, Basic Science

The Importance of the Lnc-SPRY3 Family in Non-small Cell Lung Cancer Radiation Response

Lung cancer is the number one cause of cancer related deaths in the United States. The 5 year overall survival rate for patients with non-small cell lung cancer (NSCLC) stands at 17.7% with women having a twice better overall survival rate than men. Currently, there is no solid evidence to explain the disparity between gender survival rates. Previous studies suggest molecular differences including genes located in the sex chromosomes. While protein-coding genes of the X and Y chromosomes have been relatively well characterized, the non-coding regions responsible for producing non-coding RNAs (ncRNAs) are not well understood. One class of ncRNAs expressed from all chromosomes (including the sex chromosomes) are long non-coding RNAs (lncRNAs). lncRNAs are ncRNAs larger than 200 nucleotides that function at the transcriptional and post-transcriptional level in a number of well established mechanisms. Our preliminary data show the increased expression of a Y-chromosome linked lncRNA family, the lnc-SPRY3 family, in NSCLC cell lines after radiation treatment. We observed a dose and time dependent response in expression of the lnc-SPRY3 family in radiation sensitive NSCLC cell lines but not in radiation resistant NSCLC cell lines. Furthermore, a pool knockdown of the lnc-SPRY3 family members in a radiation sensitive cell line showed a slight increase in resistance to radiation. For this reason, our hypothesis is that the Y chromosome SPRY3 lncRNAs are important in the process of radiation response in male NSCLCs and could be a factor in gender-associated differences. To test this hypothesis, we will first characterize these lncRNAs and then manipulate their expression in male NSCLC cell lines or normal lung epithelial and determine their molecular function in response to radiation therapy. In summary, the overall objective of this project is to provide evidence of a male specific factor never before characterized in healthy or malignant tissues and allow for further advancements in understanding and treating NSCLC.

Burgazli, Courtney

90

Pharmacy, Pharmaceutical Sciences, Basic Science

3D printing of novel oral fast disintegrating strips for use in Parkinson's disease

Objectives: Evaluate 3D printing as a novel technology in pharmacy compounding to print oral disintegrating strips (ODS). **Methods:** In this study, we developed ODS strips specifically targeting the Parkinson's disease patient population. The strips were designed by quality of design (QD) techniques. ODS strips were formulated using hydroxypropylmethylcellulose (HPMC) and polyvinyl alcohol (PVA). An Ultimaker 2+ with the gel printing Discov3ry module was used for the printing. Sketch-up was used to model the film and Cura software was used for generating the printer code. For each batch, the weight, thickness, disintegrating time and stability were evaluated. Five batches were generated per formulation. **Results:** We found that active compounds could be easily incorporated into a 3D printable gel with a resultant HPMC film of 15% w/w. Printed films were less than 2 mm in thickness and the dissolution tests showed that the strips can dissolve within seconds. **Implications:** 3D printing can be used to print ODS strips for patients by the compounding pharmacist. These strips can be used to treat aging patients who have trouble swallowing, and improve the therapeutic outcomes of patients.

Carlson, Andrew

143

Dentistry, Dental Hygiene, Undergraduate

Comparing Nu-Bird Suction Mirror, High Speed Suction, and Slow Speed Suction

Dental professionals need water and saliva to be evacuated from their patients' mouths quickly and efficiency in order to perform procedures. The Nu-Bird suction mirror can give professionals the benefits of improved visualization and evacuation for improved quality of treatment. The purpose of this study was to compare the Nu-Bird suction mirror's ability to evacuate fluids and aerosols to the traditional high and slow speed evacuators in stimulated oral environments. For the simulated aerosol environment, the Cavitron was attached to a ring stand and each suction device was attached to an adjacent ring stand. The Cavitron and suction device were lowered into a measuring bowl and both ran for 30 seconds. The amount of water collected each time was subtracted from the control. This procedure was completed 30 times for each of the suction devices. In the submerged environment, the high speed evacuated 1.5L of water in an average of 11.22 seconds. The suction mirror evacuated the water in an average of 27.04 seconds and the slow speed in an average of 65.02 seconds. In the stimulated aerosol environment, the high speed suction left an average of 14.77ml of water in the measuring bowl, meaning approximately 6.23ml was evacuated. The suction mirror left an average of 16.73ml of water in the bowl, meaning approximately 4.25ml was evacuated. The slow speed evacuator left an average of 18.27ml of water in the bowl, meaning approximately 2.73ml was evacuated. In both experiments, evacuation rate and efficiency was greatest in high speed evacuation, and lowest in slow speed evacuation. The data for each experiment confirmed our hypothesis and was found to be statistically significant with p-values of less than 0.0001.

Cavendish, John

80

Medicine, Neurobiology and Anatomy, Basic Science

Quantitative analysis of mitochondrial morphology in neurons of triple transgenic Alzheimer's disease mice

Alzheimer's disease (AD) is a progressive, fatal neurodegenerative disease with no known cure. Metabolic disturbances, mitochondrial dysfunction, and changes in mitochondrial morphology have been observed in patients with AD and in AD animal models, but it is not known when these changes occur or how they contribute to disease progression. To determine if mitochondrial changes occur before AD pathology, we generated primary neurons from triple-transgenic AD mice and wild type controls and measured mitochondrial structure and movement parameters in live cells. To examine mitochondrial changes associated with late-stage AD pathology, we measured three-dimensional mitochondrial structure in neurons from various brain areas using fixed tissue from aged triple-transgenic AD mice and wild-type controls. We found brain region-specific differences in mitochondrial structure that were consistent across all mice. We also found some disparities in mitochondrial size and number between the triple-transgenic AD mice and wild type mice at the oldest age. Future studies will compare mitochondrial size in younger age groups.

Chen, Charles

6

Medicine, Pediatrics, Resident

Uncommon Rash in a 16 year old Wrestler

A 16-year-old male presented with a worsening rash on his forehead following a mat burn that he had suffered one week previously. He reported drainage of pus with associated burning and itching. He was initially treated with Clindamycin with no improvement in symptoms. A wound culture was collected and grew Methicillin Sensitive Staphylococcus Aureus. On physical examination, he had erythematous, eroded lesions throughout his forehead, surrounded by numerous vesicular lesions. CBC, BMP, and hepatic function panel were within normal limits. Although varicella zoster virus, herpes simplex virus, and bacterial swabs all came back negative, the clinical presentation was suggestive of a herpetic lesion. In consultation with dermatology, the diagnosis of herpes gladiatorum was established. He was started on intravenous Acyclovir until the lesions stabilized, then transitioned to oral Valacyclovir. Clindamycin was continued for secondary bacterial coverage. He responded well to the medications and was discharged the following day. He completed a 14-day course of Valacyclovir and Clindamycin after discharge. At his hospital follow-up one week later, he had some faint crusting and hypopigmented macules on his forehead, but his rash had completely resolved. He continued to take suppressive dose Valacyclovir and had no further recurrences of the lesion. Herpes gladiatorum is caused by the herpes simplex virus and primarily affects athletes involved in contact sports, most notably wrestling. Transmission is by skin to skin contact with skin lesions or secretions. The diagnosis is primarily clinical. Patients develop clusters of fluid-filled blisters, most commonly on the head, face, and trunk. Many individuals have associated cold-like symptoms including fever, chills, sore throat, and lymphadenopathy. There may be prodromal symptoms, including tingling and burning. The appearance of the lesion can be confused with other viral and bacterial skin infections including cellulitis, folliculitis, and impetigo. The condition is treated with antivirals, usually with Acyclovir and/or Valacyclovir. It is important that patients be withheld from wrestling or activities with frequent skin-to-skin contact until their lesions have healed. Routine skin examinations by trainers and coaches may lead to early detection and diagnosis.

Chertok, Nathaniel

93

Dentistry, SOD, Clinical Sciences/Epidemiology

Association of Predisposing Characteristics and Utilization of Dental Care among Youth in the United States

Background: Regular use of dental care services is a critical component in dental health outcomes. Limited population-based research is available on youth characteristics that contribute to dental care service utilization. The Youth Risk Behavior Survey is a nationally representative survey of youth regarding characteristics and behaviors that can be related to health outcomes. Methods: A secondary data analysis was conducted using the 2015 Youth Risk Behavior Survey (YRBS) data to examine factors associated with dental care utilization using Andersen's Behavioral Model of Health Care Utilization as the theoretical framework which has three primary components of predisposing factors, enabling factors, and perceived need that contribute to health service utilization. Results: Among the 5,814 youth, 77.9% (n=4,318) reported having visited a dentist in the past 12 months and 22.1% (n=1,496) had not. In the final adjusted logistic regression model, variables that were significantly associated with higher likelihood of dental care utilization were: predisposing factors of ethnicity of non-Hispanic white ($p < 0.001$) and health behavior characteristics of not using tobacco ($p = 0.004$), not using illegal substances ($p = 0.034$), not drinking soda ($p = 0.017$), and wearing a seat belt ($p < 0.001$); enabling factor of speaking English well ($p < 0.001$); and perceived health of not being overweight ($p = 0.001$). Discussion: Use of the Behavioral Model of Health Care Utilization identified significant factors from the YRBS survey classified as predisposing, enabling, and need-related factors associated with youth's utilization of dental care services. Findings from the theory-based population study can be used to inform healthcare providers of factors that may need to be addressed in an effort to promote dental care among youth.

Clara, Kraft

7

Medicine, Emergency Medicine, Resident

Pediatric Lung Abscess: Initial Diagnosis by POCUS

The diagnosis of a pediatric lung abscess can be difficult to make, and often requires imaging beyond plain chest X-ray; the decision to further image with computed tomography should be weighed against the risks of radiation exposure, especially in pediatric patients. In this report we describe a case where diagnosis was made utilizing bedside lung ultrasound in the Emergency Department. There are relatively few case reports describing lung abscess diagnosed by bedside lung ultrasound; this case report aims to describe one such case recently observed. An eight year old boy with a history of pneumonia treated appropriately with antibiotics at an outside facility presented to the emergency department for weakness and persistent fevers and night sweats. He was nontoxic appearing, though was tachycardic and tachypneic. Physical exam was remarkable for decreased breath sounds on the left side. A bedside ultrasound of the heart appeared normal, while ultrasound of the lung demonstrated a well demarcated capsular structure measuring 5 cm by 6.5 cm surrounding a hypoechoic core, consistent with pulmonary abscess. Lab results were significant for elevated WBC of 19.7, ESR 73, CRP 106.9. Initial chest X-ray showed a large round area of consolidation in the left lung; the initial report noted concern for a possible round pneumonia with surrounding pleural effusion. Pediatrics and surgery were consulted and computed tomography imaging was performed which redemonstrated and further characterized the newly diagnosed pulmonary abscess. The patient was admitted to pediatrics service with surgical consult for drainage of a large stage II postpneumonic pulmonary abscess and decorticating of the left lung. The patient did well postoperatively, received antibiotic therapy, and had an uncomplicated postoperative course. Bacterial culture of the abscess grew *Fusobacterium nucleatum*. He was discharged one week after admission. Lung ultrasound is a simple rapid imaging modality which is highly useful in characterizing lung pathology and is not associated with the risks involved with ionizing radiation exposure. In this case the use of bedside lung ultrasound detected a pulmonary abscess rapidly. X-ray suggested the diagnosis as well, though without sonography this could easily have been misidentified as pneumonia.

Clark, Rashel

89

Other, Animal and Nutritional Sciences, Basic Science

Fruit and Vegetable Diet Intervention in Young Adults with Metabolic Syndrome: Fruvedomics Pilot Study

Background: Metabolic Syndrome (MetS) encompasses five risk factors that increase a person's risk for heart disease, diabetes, and stroke. The prevalence of MetS is on the rise, possibly due to increasing obesity, and it is important to determine strategies to prevent this continued increase.¹ Objective: Design and implement a multi-disciplinary primary dietary intervention following the USDA Dietary Guidelines for Americans 2015 for young adults with MetS. Methods: University students (18-30 years old) with MetS were recruited via flyers, class announcements, and a phone-screening questionnaire. Screened individuals completed anthropometric measures (height, weight, body fat percentage), fasting blood lipids, and serum glucose levels. Seventeen of forty-one of the initially screened participants were diagnosed with MetS. Participants (n=17, male=6; females=11) were assessed with: arterial stiffness, complete blood lipid panel, anthropometric measures, 24-hour diet recall, and body composition measurements (Bod Pod). Participants completed an 8-week diet intervention with weekly consultations reviewing data from food logs, food receipts, and adherence to the diet. Participants received a culinary toolkit at the beginning of the intervention and had the opportunity to attend one group food demonstrations throughout the 8 weeks. Results: Study participant's fruit and vegetable intake increased from baseline to post-intervention. Mean fruit intake of the group increased from 0.6 cups to 1.9 cups per day. Mean vegetable intake of the group increased from 0.97 cups to 2.54 cups per day. A t-test of both fruit ($p=0.10$) and vegetable ($p=0.05$) intake increased from baseline to post intervention. Body fat percentage mean and standard deviation decreased from baseline ($44\% \pm 7$) to post intervention ($41\% \pm 9$) with a $p=0.29$. Conclusions and Implications: Implementation of a free-living 8-week diet with intensive education and accountability gave participants the knowledge, skills, and feedback to improve fruit and vegetable consumption. Identification of young adults with MetS allows for implementation of an intervention to improve diet and decrease the individual's risk factors for cardiovascular diseases and diabetes. References 1. What is Metabolic Syndrome? National Heart, Lung, and Blood Institute Web Site. <http://www.nhlbi.nih.gov/health/health-topics/topics/ms>. Updated June 22, 2016.

Clayton, Stuart

157

Medicine, Exercise Physiology, Undergraduate

Influence of E-Cigarettes on Vascular Function

Background: Electronic cigarettes (E-cigs) have exponentially increased in popularity and usage due to the perception that e-cigs are safe, their usefulness as a cigarette-smoking cessation tool, and the appeal of heavily marketed flavors. There is little known about the long-term effects of E-cig vapor exposure, particularly in the context of vascular dysfunction. We hypothesize that the long-term use of E-cig vapor decreased aortic function, and increase aortic stiffness. Methods: Data were obtained from C57BL/6 female mice exposed to 3R4F reference cigarette (N=5-7), cappuccino flavored E-vapor (18 mg/ml nicotine, N=7), or filtered air (N=7-8) for 4 h/day, 5 d/wk for 8 months. Food and water were administered ad libitum. Before and after the exposure, in-vivo aortic stiffness (pulse wave velocity) was measured using B-mode and Doppler ultrasound by obtain blood flow signals at the aortic arch and before the carotid bifurcation from a single image, which were gated to the EKG. At the end of the exposure the thoracic aorta was dissected, sectioned into rings and mounted onto an ex-vivo wire tension myograph system. Force transduction was used to measure the changes in aortic tension in response to methacholine, or sodium nitroprusside. Results: Aortic stiffness increased (0.45 ± 0.20 m/s) in the air-exposed group, reflecting the normal aging process. However, an accelerated age-associated aortic stiffness was noted in the cigarette (1.28 ± 0.27 m/s) and E-cig (1.14 ± 0.24 m/s) groups (ANOVA, $p < 0.05$). In animals exposed to filtered air, the maximal aortic relaxation achieved to methacholine was 90%, compared to 60% and 70% in the cigarette and E-cig groups, respectively ($p < 0.05$). No differences were noted in sodium nitroprusside dilation between groups. Conclusion: Our data suggests that 8 months of E-cig significantly accelerated the age-associated increase in aortic stiffness, and significantly impaired aortic endothelial-dependent but not endothelial-independent dilation. These data show the E-cigs induce similar vascular dysfunction to cigarette smoke exposure suggesting that E-cig have similar risk to develop accelerated cardiovascular aging and disease.

Clemente, Jessica

31

Medicine, Neurobiology and Anatomy, Basic Science

Novel Roles for JNK Signaling in Cerebral Cortex Formation

Proper formation of the cerebral cortex is necessary for human function. The human brain operates in a balance between cortical excitatory neurons and inhibitory interneurons. Disruptions in interneuron migration during development can lead to diseases such as autism, epilepsy, and schizophrenia. Our lab has shown that proper functioning of Jnk1 (c-Jun N-terminal Kinase) is required for correct entry and stream maintenance of interneurons into the mouse cortex during embryonic development. In addition to Jnk1, we hypothesize that the Jnk2 and Jnk3 genes also play a crucial role in cerebral cortex formation. Accordingly, we developed a conditional triple knockout (cTKO) mouse model where Jnk1 is deleted from interneurons in mice lacking both Jnk2 and Jnk3. In preliminary studies, our lab has found striking malformations of the developing cortical plate in cTKO brains at embryonic day 15.5 and postnatal day 0. At both of these time points, deficits in the lamination of both inhibitory interneurons and excitatory projection neurons are observed. In addition, in the cTKO brains, we have seen a breakdown in the structural integrity of nestin-labeled radial glial processes. We will create a developmental time series of embryos and pups to uncover when these phenotypes emerge, and determine how long into postnatal life they persist. By studying generation, proliferation, migration, and differentiation of both interneurons and cortical excitatory cells in our cTKO model, we will further define the role of these three JNK genes in cortical development. Understanding the genetic regulation of brain development will help uncover potential causes of neurodevelopmental disorders, and can ultimately lead to better treatment of these devastating diseases.

Collins, Kristina

14

Other, Emergency Medicine, Resident

West Virginia EMS Pre-Hospital Provider Ultrasound Survey

INTRO: Ultrasound technology has, in the recent past, become increasingly mobile as size and cost decrease and image quality increases. In 2001, research demonstrated that technology was a deterrent to implementing ultrasound on flight EMS crews. Technology was not the only barrier, and many others were voiced over the years by EMS leaders. Without current interest by EMS, pre-hospital ultrasound integration would be impossible. Our novel study, sources our local EMS to determine interest and help gauge feasibility. In this survey based study we aim to evaluate West Virginia EMS members' exposure to ultrasound, current use, and lastly their interest in US educational opportunities. METHOD/RESULTS: A HIPAA compliant REDCap survey was developed with all identifying information removed and a unique web-based link was formed. The study was successfully piloted on 10 EMS members by paper survey who visited UHC/WVU EDs. The WV Credentialing Information System database of EMSPIC (EMS Performance Improvement Center) was used to create a comprehensive list of 146 WV EMS involved agencies and an email database was developed from this via phone and internet contact by the co-investigator and other key personnel. The survey link was sent via email to EMS leaders who then distributed the link to their employees. 115 Survey participants completed basic demographic questions (gender, age, highest educational degree, county areas, time in field) and ultrasound based questions (US in work place, use of US, Previous training, and Interest in US CME). As expected, there was little exposure to previous ultrasound education with 111 (96.5%) answering none. Only 2.6% (3) reported access to ultrasound in the work place. Seventy-five participants or 65.7% have been in the field for greater than 10 years. The most encouraging number demonstrated that 93.9% (108) would be interested in a US CME course. CONCLUSIONS: Our results suggest a significant interest in ultrasound educational CME opportunity, but with limited previous exposure. Using the data from this study, we have good reason to progress with developing an EMS-targeted CME ultrasound educational workshop with the further hope of integrating Ultrasound into the pre-hospital setting.

Cook, Daniel

1

Medicine, Transitional Year, Resident

Radiologic Decisions during Intern Year of Residency: A Surveyed Study Quantifying Imaging Orders and Radiologic Tasks Daniel Cook, MD Michael Cousar, MD Benjamin Crowder, MD Andrew Lu, MD Layla Nasr, MD Prashanth Sompalli, MD

The objective of this study is to quantify the number of radiology-related tasks completed by Post-Graduate-Year-1 (PGY-1) residents through the completion of daily questionnaires in an effort to gain perspective on the degree to which prior radiology training plays a role during intern year while on an inpatient medicine service. For this study, we define “Radiological Tasks” to mean the appropriate selection of radiological studies, interpreting images independently, consulting radiology, and participating in bedside ultrasound procedures. These data will help elucidate whether greater exposure to radiology in medical school via elective based rotations or integrated course work may enhance a PGY-1 resident’s radiological skill set and decision making. By quantifying the number of tasks and decisions a resident must make, we can begin to determine the importance of formal radiology education during medical school. We hypothesized that PGY-1 residents are involved in a significant number of radiological tasks, such that a structured radiology curriculum during medical school will positively impact their confidence and competence levels on radiological decision making and thus improve patient care. In the collected data, all participants had at least one radiology elective in their fourth year of medical school, which was comprised of material including lecture-based teaching, observational radiological learning, independent interpretations, and self-study reading assignments. In the pre-survey data collection, all participants reported as being minimally to moderately confident in choosing appropriate radiological studies. From the beginning of the data collection to date, participants reported as carrying an average of 5.24 (SD 1.92) patients per day and ordering a mean of 1.76 (SD 1.82) radiological studies per day for the patients they had primary responsibility. Of the studies ordered, the participants attempted to interpret the studies themselves on average 1.24 (SD 1.55) times per day. Data collection has not ended at the time of this submission and post-survey questions will be answered at the end of the survey period.

Corley, Angela

148

Dentistry, Dental Hygiene, Undergraduate

Common Infection Control Infractions Identified During Student/Patient Care Clinic Sessions

Maintaining the proper infection control protocol at the West Virginia University School of Dentistry is important to avoid cross contamination from patient to patient or patient to operator. Not adhering to protocol can place both patient and operator at risk. The purpose of this study was to assess which infection control infractions were identified in the West Virginia University School of Dentistry's main clinic. A total of 48 dental hygiene students composed of 47 females and 1 male and 81 dental students composed of 46 females and 35 males for an overall total accumulation of 93 females and 36 males giving us a total of 129 students observed in this study. A survey was created consisting the various barrier protection devices used at the West Virginia University School of Dentistry and the personal protective equipment that is used. Clinicians were observed while the patient was present in the chair. The survey was checked yes or no if the clinician had the proper coverage of the light handles, both dominant and non-dominant, light switch, headrest, suction, air/water syringe, control panel, bracket tray handles, both dominant and non-dominant, computer mouse and keyboard, and the chair adjustment controls. The Sanitize and CaviWipes must be present and personal protective violations found must be logged. The personal protective equipment violations include not wearing a mask, mask position violation, not wearing protective eyewear, not wearing side shields, not wearing a cover gown, and not wearing gloves. The frequencies were logged onto RedCap and processed. The results showed the suction was found not to be covered 21.1% of the time followed by the air/water syringe at 16.4% and the mouse at 14.1%. The control panel and headrest were found not to be covered only 0.3% of the time and a participant was seen not wearing a mask 0.3%. The dental students had more infractions for barrier devices than dental hygiene students although there were more dental students observed. Barrier infractions were most commonly found associated with the use of the computer mouse, air/water syringe, and evacuation hand-pieces.

Cuppett, Vanessa

39

Medicine, Microbiology, Immunology, and Cell Biology, Basic Science

Infertile men with liquefaction problems have antibodies to PSA in semen: first study ever

Immunoinfertility due to antisperm antibodies and semen hyperviscosity are among major causes of male infertility. Although the modulation of prostate-specific antigen (PSA) has been investigated in prostate abnormalities, its role and the effect of its dysfunction in male fertility/infertility have not been extensively examined. The present study was conducted to examine the presence of PSA antibodies locally in the seminal plasma of men having immunoinfertility and semen hyperviscosity. Seminal plasma samples from immunoinfertile men (n=25), men with hyperviscous semen (n=25), and normal men (n=24) were collected and analyzed for immunoreactivity with PSA in ELISA and Western blot. In the immunoinfertile group, seminal plasma from 20% of men reacted positively with PSA. In the hyperviscous group, seminal plasma from 28% of men reacted positively with PSA. None (0%) of the seminal plasma from the normal group showed immunoreactivity to PSA. This is the first study ever to indicate the presence of PSA antibodies in semen of men having immunoinfertility or hyperviscosity. These findings may have clinical significance in the specific diagnosis and treatment of infertility in men, and contraceptive vaccine development.

Davis, Terri

120

Medicine, School of Medicine, Clinical Sciences/Epidemiology

A Comparison Study of Commercially Available Cardiac-Assist Devices in Novice and Experienced Practitioners

Effective chest compression remains the cornerstone of successful CPR and is vital for survival and good neurological recovery. A number of CPR-adjunct devices have been developed to improve the consistency and quality of chest compressions. Little data has been published comparing the performance characteristics of these devices against each other, and to date only 1 has been tested clinically. This study recruited 42 inexperienced and 49 experienced CPR utilizers to compare CPR compressions performed for 6 minutes without an assist device to those performed with CPRsQ, TrueCPR, and Zoll Pocket CPR devices on a SimMan 3G. Depth of compression without a device was statistically better in experienced vs inexperienced CPR utilizers during both the 0-2 minute range and the 2-4 minute range, but both had poor depth compression from 4-6 minutes. With all devices, both groups had appropriate depth compression from 0-4 minutes and both had poor depth compression from 4-6 minutes. Compression rate without a device was statistically better in experienced vs naïve CPR utilizers during both the 0-2 minute range and the 2-4 minute range, but both groups had poor depth compression from 4-6 minutes. With all devices, both groups had appropriate depth compression from 0-4 minutes and both had poor depth compression from 4-6 minutes. Of the devices, Zoll Pocket CPR® showed the greatest statistical benefit over the other devices. This study showed that CPR feedback devices improve the effectiveness of CPR compressions and rate in novice practitioners to be statistically equal to experienced practitioners and statistically improve the effectiveness of experienced practitioners.

Davison, Karla

142

Public Health, Public Health, Undergraduate

Negative Life Events, Identity, and Life Satisfaction in Adolescents

We know that healthy identity development has a significant impact on positive outcomes including positive self-concept and esteem, psychological well-being, agency, and life satisfaction. We also know that Negative Life Events (NLEs) can impact life satisfaction, particularly when they are incorporated into a negative narrative identity. The current study endeavors to investigate the associations between Negative Life Events, positive Identity Formation, and Life Satisfaction. It was hypothesized that Negative Life Events would be negatively associated with Life Satisfaction and Positive Identity formation would be positively associated with Life Satisfaction. We further hypothesized the relationship between Negative Life Events and Life Satisfaction would be moderated by positive Identity formation. A quantitative cross-sectional research design was employed. Participants ($n=5,756$) were enrolled in West Virginia middle and high schools. Early adolescents in middle schools (grades 6-8th) were between the ages of 11-14 ($m=12.54$). Adolescents in high schools (grades 9-12th), were between the ages of 14-19 ($m=15.78$). Boys made up 49.5% of the sample and 81% of the participants identified as white race. The response rate was calculated to be 82.4% of sample included in this study. We analyzed the data using hierarchical multiple regression. On the first step we controlled for gender, age, race, and income (using maternal education). On the second step we added Negative Life Events (NLEs) and Identity. Finally, we added an interaction term to represent NLEs and Identity. The results of the regression indicated that the predictors explained 35.2% of the variance ($R^2=.352$, $F(7, 2976)=231.22$, $p<.01$). The interaction term was not significant. However, Identity ($\beta=.508$), followed by cumulative NLEs ($\beta=-.158$), maternal education ($\beta=.074$), and white race ($\beta=.057$) were all significantly predictive of life satisfaction ($p<.01$). Although only one of our hypotheses was supported by the data analysis, we are encouraged to move forward in this line of research. Our findings seem to suggest that positive identity formation is very important to life satisfaction, over and above demographic variables and even the experience of multiple NLEs.

DeRoos, Katherine

162

Medicine, Immunology, Microbiology, & Cell Biology, Basic Science

Evaluating The Role of Interleukin-17 in *Bordetella pertussis* Infections Using an IL-17-GFP Mouse Model

Due to a recent reemergence of *B. pertussis* cases in the US, there has been a call for a more efficacious vaccine and additional research into the host-pathogen interactions that occur over the course of infection. In a series of experiments, interleukin-17 (IL-17), a pro-inflammatory cytokine that is characteristic of T cell subtype 17 (Th17), was studied using an IL-17 green fluorescent protein (GFP) reporter mouse such that IL-17 activity is marked by GFP. We hypothesized that additional cell types aside from Th17 will produce IL-17 during infection with *B. pertussis*. Naïve mice were infected intranasally with *B. pertussis* and subsequently euthanized at days 1, 3, and 7 post-infection. Isogenic mutants of *B. pertussis* were used to determine the effects of individual antigens on IL-17 expression, including wild-type bacteria, (WT), knockout pertussis toxin (Δ PTX), and knockout adenylate cyclase toxin (Δ ACT) mutants. Samples of the following were harvested: blood, lung, nasal wash, trachea, thymus, and bone marrow. Lung, nasal wash, and trachea homogenates were plated to measure bacterial load. Cytokine quantifications of IL-6 and IL-17 were performed on lung and serum. All tissues were analyzed by flow cytometry for percent of the live cell population that were IL-17+ (GFP+) myeloid, B cells, and T cells. Results indicate high amounts of IL-6 (103 μ g/mL) in response to WT infection, which drives an increase in IL-17 production over the course of infection. Flow cytometry data show that in response to WT infection, IL-17+ B cells in the blood increased five-fold between days 1 and 7. IL-17+ myeloid cells in the blood increased 27-fold. In contrast, IL-17+ T cell changes were not as drastic, and at day 7 were <6% of live cells in all tissues. Mutant experiments suggest that both PTX and ACT influence the both IL-17+ and non-IL-17+ response to infection. Bacterial load data show that WT *B. pertussis* experienced uninterrupted growth over time, while Δ PTX and Δ ACT mutants had compromised ability to persist in the host.

Exercise Reverses Metabolic Syndrome Perivascular Adipose Tissue impairment of Aortic Relaxation.

Thoracic aorta perivascular adipose tissue (PVAT) mediates aortic function through paracrine signaling. In health PVAT is “brown-like” in phenotype and predominately releases anti-inflammatory cytokines, which aide in proper vascular function. However, in metabolic syndrome (MetS) PVAT loses this beneficial phenotype and becomes “white-like”. This phenotypic shift is accompanied with oxidative stress and expression of pro-inflammatory cytokines, which can impair aortic endothelial nitric oxide (NO) production and alter extracellular matrix composition. The objective of the study was to determine the therapeutic efficacy of aerobic exercise in an animal model of MetS (obese zucker rats: OZR) specifically on PVAT mediated NO production, aortic relaxation, and aortic stiffness. MetS PVAT expression of UCP-1 decreased 40- fold accompanied by a greater than 9 fold increase in both TNF α . This inflammatory secretion profile further diminished endothelial dependent relaxation of the aorta (lean zucker rat (LZR) Ao only-83%, OZR Ao only- 67%, OZR Ao+PVAT- 58%). Using the DHE assay to assess superoxide production in the PVAT showed a marked increase in fluorescence in OZR v. LZR ($p<0.01$). Little is known about exercise’s impact on PVAT. Expression of UCP-1 and SOD-1 increased, while TNF α decreased following treadmill training. Exercise improved OZR aortic relaxation 10%, additionally PVAT increased relaxation another 10% ($p<0.01$). Diminished superoxide production (DHE, $p<0.05$) in the PVAT helped restore a healthy inflammatory balance improving NO bioavailability. Exercise also reduced constricting responses to phenylephrine with and without PVAT. Structurally MetS causes increase deposition of collagen with fragmentation of elastin increasing the aorta’s resistance to deformation. OZR have increased elastin modulus compared to LZR (561 to 304 N, $p<0.01$) showing increased stiffness this is completely reversed by exercise training (561 to 337 N, $p<0.01$). OZR PVAT gene expression showed increase in MMP9, a marker that correlates strongly with stiffness, which exercise training completely returns LZR levels. This establishes a correlative relationship between PVAT expression of MMPs and mechanical aortic stiffness. In summary MetS PVAT mediates increases in both functional and structural stiffness. Treadmill training in OZR promotes beneficial PVAT gene expression leading to reduced superoxide production, decreased inflammatory cytokines, and retention of elastic properties.

Dilan, Tanya

52

Medicine, Biochemistry, Basic Science

Bardet-Biedl syndrome-8 (BBS8) is essential for morphogenesis of photoreceptor outer segments

Photoreceptor neurons are polarized cells with distinct compartments; an outer segment (OS) that houses all the phototransduction proteins, inner segment (IS), the site of protein biosynthesis and synapse, essential for transmission of visual information to downstream neurons. It is thought that Bardet-Biedl Syndrome complex (BBSome), a multiprotein complex linked to blindness, is needed for anterograde protein trafficking from IS to OS. Alternatively, the BBSome has been shown to be important for ciliogenesis in cell culture but the role for the BBSome in photoreceptor ciliogenesis is not clear. Additionally, recent studies have questioned the role for BBSome in anterograde GPCR protein trafficking in photoreceptors. The purpose of this study is to tease out the molecular mechanisms underlying the photoreceptor pathology in Bardet-Biedl Syndrome (BBS). We have generated multiple animal models lacking BBS8, a core component of the BBSome, focusing on identifying the role of BBS8 in vision. Ultrastructural analysis of our BBS8 KO mice revealed dysmorphic photoreceptor outer segments at early stages of photoreceptor development (postnatal day 10-P10) suggesting the critical need for BBSome in OS morphogenesis. Defective OS development correlated with progressive loss of photoreceptor function. Interestingly the photoreceptor OS axoneme, a microtubule-based scaffold, was shorter in the absence of BBS8 (P10). Intriguingly, at P10, exo-vesicles were abundant in the extracellular space. Cone-specific model revealed the need for BBS8 in survival and function of cone photoreceptors. Additionally, in the absence of BBS8, we observed dynamic changes of other BBS partner subunits. Ablation of BBS8 led to the accumulation of Syntaxin3 (STX3), a protein normally found in the IS and synapse, in the rod and cone OS. Our results show the need for BBS8 in development of photoreceptor outer segments. In comparison to other animal models for BBS, removal of BBS8 results in early and severe dysmorphogenesis of the OS. Mislocalization of STX3 in the OS suggests a defective retrograde trafficking. Alternatively, structural abnormalities in the absence of BBS8 may contribute to observed protein mislocalization or accumulation of exo-vesicles in the extracellular space. Our current efforts are focused on distinguishing between these two mechanisms with the use of inducible animal models.

Divel, Amanda

149

Dentistry, Dental Hygiene, Undergraduate

An Evaluation of the Accuracy of WVU School of Dentistry (SoD) Patient Odontograms Using a Radiographic Approach

According to the American Board of Forensic Odontology (ABFO) guidelines, identification of human remains are generally based on restorations, caries, missing teeth, and/or prosthetic devices. In order for correct identifications to be made, dental records must be accurate. We conducted this study in order to see if the West Virginia University School of Dentistry (WVU SoD) kept accurate records that would assist in making positive identifications. A random sample of 81 full mouth series of radiographs were taken out of a total of 102 that were obtained at the WVU SoD during the period of April 1st to May 2nd of 2016. These radiographs served as antemortem records. We then used the corresponding patient odontograms as postmortem records. The records were compared and findings were entered into a REDCap database to analyze the accuracy of the charting. The results of our study show that tooth status charting met the 95% accuracy standards for all statuses except for restored and virgin teeth. Surface accuracy charting for all surfaces exceeded the 95% minimum threshold. Lastly, when combining restorative materials with their surfaces, no combination met the 95% minimum accuracy. Our study found that there are too many inaccuracies in the WVU SoD patient odontograms to ensure proper identification.

Doolittle, Julia

154

Dentistry, Dental Hygiene, Undergraduate

Dental Hygienists' Comfort Levels with the Presence of a Parent/Guardian in the Operatory During the Provision of Care to Children

This study is to identify dental hygienists' comfort levels with parental/guardian presence in the dental operatory during the provision of care to impaired children. A closed-response survey, asking dental hygienists to identify their comfort level with parental/guardian presence during the provision of oral hygiene instruction, fluoride application, child prophylaxis, orthodontic procedures, sealant placement, nitrous oxide administration, and local anesthesia administration on impaired children, was emailed nationwide to 19,397 active American Dental Hygiene Association members. A total of 2,048 participants responded to our survey. The participants were predominantly females (97.9%), had children of their own (67.9%), worked in a general practice (78%), and allowed parental/guardian presence (93.8%). ANOVA, chi-square tests, odds ratios, and confidence intervals were used to report the results of this study. By gender, males and females were equally as comfortable for all procedures. Dental hygienists from all practice types were equally as comfortable with parental/guardian presence when performing all procedures except sealant placement on physically impaired children. Odds ratios and confidence intervals were calculated to determine if there were variances amongst comfort levels between dental hygienists based on whether or not they allow parental/guardian presence during the provision of care. Dental hygienists that allow parental/guardian presence in the operatory were more likely to report being comfortable than those whom do not. By parental status, dental hygienists who were parents were more likely to report being comfortable than dental hygienists who were not parents. Overall, dental hygienists were more likely to report being comfortable with parental/guardian presence in the operatory when working with children with physical impairment while being more likely to be the least comfortable while working with children with a sensory impairment. Although hygienists reported being comfortable with parental/guardian presence while providing care, they were more likely to be comfortable in some situations than others.

Ede, Gregory

40

Medicine, Medicine, Basic Science

The Effects of E-Cigarette Exposure on Cardiac Function in Mice.

Introduction: Numerous studies have demonstrated the many harmful health effects of tobacco cigarettes, however not many studies have looked at the health effects of electronic cigarettes (e-cig). In this study, the effects of 5-months e-cig exposure were examined on cardiac function. Methods: Data were obtained from C57BL/6 female mice exposed to 3R4F reference cigarette (N=5-7), cappuccino flavored E-vapor (18 mg/ml nicotine, N=7), or filtered air (N=7-8) for 4 h/day, 5 d/wk. Measurements are obtained from B-mode images obtain from transthoracic echocardiography with the mice under isoflurane anesthesia, once before and following 5 months exposure (additional data was collected after 8-months exposures, but are not yet analyzed). Results: Cardiac output was not different between the groups. Heart rate was not different between e-cig and air groups, but tended to be lower in 3R4F cigarette exposed mice compared to air (439 ± 18 vs 491 ± 24 , respectively, $\text{mean} \pm \text{SE}$, $p=0.07$). Stroke volume was lower in e-cig mice compared to air (26 ± 1.6 vs 32 ± 2.1 μL , respectively, $p < 0.05$), but not different between 3R4F and air. Left ventricular diastolic and systolic volumes in e-cig mice were significantly decreased by 35% and 151%, respectively, when compared to air-exposed mice ($P < 0.05$), but neither were different in 3R4F vs air groups. The calculated ejection fraction (EF) in e-cig mice was increased by 9.6%, and fractional shortening (FS) increased by 18.4%, in e-cig mice compared to air ($p < 0.05$). FS, but not EF, increased in 3R4F vs Air (19%, $p < 0.05$). Left ventricular mass tended to be greater in e-cig compared to 3R4F ($p=0.053$), but not different compared to air-exposed mice. Conclusions: These data suggest that 5-months exposure to E-cig vapor did not significantly alter cardiac output in mice, however the effects on heart rate and stroke volume were different between e-cig and 3R4F cigarette. Interestingly, diastolic and systolic volumes were both decreased in e-cig mice, yet an increase in ejection fraction was observed; this may represent a compensatory effort by the heart to counter the e-cig effects on cardiac function. Longer-term effects are still unknown, but these data suggest they are needed to more fully understand the effects of e-cig vapor on cardiac function.

The Prevalence of Eating Disorders and Body Dissatisfaction Among Elementary School Children in Rural West Virginia

Introduction: It is highly accepted that the prevalence of eating disorders and body dissatisfaction begins to emerge when children reach adolescence. Consequently, many schools and other institutions have programs to educate adolescents about healthy weight and weight management, but also to identify adolescents with or at risk for an eating disorder or low self-esteem due to body dissatisfaction. Societal pressures influence children to become more self-conscious of appearance and weight at an earlier age; however, very few studies have evaluated the prevalence of eating disorders and body image perception in a younger age group. The purpose of this study was to evaluate the prevalence of eating disorders and body image dissatisfaction among elementary school children and identify factors that may contribute to or lessen the prevalence of body dissatisfaction. Methods: A sample of 120 students, in grades 3-5 completed the Kids' Eating Disorder Survey (KEDS). From this data, we calculated prevalence of eating disorders, unhealthy weight management techniques, and body image dissatisfaction. Results: 56 percent of children reported that they wanted to lose weight. Among those who wanted to lose weight, 77 percent reported using an unhealthy method to lose weight, including fasting, vomiting, and excessive exercise. Excessive exercise was the commonly reported method to lose weight in this group. Further, 71 percent of children who wanted to lose weight were in either the underweight or normal weight BMI range. Conclusions: Our study is one of the few to assess the prevalence of eating disorders or body dissatisfaction in children rather than adolescents. We observed that a large proportion of children express a desire to lose weight, many of whom are already at or below a healthy weight, and are willing to utilize unhealthy methods to lose weight. This study indicates that current children may be at higher risk of eating disorders than those of earlier generations. There is a critical need to educate children on healthy weight and weight management to reduce the risk of developing eating disorders and to offer support to those with body dissatisfaction.

Ellis, Rebecca

144

Dentistry, Dental Hygiene, Undergraduate

Does Increasing Oral Irrigator Water Temperature Result in Increased Plaque Removal?

Using an oral irrigator can reduce the amount of plaque on tooth surfaces. Plaque is a risk factor of causing oral diseases. The purpose of this study is to determine if increasing oral irrigator water temperature will result in increased plaque removal. After getting IRB approval, students in a dental hygiene class during fall of 2016 were approached and presented with a summary of the purpose and methodology of this study. To be eligible to participate in this study, the participant must have full dentition minus third molars and no dental restorations. The first eligible participant that volunteered was enrolled in this study, and then this student was given a consent form to sign. The participant will be trained on how to properly use the oral irrigator. The participant will be asked to refrain from using and mechanical or chemotherapeutic oral hygiene for 24 hours prior to the study, and then the participant will return 24 hours later. In a clinical setting, researcher A will do plaque score and leave the operatory. Researcher B will then arrive with the oral irrigator filled with one of the three water temperatures approved. Researcher B will supervise the use of the oral irrigator by the participant. After ninety seconds of use, researcher B will leave and researcher A will return to complete a second plaque score. This process will continue for 30 consecutive days. The most effective temperature for plaque removal when using an oral irrigator was 42C. This temperature showed a reduction in plaque of 54.1%. When using room temperature water at 37C the plaque reduction decreased to 32.6%. The least effective temperature of 32C only showed a plaque reduction of 23.7%. Plaque removal is significantly ($r = 0.73$) reduced at 42C.

Emery, Eric

38

Medicine, Orthopedics, Basic Science

Evaluation of Wild Type and Transfected K7M2 Osteosarcoma Microenvironments in a Murine Model

Osteosarcoma is the most common primary malignancy of bone in children and young adults accounting for approximately 56 percent of all bone cancers in individuals under 20 years old. Osteosarcoma metastasizes to other organs primarily other bones and to the lungs. Despite the improvements in the current treatments to increase the survival rate, once metastatic disease occurs osteosarcoma carries a low 15-20% long-term survival rate and has not changed in over two decades. Therefore the current standard treatments require more effective strategies in treating primary and metastatic tumors efficiently. Immunotherapeutics aim to activate the patient's own immune system to fight malignancies. The overarching aim of the research project is to test the efficacy of interleukin-12 (IL-12) and anti-PD-L1 combination therapy against osteosarcoma primary tumors and metastatic disease. The current study was undertaken to study the tumor microenvironment in BALB/c mice inoculated with WT-K7M2 murine osteosarcoma cell line (ATCC CRL-2836) and Transfected K7M2 (T-K7M2) cells. WT-K7M2 was stably transfected with the Luciferase reporter gene (*Photinus pyralis*) via pGL 4.51 Vector that was stable for several generations. Primary tumors and metastatic lung tumors were detected and monitored using a non-invasive In-Vivo Imaging System (IVIS). To examine the microenvironment of the primary tumors several surface markers and intracellular markers were studied in tumors obtained from both WT-K7M2 and T-K7M2 mice. The tumor surface markers: CD95, PD-L1, CD 146 and tumor infiltrating lymphocytes: CD45, CD4, CD8, NKp46, DNAM-1, NKG2D, CD178, CD11b, Ly6G, FOXP3 were evaluated using flow cytometry. Analysis of data with one-tailed t tests was performed. Our results indicated that majority of the tumor and tumor infiltrating lymphocytes had no significant difference between WT-K7M2 and T-K7M2 groups except a few (PD-L1, NKp46, NKG2D, and CD178). However more studies and a follow-up analysis are necessary to determine the effect of transfection on the K7M2 tumor microenvironment in a murine model. If successful the T-K7M2 osteosarcoma model could be a pivotal tool in monitoring, evaluating and treating primary and metastatic tumors.

Epperly, Matthew

167

Medicine, Microbiology, Immunology, and Cell Biology, Basic Science

Identifying potential virulence factors associated with the rugose phenotype in *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a major nosocomial pathogen and our laboratory has identified several strains of this bacteria with a rugose, or wrinkled, phenotype. One of these mutant strains had a mutation in the gene *mntH1*. This gene encodes the uptake protein MntH1 that aids the bacteria in acquiring and utilizing manganese. Metal ions such as this play roles in biofilm forming processes as well as detoxifying reactive oxygen species such as those present in macrophages. This study focused on comparing *mntH1* mutants to wild type strains of *P. aeruginosa* in their ability to form biofilms as well as resist phagocytosis. A secondary goal was to genetically engineer a plasmid containing a functional copy of *mntH1*, use it to complement the mutation, and confirm that MntH1 is responsible for the different phenotypes observed. We hypothesize that strains deficient in *mntH1* are less capable of forming biofilms and neutralizing reactive oxygen species. If the experimental data supports our hypothesis, further studies in this area could lead to more effective treatments for patients with *Pseudomonas aeruginosa* infections.

Erdreich, Brett

4

Medicine, Internal medicine, Resident

E-Cigarette Vapor Inhalation Leads to Impaired Arteriolar Vascular Function in Mice

Rationale: Electronic nicotine delivery systems (ENDS) also known as 'E-cigarettes' have been touted by tobacco companies as a safe alternative to cigarettes. Thus far, few studies have investigated the acute or chronic effects of E-cigarette vapor on cardiopulmonary and vascular function. Our objective is to evaluate the acute effects of inhaled E-cigarette vapor on microvascular reactivity to determine systemic consequences of the use of ENDS. Methods: Baseline measurements of third order arterioles were assessed in skeletal muscle (gluteus maximus m.) microvasculature of wildtype (WT) C57Bl/6 male mice using intravital microscopy (IVM). E-cigarette vapor exposure consisted of 5 minutes using a 3rd generation tank-style device with E-juice containing 18 mg/ml of nicotine. Vessel diameters were measured before and two times (i.e. 0 and 60 minutes) after the exposure. The vessels reactivity in response to acetylcholine (ACh) were also measured at each time point. Results: Immediately following E-cigarette exposure, there were no significant changes in baseline arteriolar vessel diameter; however, at 1-hour post exposure arteriolar diameters were decreased by an average of 31% ($p < 0.001$). ACh-induced vasodilation was reduced by 9% ($p < 0.001$) and 7% ($p < 0.05$) at 0 and 60 minutes following the exposure, respectively. Conclusions: Baseline arteriolar measurements 1-hour after E-cigarette exposure show evidence of enhanced peripheral vasoconstriction and impaired vaso-reactivity to ACh. These data provide evidence that acute E-cigarettes exposure leads to vascular dysfunction. Further studies are needed to identify the consequence of E-cigarette vapor, and/or inhaled nicotine, toward the development of cardiovascular, pulmonary and peripheral vasculature disease.

Ernest, Emily

141

Medicine, Orthopaedics, Undergraduate

Standardized Model of Staphylococcus aureus Femoral Implant Associated Infection

Introduction: The infection burden of total joint arthroplasty is expected to rise significantly over the next 15 years. Prosthetic joint infections (PJI) are often due to biofilm producing organisms. Standard in vitro quantification is vital in the assessment of novel treatment modalities. Coupons of common orthopaedic biomaterials are currently utilized for in vitro biofilm development; however, these coupons do lack the geometry and surface area to replicate clinical presentations of PJI. The purpose of this study was to establish a novel standardized femoral implant infection model in order to assess the impact of proposed translatable treatment strategies. **Methods:** A custom femoral component reactor (FCR) system was created that provided a temperature controlled environment, in which the component is stabilized and exposed to shear forces in a bacterial culture of Staphylococcus aureus. Specific 1 cm² were identified for quantification. FCR biofilm quantification either consisted of scraping technique to determine colony forming units or crystal violet staining with to determine absorbance. This was repeated by two separate technicians for reproducibility. **Results:** These methods produced consistent, technician-independent results with no significant differences between medial and lateral condyles for both quantification methods ($p > 0.05$). Across both condyles, one technician produced an average 1.53×10^7 CFU/cm² and 0.084 absorbance, as where a different, previously unaffiliated technician produced an average 1.58×10^7 CFU/cm² and 0.090 absorbance ($p > 0.05$). **Conclusion:** This model provides a rugged platform in which we can assess new treatment modalities in efforts to treat adherent biofilm found in prosthetic joint infections.

Inhalation of Gas Metal Arc-Stainless Steel Welding Fume Promotes Lung Tumorigenesis in A/J Mice

Epidemiologic studies suggest an increased risk of lung cancer with exposure to welding fumes, but controlled animal studies are needed to support this association. Oropharyngeal aspiration of gas metal arc-stainless steel (GMA-SS) welding fume has been shown by our laboratory to promote lung tumor formation in vivo using a two-stage initiation-promotion model. Our objective in this study was to determine if GMA-SS fume also acts as a lung tumor promoter when delivered via inhalation to lung tumor susceptible mice. Male A/J mice received intraperitoneal (IP) injections of corn oil or the chemical initiator 3-methylcholanthrene (MCA; 10 $\mu\text{g/g}$) and one week later were exposed by whole body inhalation to air or GMA-SS welding aerosols for 4 h/d x 4 d/w x 9 w at a target concentration of 40 mg/m³. Lung nodules were enumerated at 30 weeks post-initiation. GMA-SS fume significantly promoted lung tumor multiplicity in A/J mice initiated with MCA (16.11 ± 1.18) compared to MCA/air-exposed mice (7.93 ± 0.82). Histopathological analysis found that the increased number of lung nodules in the MCA/GMA-SS group were hyperplasias and adenomas, which was consistent with developing lung tumorigenesis. Lung metal deposition analysis revealed that a markedly lower deposited dose (approximately 5 fold) elicited a similar fold-change lung tumorigenic response when compared to our previous aspiration study. In conclusion, this study demonstrates that inhalation of GMA-SS welding fume promotes lung tumor formation in vivo and provides further support for the epidemiologic studies that show welders are at an increased risk for lung cancer.

POCUS First for Appendicitis: The Most Efficient Option

Introduction: Appendicitis is the most common abdominal surgical emergency in adults and children with more than 250,000 cases of acute appendicitis diagnosed each year in the United States. Accurate and early diagnosis can limit complications and decrease healthcare costs. **Purpose:** The current gold standard for diagnosis is CT scan imaging; however bedside ultrasound allows for faster diagnosis with less risk and cost to the patient. The aim of this study is to examine the diagnostic accuracy of bedside ultrasound performed by EM physicians for appendicitis. **Methods:** This study is a retrospective chart review of patients of all ages who were seen in the ED between January 1, 2015 and December 31, 2015 and received abdominal ultrasound with mention of the appendix. The following information was extracted from 105 charts that met the inclusion criteria: ultrasound result, if CT was obtained, CT results, if dx was made < 72 hours or > 72 hours following presentation, patient disposition, age, gender, BMI, ED length of stay, whether or not the patient had surgery, final pathologic diagnosis, complications following surgery, and if patient had follow up. **Results:** Of 105 patients who received a bedside abdominal ultrasound with mention of the appendix, 21 of 24 (87.5%) with ultrasound findings of appendicitis had a final diagnosis of appendicitis whereas only 11 of 81 (13.5%) with a nondiagnostic ultrasound had a final diagnosis of appendicitis. The sensitivity and specificity of ultrasound for the diagnosis of appendicitis were 65.63% and 95.89% respectively, compared to sensitivity and specificity of CT scan, which were 71.88% and 100% respectively. **Conclusions:** This study showed that while it is known that ultrasound has a lower sensitivity than CT scan for appendicitis, the specificity of ultrasound is very close to that of CT scan. When this high specificity (95.89%) is combined with the advantages of ultrasound: faster diagnosis, reduced cost, decreased length of stay in the ED, and no radiation to the patient, it can be argued that point of care ultrasound is the most efficient option. Further imaging after positive ultrasound only delays care and increases cost without patient benefit.

The significance of Tie-2 expressing monocytes as a prognostic indicator of prostate cancer progression.

The presence of TEMs (Tie-2 expressing monocytes) has been associated with chronic inflammation, higher grade malignancies, and poorer prognosis in several malignancies (Matsubara et. al., 2013). While Tie-2 is expressed on other prostate microvascular cells (Kobayashi et. al., 2008), the presence of TEMs, or the association of TEMs with prognostic indicators or clinical outcomes, in prostate cancer progression requires elucidation. TEM gene expression, and other genes commonly associated with TEMs, was explored by using mRNA sequence Z-scores and related clinical data from cBioPortal (Prostate Adenocarcinoma TCGA, Provisional) database to describe Gleason score (GS) and prostate cancer outcome relationships. Results: Summary statistics described the expression of the TEK (Tie2 receptor gene), FCGR3A, and ANGPT1 in concert with defined GS groups. TEK, FCGR3A, and ANGPT2 expression increased in accordance with GS subgroups while ANGPT1 expression decreased; genes FCGR3A (n=497, R-Squared = 0.089, p-value < 0.001), ANGPT2 (n=497, R-Squared = 0.039, p-value < 0.001), and ANGPT1 (n=497, R-Squared = 0.043, p-value = 0.001) were significantly different among as determined via ANOVA analysis. Principle component analysis was used to determine that the 3rd principal component, consisting of FCGR3A, ANGPT2, and ANGPT1, provided the most meaningful split between GS groups "3+4" and "4+3". The difference between ANGPT1 and ANGPT2 was highly correlated with the 3rd principal component as illustrated in Figure 2 suggesting z-score differences between ANGPT1 and ANGPT2 can serve as a surrogate for the 3rd principal component. A Kaplan-Meir survival curve analysis revealed no difference in biochemical failure, overall survival, or disease-free survival in groups overexpressing the TEK gene. Discussion The analysis described an increase in the expression of the TEK, FCGR3A, and ANGPT1; genes associated with TEMs among GS groups with significant differences in expression of FCGR3A, ANGPT2, and ANGPT1. TEK did not statistically confer with prostate survival or failure outcomes or contribute to the principal component analysis. However, increased expression of Ang2 (and decreased Ang1) was associated with GS and moderately correlated with TEK expression. TEK expression also increased with GS although the differences were not statistically significant. Additional longitudinal study of TEK and associated genes is required.

Fletcher, Marissa

130

Medicine, Health Sciences, Masters

Distracted Driving

There are 1.6 million car crashes in the U.S. annually that are related to cell phone usage while driving, with approximately 330,000 of those resulting in injuries or death. In 2014, 271 vehicular fatalities occurred in West Virginia. Distracted driving is a national issue that can be easily avoided, but it is unknown if cell phone usage is more frequent in men or women drivers, and if residence impacts cell phone use while driving. Cell phone use data were collected in metropolitan, non-metropolitan, and rural areas. Traffic was observed in one direction Monday thru Friday, in the mornings and evenings at approximately the same times each day. Each driver was recorded for use of cell phone, sex, and style of vehicle (before or after 2000, luxury or economy, and commercial or noncommercial). We hypothesized that 1) cell phone use differs by sex; 2) cell phone use differs by metropolitan status. Overall, there was a significant difference in phone use between male and females drivers (p -value <0.05). Future studies could incorporate focus groups to determine the reasons people are using cell phones while driving.

Fronckoski, Alexandra

152

Public Health, Undergraduate Program, Undergraduate

School Climate and Student Self-Reports of Anxiety, Depression, Problem Behavior, and Perceived Stress

Purpose: Prior research suggests students whose basic psychological needs are being met using pro-social means are less likely to participate in risky behaviors related to academic failure. This study examined school climate as a pro-social source of meeting the basic psychological needs of early and late adolescents and a means of reducing risk. **Procedures:** Two thousand four hundred and five students ($n=2,405$; 2, 43% female, 89% white) from 6 mid-Atlantic middle and high schools completed paper and pencil surveys (RR=88.2%). Structural equation modeling was used to describe the associations between variables and groups. Three models were developed for each grade level. All models included factors related to school climate and developmental needs. Models varied by outcomes related to school dropout, substance use, and teen parenting. Comparisons were made between high school and middle school groups by outcome. **Measures:** School Climate Measure (Zullig, et al., 2010); Basic Psychological Needs Satisfaction (Deci & Ryan, 2000); Achievement: Self-reported, averaged Math & English GPA; Substance Use: Log natural of the sum score for tobacco, alcohol, and drug use; Sexual risk: number of sexual partners. **Analysis:** Structural Equation Modeling (Mplus Version 7.3). Model controls for: Grade level (middle/high), Race (White/non-white), Maternal education (income), and Household configuration. **Findings:** All six models indicated a strong fit (minimum CFI=.96) and evidence supported school climate as a means of meeting student developmental needs and reducing risk. **Conclusions:** Evidence suggests positive school climates can be a pro-social source of meeting student developmental needs and reducing risks related to academic failure.

Increased Risk of Respiratory Diseases in Adults with Diabetes

Respiratory disorders mortality is increased 2 to 10 fold in persons with Type 1 and Type 2 diabetes, respectively. Diabetes is linked with a decrease in lung elasticity and in capacity to transfer carbon monoxide. Systemic inflammation, a common concern in persons with diabetes, may contribute to airflow obstruction. We examined the association of diabetes with respiratory diseases among 56,315 adults from the C8 Health Project. Participants were categorized into three groups: Type 1 (T1D, n=790), Type 2 (T2D, n=4,287), or no diabetes (n=51,238). ORs (95% CIs) for the association of diabetes with the following respiratory diseases were computed: emphysema, chronic obstructive pulmonary disease (COPD), chronic bronchitis, and asthma. Covariates controlled for were age, sex, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), smoking history, BMI, and perfluorooctanoic acid (C8). Respiratory diseases were present in 26%, 21% and 13% of persons with T1D, T2D, and no diabetes, respectively. In multivariable analyses, persons with T1D were twice as likely to have any respiratory disease (OR: 2.0, CI: (1.7-2.4)), while those with T2D were 1.5 times as likely (OR: 1.5, CI: 1.4-1.6). Compared to those without diabetes, in those with T1D and T2D diabetes respectively, ORs (CIs) for COPD were 2.5 (1.8-3.4), 1.6 (1.4-1.9), asthma: 1.9 (1.6-2.4), 1.7 (1.5-1.9), chronic bronchitis: 2.6 (2.1-3.2), 1.6 (1.5-1.8) and emphysema: 1.5 (1.0-2.1), 1.2 (1.1-1.5). Smoking differentially increased risk of respiratory diseases by diabetes status. ORs (CIs) for ever smokers with diabetes were: emphysema 3.9 (2.6-5.8), COPD 2.5 (1.8-3.5), asthma 1.4 (1.1-1.7), chronic bronchitis 1.5 (1.2-1.9). For those without diabetes this was: emphysema 7.5 (5.9-9.5), COPD 4.8 (3.9-6.0), asthma 1.2 (1.1-1.3), chronic bronchitis 1.6 (1.5-1.8). Population attributable risks associated with smoking were 27% and 23%, for those with and without diabetes respectively. CRP increased the risk of respiratory diseases similarly by diabetes status (ORs ranged from 1.1-1.3, $p < 0.0001$ for all). C8 showed no association. Diabetes, more so in T1D, appears to increase respiratory disease risk. Smoking was a weaker risk factor in diabetes, but still accounted for nearly 30% of respiratory disease cases in the diabetic population.

Oral Anti-Diabetic Drugs are not associated with Cardiovascular Mortality: A Systematic Review with Meta-analysis

Objective: There is rising uncertainty regarding the cardiovascular safety of oral hypoglycemic agents (OHAs). Recently, the Food and Drug Administration (FDA) revised regulatory guidelines for anti-diabetic drug approval with respect to the cardiovascular safety within a predefined margin of statistical certainty. The objective of current study was to conduct a systematic review with meta-analysis to assess the association between oral anti-diabetic agents, marketed after FDA regulation, on cardiovascular mortality. Methods: The inclusion criteria were: (1) randomized controlled trials, (2) adult humans with type-2 diabetes mellitus (T2DM) either with or without cardiovascular risk factors, (3) participants taking at least one oral anti-diabetic drug, (4) cardiovascular mortality as an outcome, and (5) published studies in English language up to March 31, 2016. PubMed, Scopus and clinical trial registries were searched based on criteria decided a priori. Odds ratios were calculated for each result and pooled using random-effects models. Non-overlapping 95% confidence intervals (CI) were considered statistically significant. Heterogeneity was estimated using the Q statistic with an alpha value ≤ 0.10 considered statistically significant. Inconsistency was assessed using the I² statistic. Results: A total of 431 studies were initially identified. After eliminating duplicates and examining the studies based on previously decided inclusion criteria, 10 studies were included for analysis. Overall, there was no statistically significant association between OHAs and cardiovascular mortality (OR = 0.89, 95% CI 0.74, 1.06). Conclusion: The results of the current study suggest that OHAs are not associated with cardiovascular mortality. A more inclusive network meta-analysis is needed to further our understanding of this important issue.

Grammer, Robert

17

Medicine, Department of Radiology, Resident

Radioembolization of Hepatocellular Carcinoma: Institutional Experience and Literature Review

PURPOSE. Radioembolization (RE) is a type of intra-arterial locoregional therapy utilizing resin or glass microspheres in the management of primary and secondary hepatic malignancies. Using our instructional experience, the relative clinical efficacy of RE for the treatment of liver metastases is compared and contrasted to that of hepatocellular carcinoma (HCC). In addition, a literature review is presented to illustrate technique, clinical applications, and current research in liver directed radiation therapy. **MATERIALS AND METHODS:** A systematic review of the literature was performed emphasizing the clinical efficacy of RE for patients with HCC relative to metastatic liver disease. In addition, a 15 year institutional experience is presented. The institutional review board approved this retrospective analysis. Comparisons and contrasts are drawn between the existing literature data and our institutional data. **RESULTS:** Radioembolization is an important locoregional intra-arterial procedure utilizing microspheres for the management of hepatocellular carcinoma. Important technical considerations include: microsphere selection, identification and management of variant vascular anatomy, and periprocedural dosimetry. Two types of microspheres used: resin and glass microspheres. SIR-Spheres are a type of resin microsphere currently used at our institution. Radioembolization has been shown to prolong survival for patients with inoperable HCC. In addition, radioembolization is shown to be effective in the treatment of hepatic metastatic disease such as colorectal and neuroendocrine. Regarding the application of radioembolization to hepatic metastatic disease, we discovered heterogeneity in response from patient to patient and disease to disease. **CONCLUSION.** Radioembolization is important for the management of HCC and metastatic liver disease. Due to the heterogeneity in treatment response between patients and disease, more research is necessary to uncover the molecular etiology governing treatment response.

Green, Claire

150

Dentistry, Dental Hygiene, Undergraduate

Participant Comfort Levels with Dental Health Care Provider's Lighting Options

The oral cavity is a dark area that needs lighting to illuminate the working areas for treatment. One thing dental health care providers are not aware of is if patients have a preference for which type of dental lighting is used. The purpose was to compare patient comfort levels while receiving dental hygiene therapy while the clinician uses a LED headlight, an overhead light, or both lights together, and to determine if there was a difference in how the use of the LED headlight affected the patient's perception of the clinician's competence level. A total of twenty participants age eighteen or older were recruited during regularly scheduled dental hygiene appointments. Periodontal probing was conducted on each participant using each lighting scenario. Participants were asked to rate their comfort levels (1= very uncomfortable, 4= very comfortable), before and after performing the periodontal probing, regarding: oral comfort, visual comfort, and personal space comfort. Descriptive statistics were used to report average comfort levels. T-tests were used to compare pre and post exercise comfort levels within each lighting scenario. ANOVA was used to compare changes (pre/post) in comfort levels across lighting scenarios. The results show the average reported change in participant comfort levels. There was no change when using the overhead light only while the headlamp only had an average decrease of 0.136 and the combined use of both lights had an average increase of 0.045 in participant reported oral comfort levels. For visual comfort, the overhead light only, the headlamp only, and the combined use of both lights all had an average decrease of 0.045 in regards to participant reported visual comfort levels. As for personal space comfort, the overhead light only and the headlamp only had an average decrease of 0.182 while the combined use of both lights had an average decrease of 0.091 in participant reported personal space comfort levels. Slight, not statistically significant, differences were reported within comfort levels across each lighting scenario. Participants with a lighting preference prefer the combined use of the overhead light with the headlamp.

Grisez, Brian

8

Medicine, Orthopaedics, Resident

Surgical Approach and BMI Can Influence Effectiveness of TXA Administration in Total Hip Arthroplasty

INTRODUCTION: Total hip arthroplasty is associated with significant blood loss that results in increased transfusions, morbidity, and mortality. Administration of tranexamic acid (TXA) has significantly decreased the blood loss associated with these procedures, but uncertainty regarding the optimal route of administration persists. The purpose of this study was to determine the influence that surgical approach and obesity have on the effectiveness of intravenous (IV) and topical TXA in limiting blood loss.

METHODS: We retrospectively reviewed the charts of patients who received IV or topical tranexamic acid during a total hip arthroplasty at our university based hospital between August 2013 and September 2014. Surgical approach, route of TXA administration, calculated blood loss, and body mass index were recorded. ANOVA was used to compare blood loss and BMI. Student's t-test was calculated to compare route of TXA administration and blood loss within surgical approach groups. **RESULTS:** Inclusion criteria returned 156 patients. Patients undergoing a posterior surgical approach lost significantly less blood when TXA was administered intravenously as opposed to topically (1057.70 ml versus 1642.75 ml) No significant differences were noted in calculated blood loss with regard to IV versus topical administration in lateral and anterior approaches. A significant correlation between BMI and calculated blood loss was observed. A significant correlation between calculated blood loss and BMI in patients receiving IV TXA was noted, but no correlation was observed in patients receiving topical TXA. **DISCUSSION AND CONCLUSION:** This study supports the use of IV TXA over topical in patients undergoing total hip arthroplasty from a posterior approach. Additionally, our findings indicate that blood loss in total hip arthroplasty patients increases linearly with BMI, and that topical administration of TXA is more effective at curbing this increase.

Hagedorn, Rebecca

131

Other, Animal and Nutritional Sciences, Masters

Profile of Food Insecurity Among College Students at West Virginia University and Self-Reported Health Status

According to the United States Department of Agriculture (USDA), in 2013 food insecurity effected roughly 15 percent of the population at some time during the year. Previous studies have shown food insecurity to be present in the college population on the west coast and pacific rim. However, evaluation in a more rural region, such as Appalachia, is limited. The objective of this cross-sectional study was to measure the prevalence of food insecurity in students attending West Virginia University (WVU), in central Appalachia. Food security was classified using the USDA Household Food Security Module which separated individuals into 4 categories (high, marginal, low, and very low food security). A 56 question tool was developed by an Appalachian Multistate Collaborative to investigate food insecurity in college students attending an Appalachian Higher Education Institution. After Institutional Review Board, recruitment included sending emails to 1191 professors at WVU to reach students during Fall 2016 semester starting the first week of October through the end of November. A total of 639 undergraduate (n=505) and graduate (n=134) students responded to the survey with an average age of the individuals at 21 ± 4 years. Respondents were predominately single (94%), Caucasian (89%), females (71%), and of undergraduate status (77%). Of the total population, 35% of students (n=244) reported food insecurity (low or very low food security). Of 91 students reporting fair or poor health, 60% were classified as food insecure. Food insecure students had higher weight (161.1 ± 39.8 lb) compared to food secure students (155.8 ± 35.4 lb) that trended toward statistical significance by two-tailed t-test ($p=0.09$). These results suggest that food insecurity may attribute to poor self-reported health status and increased weight gain. Further investigation is warranted to determine this relationship in young adults attending schools in the Appalachian Region.

Hames, River

163

Other, Biology, Undergraduate

Revisiting cortactin as a driver of collective invasion in 11q13 amplified HNSCC

Head and neck squamous cell carcinoma (HNSCC) is a highly invasive cancer with a five-year overall survival of approximately 50%. HNSCC incidence is increasing in WV and other Appalachian areas due to high tobacco consumption and HPV exposure. Genomic instability is a hallmark of tobacco carcinogen exposure, resulting in amplification of chromosome 11q13 in 25% of all HNSCC cases. 11q13 amplification results in poorer prognosis and increased tumor aggressiveness. The CTTN locus resides in the 11q13 amplicon and encodes the actin-regulatory protein cortactin. Increased cortactin expression resultant from CTTN amplification drives HNSCC invasiveness through enhanced tumor cell migration and invadopodia formation. Invadopodia are tumor cell membrane protrusions responsible for degrading the basement membrane and stromal extracellular matrix (ECM) proteins, facilitating regional tumor dissemination. Prior studies have demonstrated that reduced cortactin expression by RNA interference impairs invadopodia formation and function. However, recent work from our group utilizing 3D in vitro and transgenic knockout mouse models indicates that cortactin removal fails to block HNSCC invasion. The purpose of this study is to unequivocally determine the role of cortactin in HNSCC invadopodia function and tumor invasion using CRISPR-Cas9 knockout technology in HNSCC cell lines. The overall hypothesis is that HNSCC may have compensatory cortactin and/or invadopodia-independent mechanisms capable of driving tumor invasiveness. In support of this, incomplete ablation of cortactin expression by short hairpin (sh)RNA interference does not fully inhibit the invadopodia-mediated degradative capacity of several HNSCC cell lines. We have produced multiple cortactin knock-out (k/o) HNSCC clonal cell lines using CRISPR-Cas9 that completely lack cortactin expression. These lines will be evaluated for invadopodia formation and function and in vitro 3D models designed to physiologically mimic the HNSCC microenvironment. Clearly defining the role of cortactin in HNSCC invasion is critical to understanding the consequences of 11q13 amplification in this disease, ultimately allowing for rational clinical intervention and target design in this patient subset with the worst clinical outcome.

The role of descending corticospinal input in the formation of motor commands

Neural control of movement requires the integration of both intrinsic and extrinsic system dynamics into the formation of functional motor commands. These commands must recruit synergistic muscle groups in an appropriate spatial and temporal pattern to achieve a desired movement. Numerous studies have attempted to explore the relationship between neural activity, particularly in the motor cortices, and kinematic output. However, there is still a significant knowledge gap as to how the nervous system forms these commands and what specific information may shape them. We hypothesize that descending motor commands are temporally modulated to compensate for limb dynamics to achieve a desired task. We recruited 9 healthy human participants to complete three reaching tasks with distinct dynamic properties. Participants' movements were guided by visual targets presented in a virtual environment. At varying time points throughout each movement, we noninvasively stimulated the primary motor cortex using single-pulse transcranial magnetic stimulation and recorded the corresponding motor evoked potentials using electromyographic recordings of twelve muscles spanning the shoulder, elbow, and wrist. Subject kinematics were also recorded using motion capture and joint torques due to gravity, muscle contraction, and net/interaction forces were calculated using an inverse dynamics model of the arm. Temporal profiles of corticospinal excitability modulation were interpolated using integrated values of motor evoked responses due to stimulation for each movement. These profiles were then compared to system dynamics with a novel hierarchical clustering analysis. We found that distinct dynamic movements lead to differential clustering of muscle responses, suggesting that corticospinal excitability is modulated differentially for different movement types. Additionally, MEPs accounted for a larger percentage of variance in muscle activity than Ia afferent sensory input did. This finding suggests that voluntary reaching tasks may rely more on descending corticospinal input than spinal reflexes. These findings support the potential of cortical stimulation to shape dysfunctional motor commands to alleviate motor deficits.

Harris, Alexa

147

Public Health, Social and Behavioral Sciences, Undergraduate

Current Treatment Recommendations for Low Back Pain at Primary Care Clinic in West Virginia

Background: Back injuries are among the most common and expensive work-related injuries. The Keele STarT Back Tool (SBST) was designed as a way for practitioners in primary care settings to recommend more efficacious treatments based on low back pain prognosis and risk. As part of a larger study with the overall goal to identify effective ways to manage and treat low back pain in West Virginia by comparing current treatment recommendations for low back pain to SBST treatment recommendations, the current project aimed to determine the characteristics of patients diagnosed with low back pain and identify the relationships between patient variables and treatments recommended at a primary care clinic in West Virginia. Methods: All components of this study were approved by the WVU Institutional Review Board (protocol #1609280294). International Classification of Diseases Ninth and Tenth Revisions (ICD-9-CM and ICD-10) codes for the initial diagnosis of low back pain, 724.2 and M54.5 respectively, were used. The following de-identified demographic data were collected from electronic medical records for 260 patients receiving a low back pain diagnosis between July 1, 2015 and June 30, 2016: age, sex, ethnicity, race, employment status, smoking status, weight, and height. Regression analyses are being conducted to determine the relationship between these demographic variables, diagnosis of low back pain, and treatment types. Results: Patients were 18-89 years of age; 38% male and 62% female; 97% Non-Hispanic; 92% White; 57% employed, 23% unemployed, 20% unknown employment status; 32% current smokers, 32% past smokers, 34% never smokers, 2% exposed to secondhand smoke; 4'9" to 6'3" in height. Incomplete data were provided for weight and employment status and were not included in the current analyses. Treatments fell into pharmacologic and non-pharmacologic types, referrals, or additional diagnostic tests. Regression analyses will be completed by time of presentation. Conclusions: Further steps in the larger study include collecting data from additional clinics, conducting cluster analyses to compare treatment recommendations to SBST treatments, and providing data back to primary care clinics as a population health approach to managing low back pain.

Hathaway, Quincy

27

Medicine, Human Performance, Basic Science

PNPase mitochondrial microRNA import

Cardiovascular disease is the primary cause of mortality for individuals with type 2 diabetes mellitus. During the diabetic condition, cardiovascular dysfunction can be partially attributed to molecular changes in the tissue, specifically in microRNA (miR) interactions. MiRs have been reported in the mitochondrion and their import can alter cellular bioenergetics, leading to decrements in functional capacity. In this study, we examined the roles of Argonaute 2 (Ago2), a protein associated with cytosolic and mitochondrial miRs, and Polynucleotide Phosphorylase (PNPase), a protein found in the inner membrane space of the mitochondrion, to understand their participation in mitochondrial miR import. In human and mouse models of type 2 diabetes mellitus, Ago2 and PNPase protein expression levels were evaluated. PNPase expression was increased in models of type 2 diabetes mellitus despite no change in Ago2 levels. There was an increased association between both proteins following diabetic insult. Mitochondrial expression of miR-378 and ATP6, as well as ATP synthase activity were measured in both animal and cell culture models. MiR-378 was found to be significantly increased in db/db mice, leading to decrements in ATP6 levels and ATP synthase activity, which was also exhibited when overexpressing PNPase in HL-1 and HL-1-378 cardiomyocytes. Flow Cytometry allowed for measuring the selectivity of PNPase during miR import through fluorescein-labeled LNA, revealing that PNPase may require sequence recognition for mitochondrial miR import. In conclusion, this study establishes PNPase as a contributor to mitochondrial miR import through the transport of miR-378, which may regulate bioenergetics during type 2 diabetes mellitus.

Hayes, Karen

172

Medicine, WVU Cancer Institute, Postdoc

The Discovery of Novel Non-Coding Circular RNAs Generated by High-Risk Human Papillomavirus Type 16

Recently, several studies discovered thousands of conserved non-coding human circular RNAs (circRNAs), however, there are no studies suggesting the existence of circRNAs produced by human viruses. This study explores our hypothesis that human papillomavirus (HPV)-16 creates viral circRNAs that alter host activity to promote viral replication and induction of carcinogenesis. CircRNAs are non-coding RNAs generated by the alternative splicing of a 5' acceptor and 2' or 3' donor sites, creating a "head" to "tail" covalent junction of exonic and/or intronic regions. Although the role of circRNAs is largely unknown, studies have demonstrated several functions for circRNAs including sequestering microRNAs and regulation of transcription. Recently, circRNAs have been associated with colorectal, breast, and gastric cancers. Infections with high-risk HPVs, types 16 and 18, are responsible for the majority of cervical cancers and a subset of head and neck squamous cell carcinomas. HPV is a small double-stranded circular DNA encoding six early proteins (E-1, -2, -4, -5, -6, and -7) and two late proteins (L-1, -2). HPV mRNA undergoes complex splicing to achieve the expression of these proteins. Our results suggest that HPV-16 extensive splicing generates at least two viral circRNAs (hvp-circRNAs) that may potentially regulate host cellular processes promoting tumorigenesis. We demonstrated the existence of the "head" to "tail" junctions of hvp-circRNAs in HPV-16 viral RNA with RT-PCR amplification using divergent primers in RNA extracted from cervical tumor cell lines. Quantitative RT-PCR analysis showed the retention of the hvp-circRNAs in RNase R (targets linear not circular RNA) treated samples. Moreover, these viral circRNAs persisted even after cells were treated with Actinomycin D (to inhibit RNA synthesis), confirming the stability of these hvp-circRNAs in comparison to the short-lived lariat structures that naturally occur during splicing. siRNA-mediated knockdown or over-expression of exogenous hvp-circRNA- K alter proliferation of the HPV+ cervical cancer cells. Together, our data suggest the existence of viral circRNAs that may promote tumorigenesis by increasing cell proliferation. This project will be significant because it may provide novel mechanisms by which high-risk HPV infection contributes to carcinogenesis.

Henkel, David

9

Medicine, Emergency Medicine, Resident

Reliability of Last Seen Normal Times by EMS in Patients with Symptoms of Stroke

Background: In patients presenting with stroke-like symptoms, the time the patient was last seen normal without symptoms is an important time in determining eligibility for treatment with tissue plasminogen activator (tPA) and endovascular clot retrieval (thrombectomy). For a patient to be eligible for tPA, they must present to the Emergency Department (ED) within 3-4.5 hours of their last seen normal time and within 6 hours for thrombectomy to be considered. Given that the majority of patients with stroke-like symptoms present to the emergency department by EMS, it is essential for EMS to obtain an accurate last seen normal time from the patient or family members who were present when the patient was last normal so that physicians can make informed and safe treatment decisions. This study seeks to evaluate the accuracy of the reported EMS last seen normal time by comparing the EMS time with the final time utilized in clinical decision making as determined by discussions with the patient and family after ED arrival. **Methods:** A retrospective chart review was performed of all stroke pages presenting to Ruby Memorial's ED between October 2016-present. Data was collected on an EPIC note template utilized by ED providers. The reported times were reviewed and compared to evaluate the frequency of discrepancy between the last seen normal times. **Results:** Data was collected from 354 stroke pages between October 2016 and January 2017. 184 patients met inclusion criteria of patient seen in the ED, brought by EMS, with recorded times of last seen normal by EMS and ED physicians. Discrepancies were found in 20.0% of cases with a mean difference of 34 minutes. Subgroup analysis of 94 patients who presented directly to Ruby Memorial's ED showed agreement of the last seen normal times in 76.3% of patients with a mean difference of 48 minutes. **Discussion:** Given the critical nature of an accurate last seen normal times to evaluate eligibility for treatment with tPA or thrombectomy, a 20% discrepancy in reported last seen normal times and a 34 minute difference represents a potentially clinical significant area for further intervention in the form of EMS outreach and education.

Hickling, Skye

56

Medicine, Biochemistry, Basic Science

JNK signaling controls the guided migration of cortical interneurons through nucleokinesis and leading process dynamics

Aberrant migration of inhibitory interneurons can alter the formation and function of cortical circuitry leading to severe neurological and psychiatric disorders including epilepsy, autism and schizophrenia. During embryonic development, cortical interneurons travel tangentially in two migratory streams to reach the cerebral cortex and then turn radially to exit migratory streams and invade the cortical plate. The molecular mechanisms governing the timing of migratory stream exit and cortical plate invasion are poorly understood, yet are of fundamental importance to cortical development. Our lab previously found that disruption of the c-Jun N-terminal kinase (JNK) signaling pathway results in premature departure of cortical interneurons from migratory streams. We are interested in uncovering the mechanisms by which JNK activity coordinates the intracellular processes essential for the guided migration of cortical interneurons. Two of the main biological processes that are essential for migrating interneurons to travel and sense extracellular cues are nucleokinesis and leading process branching. Migrating cortical interneurons must remain in constant contact with both extracellular signals and intracellular machinery to mediate these processes. During migration, the cell bodies of cortical interneurons translocate into a cytoplasmic swelling formed in the leading process, known as nucleokinesis. The leading process is a highly dynamic structure of the interneuron that extends and branches in order to sense extracellular guidance cues through the course of migration. We have developed an MGE explant culture assay to examine how loss of JNK function impairs nucleokinesis and branching in migratory cortical interneurons. Our results will give insight into the future aims of this project, which will assist in the understanding of cortical development and ultimately aid in developing treatments for neurodevelopmental disorders.

Himebaugh, Jesse

18

Medicine, Ophthalmology, Resident

Bad Hooch: A Case of Ocular Methanol Toxicity

The production of home-made liquor has a decades-long history in the state of West Virginia and is still practiced in many areas. "Moonshining" as it is called, must be performed carefully as any careful practitioner will say. Done incorrectly, the alcoholic fermentation can yield methanol, a metabolically toxic substrate. Methanol produces severe metabolic distress in individuals who consume it with a high anion gap metabolic acidosis. The metabolic products of methanol can also interfere with normal mitochondrial activity which can lead to acute toxicity in ocular structures including retinopathy and optic neuropathy. We discuss a case of a patient who presented to the hospital in metabolic acidosis and "No light perception" vision most consistent with methanol-induced toxic optic neuropathy and discuss this entity's background, diagnosis, prognosis and management.

Holcomb, Paul

79

Medicine, Blanchette Rockefeller Neurosciences Institute, Basic Science

A Novel Cell Polarity Program During Innervation of a Non-Laminar Nucleus in the Auditory Brainstem

Laminar sensory structures--rod and cone cells of the retina and the hair cells of the cochlea--restrict potential sites of innervation through both polarized expression of synaptic proteins and structural segregation of cells into apical and basal regions. Many cells in the central nervous system, however, lack the lateral cell-cell connectivity necessary to make such a polarized distinction. Is cellular polarity still evident in these systems, and if so, does it influence terminal placement irrespective of the lack of structural limitations evident in laminar systems? We utilized the calyx of Held (CH) – principal cell connection in the medial nucleus of the trapezoid body (MNTB) of the mouse, one such non-laminar system, to explore these questions. By applying serial block-face scanning electron microscopy (SBEM), three-dimensional reconstruction of neurons and terminals, and morphological measurement techniques, we showed polarity in the principal cells of the MNTB at early postnatal (P2-P9) ages; specifically, the nuclei of these cells are asymmetrically located, defining a nucleus-poor “cytoplasmic” pole and a nucleus-filled “nuclear” pole and establishing what we refer to as “intrasomatic polarity”. The asymmetric location of the nucleus increases significantly during development due to principal cell growth away from the position of the nucleus. Terminal placement was assayed using the apposed surface area (ASA) between vesicle-filled contacts and the principal cell membrane as a measure of terminal size. As development proceeds, we found that the CH:MNTB connection not only becomes larger but also more polarized, with greater than 80% of the ASA of the largest terminals at P6 occupying the cytoplasmic pole surface opposite the nucleus. Competing inputs (2-3 inputs/cell with less than 1:5 ratio in size) fell into three categories: (1) the largest terminal is most polarized, (2) the second largest terminal is most polarized, or (3) the two largest terminals are equally polarized. This implies either a “flip-flop” of largest for second largest terminal or polarized growth towards the cytoplasmic pole or both. These findings suggest that the non-laminar MNTB still exhibits polarity on the cellular level that influences the placement and growth potential of terminals in the formation of the CH:MNTB circuit.

Holliday, Tyler

122

Medicine, Emergency Medicine, Clinical Sciences/Epidemiology

Testicular Rupture: A Tough Nut to Crack Made Easier with PoCUS

Background: Injuries involving the scrotum and testicles are common in the emergency department. History and physical examination are inadequate to differentiate between surgical and non-surgical testicular emergencies. Early and accurate diagnosis is critical to preserve the structure and function of the testes, and timely ultrasound is essential for rapid, definitive diagnosis. Objective: To report a case of testicular fracture diagnosed by an emergency physician using Point-of-Care-Ultrasound. Case Report: An 18-year-old male presented to the emergency department with left testicular pain and swelling following an injury where he was accidentally struck in the groin by his opponent during a lacrosse match. Physical exam revealed a tense and swollen left testicle when compared to the right. Due to the nature of his presentation, ultrasonography was immediately performed by the emergency physician, leading to a rapid diagnosis of testicular rupture. For the ultrasound examination, a high-resolution linear transducer (6-15MHz) with Color Doppler was employed. Sonographic findings included heterogeneous echogenic parenchyma in the lower pole, discontinuity of the tunica albuginea, and complex hypoechoic fluid collection within the left hemiscrotum with preserved testicular blood flow including the fractured segment by Color Doppler. Urology was consulted. After their evaluation, the patient was promptly taken to the operating room for scrotal exploration, partial orchiectomy, and debridement of the left testis. Discussion: A previous study has shown that emergency physicians can accurately diagnose acute testicular pathologies by utilizing bedside ultrasound. As demonstrated by this case, use of routine bedside ultrasonography for injuries involving the scrotum and testicles by emergency physicians may help expedite diagnosis and can be used to stratify patients on the need for emergent urologic consultation and surgical intervention to improve patient outcomes.

Holmes, J. Scott

108

Medicine, Neurobiology and Anatomy, Basic Science

A novel classification system for vallate papillae of the tongue based upon morphology and anatomical features.

The vallate papillae, commonly referred to as circumvallate papillae, are lingual papillae located at the posterior dorsum of the tongue, which form a V-shaped row immediately anterior to the sulcus terminalis. As the name suggests, vallate papillae are normally surrounded by a vallum, a small mound of tissues, which creates a sulcus (or trench) around the papilla. The inner surface of the vallum houses approximately half of the taste buds located within the tongue. Therefore, vallate papillae are important anatomical structures in gustation; however, little data exists regarding the gross morphology of the vallate papillae. In this study, 103 human cadaveric tongues were dissected at West Virginia University, with approval of the West Virginia Anatomical Board, to identify and photograph individual vallate papillae. A total of 1,069 individual vallate papillae were identified and characterized into thirteen separate categories, based upon their morphology and associated anatomical features. Categorization was largely based upon the presence of a vallum (691 of 1069; 64.6%), and whether the vallum fully encompassed the papilla or partly encompassed the papilla. Other categorization included whether the papilla itself was fully formed or segmented. The results of this study demonstrate a wide variety of morphological categories of vallate papillae. Because vallate papillae are important in gustation, the anatomical differences may partly explain physiological differences in taste function.

Hone, Emily

164

Medicine, Neurobiology and Anatomy, Undergraduate

Mouse microRNA-34a and -146a levels in brain and serum: potential biomarkers for Alzheimer's disease

MicroRNAs (miRs) are important determinants of human health and disease and function by inhibiting translation of target proteins. Both miR-34a and -146a are important in inflammation and aging. Our recently published studies have shown that miR-34a and -146a are increased in the hippocampus of AD patients, but not in cerebellum; however, the impacts of age, sex, and disease progression on miR expression levels have not been studied. The goal of the current study was to determine the effects of these variables on miR-34a and -146a gene expression in brain regions and to determine if brain miR levels correlate with serum miR levels. We hypothesized that miR-34a and -146a levels are upregulated in AD and their levels in the brain would correlate strongly with serum levels. Brain tissues from four regions (hippocampus, temporal cortex, cerebellum, and frontal cortex) and serum samples were collected from different age groups (3-24 months) for both sexes of wildtype (WT) and AD mouse models. miR-34a and -146a levels were measured by quantitative real time PCR. Results show that miR-34a levels in males were significantly dependent on AD disease severity in hippocampus and frontal cortex; in contrast, age but not AD severity significantly altered miR-34a expression in females. Similar associations were identified for miR-146a levels in these brain regions. Ongoing studies will address whether the correlation between brain and serum miRNA levels can serve as a biomarker of disease severity. Collectively, these results demonstrate that brain miR levels are differentially regulated by age, sex, and AD severity.

Hoskinson, Hannah

136

Medicine, Exercise Physiology, Masters

Chronic E-Cigarette Usage on Blood Glucose

Introduction: Traditional cigarette usage has been linked to a number of nefarious metabolic effects, including insulin resistance, however the effects of electronic cigarettes (E-cigs) are not currently known. Advertised as a safe alternative for traditional tobacco cigarettes, long-term studies investigating the metabolic effects of E-cigs are lacking. The purpose of this study was to gain a better understanding of the possible metabolic consequences of E-cig usage. We hypothesize E-cig usage will induce insulin resistance in mice. Methods: C57BL/6 mice were divided between E-cig (n=13) and control (n=13) groups and exposed to either vaporized cappuccino flavored E-cig liquid (18 mg/mL nicotine) or filtered air for 4h/d, 5 d/wk for 6 months. Fasting blood glucose (FBG) and glucose tolerance (GTT) were assessed following an overnight fast. A glucose bolus was administered via gelatin pellet (3g glucose/kg) which was ingested within 2 min. Blood was collected by tail nick and glucose measured using Bayer Contour glucometer and test strips. Results: After 6 months exposure, total body mass ($28.1 \pm 3.2\text{g}$ vs $27.3 \pm 3.1\text{g}$) and lean body mass ($18.71 \pm 0.25\text{g}$ vs $18.38 \pm 0.27\text{g}$) were similar between E-cig and air exposed groups, respectively. Preliminary results suggest E-cig exposure did result in significant difference in FBG ($143.8 \pm 6.2\text{mg/dL}$ vs $118.8 \pm 8.6\text{mg/dL}$, $p=0.05$), GTT Area under curve (18229 vs 15069 , $p=0.02$) and peak glucose response ($225 \pm 6\text{mg/dL}$ vs $180 \pm 15\text{mg/dL}$, $p=0.03$). Conclusion: These preliminary results suggest there may be some initial differences in glucose response in animals exposed to E-cigs when compared to controls. Future studies are needed to determine if greater levels of nicotine exposure via E-cigs contribute to total impairment of glucose metabolism.

Hu, Heng

173

Medicine, Physiology & Pharmacology, Basic Science

MiR-34a Opens Blood-brain Barrier and Exacerbates Stroke

Background and Objective Stroke is the second leading cause of death and the leading cause of disability worldwide. The blood-brain barrier (BBB), a highly specialized vascular interface that maintains homeostasis in brain, is disrupted in acute ischemic stroke, and blood solutes penetrate into the central nervous system CNS parenchymal extracellular space then cause cerebral edema. We have recently demonstrated that mitochondria play a critical role in maintaining BBB integrity. Bioinformatics analysis suggests miR-34a targets several mitochondria-associated genes. The aim of the study is to investigate whether miR-34a plays a role in BBB openings and stroke outcomes. **Methods** Cerebrovascular endothelial cells (CECs) culture; mitochondrial function evaluation; ATP evaluation; flow cytometry; real-time PCR; transient middle cerebral artery occlusion (tMCAO) stroke model in mice. **Results** In vitro, miR-34a triggered the breakdown of BBB in the monolayer of CECs paralleled by reduction of mitochondrial oxidative phosphorylation and ATP production, and decreased cytochrome c levels. In vivo, using tMCAO stroke model, we demonstrated that miR-34a was upregulated in the brain and serum of post-stroke mice. Furthermore, we demonstrated that knockout of miR-34a reduced stroke infarction compared to wild type control mice following 60 minutes tMCAO and 24 hours reperfusion. **Discussion and Conclusions** We have found that a novel mechanism underlying BBB integrity: miR-34a mediates regulation of BBB through a mitochondrial mechanism. The data suggest that miR-34a opens BBB and worsens acute ischemic stroke outcomes. Therefore, targeting of miR-34a might have application as a novel therapy for this devastating neurologic condition. This work was supported by AHA (16SDG31170008) and NIH (P20 GM109098, P01 AG027956 and U54 GM104942).

Hughes, Krystal

160

Other, Orthopaedics, Undergraduate

Identifying the Antimicrobial Efficacy of Silver Nanoparticles in the Treatment of Extracellular *Staphylococcus aureus*

With antibiotic resistances increasing at an alarming rate, it is imperative that alternative treatments are discovered to treat microbial infections. *Staphylococcus aureus* (*S. aureus*), a contagious bacterium, is the most common nosocomial infection. Epidemiologically, 45% of the population are carriers. Silver (Ag), a broad-spectrum antimicrobial, has been known for centuries for its antimicrobial properties and has shown to be an effective treatment for both Gram negative and Gram positive bacteria. However, the toxicity of Ag has limited its clinical applications. Recently, there is a renewed interest in Ag due to the shortage of antimicrobials for antibiotic resistant bacteria and the potential to improve antimicrobial properties via nanotechnology. This study was aimed to identify the efficacy of Ag nanoparticles in treating extracellular *S. aureus* at different concentrations, varying sizes of nanosilver, different incubation times, and with addition of combined treatments with various commonly prescribed antibiotics. The antibiotics used were Vancomycin and Gentamicin, they were chosen due to their varying mechanisms of actions. Vancomycin inhibits cell wall synthesis while Gentamicin inhibits protein synthesis thus preventing the tRNA from binding to the 30S ribosome. We found that the bacterial killing percentage increased with increasing concentration of Ag nanoparticles (40 nm), and 100% killing was achieved at concentrations as low as 6 µg/ml. In comparison, much higher concentrations of Ag nitrate, Vancomycin and Gentamicin were needed to achieve 100% killing. Meanwhile, the size of the nanoparticles influenced the antimicrobial outcomes. Ag nanoparticles of 40 nm were much more effective in killing *S. aureus* compared to Ag nanoparticles of 100 nm. The kinetics studies showed that Ag nanoparticles, Vancomycin and Gentamicin had very different kinetics profiles. Moreover, Ag nanoparticles in combination with conventional antibiotics had greater efficacies of killing than when the treatments were administered independently. For the combination of Ag nanoparticles with Gentamicin, a synergistic effect was seen the greatest; Ag nanoparticles (40 nm, 4 µg/ml) in combination with Gentamicin (50 nM) yielded a 100% killing efficacy while the independent treatments yielded 30.1% and 32.8% killing efficacies, respectively.

Iaquinta, Monica

128

Nursing, School of Nursing, Basic Science

The Lived Experience of Establishing a Home after a Period of Homelessness

The purpose of this hermeneutic phenomenological study was to uncover the structure of meaning of the lived experience of establishing a home after a period of homelessness. Fourteen semi-structured interviews were conducted using a unique line of inquiry based upon story theory and phenomenology. Questions were posed beginning with the present daily life in a home, followed by the past experience of homelessness, and ending with establishing a home in the future. Stories were reconstructed, using the participant's own words, and confirmed during a second interview. The strategies for data analysis were rooted in the theoretical framework including identifying essential statements, raising statements to abstract core qualities, and explicating themes from the core qualities. A rich, description was composed including participants' anecdotes. Seven themes were identified including: 1) spinning on a downward spiral from having a home to being homeless, 2) mustering resourcefulness to move from the street to a home, 3) creating a home that is secure and personal, 4) grappling with responsibility to hold on to home, 5) building relationships that are both affirming and limiting, 6) recognizing gratitude for life in the present that is peaceful, joyful, and fulfilling, and 7) yearning for a future life of promise. The findings of this study may add to the body of nursing knowledge, reduce the gap in the literature, and influence local policy development.

Iglesias, Mannhu

118

Dentistry, Dentistry, Basic Science

Depression Among Dental Students and How It Affects Their Quality of Life.

Background: Student wellness is critical in developing healthy practitioners. It is important that students handle the stress associated with professional academics in a manner in which their own health is not compromised. The purpose of this study is to examine wellness among dental school students and how it affects their quality of life. Methods: One hundred seventy-three dental students (50 first year, 45 second year, 50 third and 28 fourth year) responded to the following surveys: Center for Epidemiologic Studies Depression (CES-D 10), Pittsburg Sleep Quality Index (PSQI) and Quality of Life Scale (QOLS). CES-D 10 is a 10-item self-report for depression. PSQI is a self-report questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, creating 7 components that produce one global score. QOLS is a 16-item psychological assessment instrument of the self-perceived quality of life. Results: The means of the three tests were: 14.12 (CESD-10), 6.83 (PSQI), and 71.03 (QOLS). A Chi-square test was used to compare dichotomized CES-10 scores among first/second-year dental students and third/fourth-year dental students. The difference failed to reach significant among first/second-year and third/fourth-year dental students ($p > 0.05$). Conclusion: Student wellness, as described by the CES-D 10, PSQI, and QOLS remains a concern in dental school education.

Jenkins, Emily

137

Public Health, Epidemiology, Masters

Protective psychosocial factors and chronicity of depressive symptoms in police officers

Objectives: National Health and Nutrition Examination Survey data estimate 7.6% of Americans aged 12 and over experienced depression during 2009-2012. The estimated cost of depression in the U.S was \$210.5 billion in 2010, including workplace, direct, and suicide-related costs. Policing is a high-stress occupation with an estimated 806,400 police officers in the U.S. in 2014 (U.S. Department of Labor Statistics). Police work involves exposure to psychologically challenging and dangerous events that may increase the risk of stress-related health problems including depression. Protective psychosocial factors may reduce the impact of stressful exposures and the risk of psychological symptoms. Our objective was to assess the association between baseline protective factors and change in depressive symptoms among police officers. Methods: Participants were from the Buffalo Cardio-Metabolic Police Stress (BCOPS) Study, (2004-2014). Protective factors included coping, hardiness, personality traits, and social support and were measured at baseline using validated instruments (i.e., the Brief COPE, Hardiness Scale, NEO Five Factor Inventory, and Social Provisions Scale). Resulting scores were grouped into tertiles. Depressive symptoms were measured at baseline and follow-up using the Center for Epidemiologic Studies-Depression (CES-D) scale where a score ≥ 16 identified risk for clinical depression. The mean CES-D change scores were compared across tertiles of protective factors using analysis of variance. Logistic regression models assessed associations between tertiles of protective factors and incidence of depression. Models were adjusted for age, sex, education, and marital status. Results: Among 214 police officers (73% male), there were no significant associations between the protective factors and mean CES-D change scores over the follow-up (mean [SD]: 6.92 ± 0.97 years). However, 23 participants (10.8%) developed depression. The odds of depression were 9.51 (95% CI:2.34-38.63) times higher for those with the highest levels of neuroticism, 3.64 (95% CI:1.05-12.59) times higher for those with the lowest levels of extraversion, and 4.43 (95% CI:1.20-16.39) times higher for those with the lowest levels of agreeableness. No significant associations were identified with coping, hardiness, or social support. Conclusion: Personality characteristics may be associated with the incidence of depression in police officers. Future studies with larger sample sizes and additional protective factors are warranted.

Johnson, Morgan

114

Medicine, WVU School of Medicine/ Jon Michael Moore Trauma Center, Clinical Sciences/Epidemiology

Description of Blunt Aortic Injuries Managed in a Rural Trauma Center Morgan Johnson MS3, Nicole Cornell MS CCRC, Khumara Huseynova MD, William Krantz MD, Chris Bailey DO, Uzer Khan MD, Alison Wilson MD

Blunt aortic injuries (BAI) are the second leading cause of death in trauma patients. Several studies estimate that only 20% of patients sustaining blunt aortic injuries survive long enough to reach a trauma center to receive treatment for their injuries. The management of aortic injuries involves an open repair, endograft repair, or non-operative surveillance. For endovascular repair, little is currently known on long-term outcomes and patient compliance with follow up. There is no standard follow-up schedule for patients. This was a retrospective Trauma Registry and chart review study analyzing adult trauma patients with aortic injuries treated at a rural Level 1 trauma center from 2008-2014; patients that had an emergency thoracotomy, followed up outside of WVU, or died before discharge were excluded from the study. We defined our rural center's experiences with traumatic aortic injuries including age, gender, grade of aortic injury (severity), injury severity score (ISS), management approach, distance that patients traveled for follow-up, complications, and rates of compliance with follow up. Our study included 22 patients who had either endograft repair (14) or non-operative surveillance (8). Of patient receiving endograft repair, the complication rates before and after discharge were 14% each. Overall follow-up rate of compliant patients for the study was 77%, and 91% of patients had at least one follow-up appointment within a year of hospital discharge. Out of patients that attended appointments, 25% of patients did not get a CTA despite one being scheduled. Data reveals that patients with higher ISS ($p < 0.001$), higher grade of aortic injury ($p = 0.04$), and those treated with operative repair ($p = 0.03$) were found to have better follow up 6 months to a year after injury. This could be due to more severe injuries being followed more frequently and for a longer period of time by the physician, but also due to higher patient education. Despite a distance and time burden, rural patients attended appointments; however, non-compliance with imaging was noted. A limitation to our study is small sample size; however, this is a common theme with studies analyzing BAI due to the nature of the injury.

Jones, Garrett

45

Medicine, WVU SOM / Neuroscience, Basic Science

Role of Wnt Signaling in Auditory Brainstem Development

Neural circuit formation and maintenance has major implications in neurological disorders including Autism Spectrum Disorder and Alzheimer's disease. It involves the execution of precise genetic programs coordinated amongst an array of cell types within central nervous system tissue. The calyx of Held (CH) is a large excitatory terminal that projects onto principal neurons in the medial nucleus of the trapezoid body (MNTB). Given its short developmental time frame and relatively homogenous population of postsynaptic neurons, the MNTB is an ideal model system to study neural circuit formation. A developmental microarray study of the MNTB tissue demonstrated significantly changing expression of Wnt mRNA levels over the first postnatal week in mice. Wnt ligands have been implicated in giant synaptic terminal development and signal transduction occurs via Frizzled (Fzd) receptors. Immunofluorescent colocalization studies of Fzd3 and Fzd5 were performed at timepoints across the first postnatal week. The CH contained Fzd3 and Fzd5. The principal neuron and all oligodendrocyte developmental stages expressed Fzd3. It is hypothesized that Wnt signaling plays major roles in MNTB development. Wnt signaling will be studied in the MNTB by inhibiting the Wnt pathway using several pharmacological and genetic approaches. This may have implications in expanding treatment options for disorders of the neural circuit.

Julian, Katie

155

Dentistry, Dental Hygiene, Undergraduate

Perceptions of Head/Neck Piercings on a Dental Professional

Head and neck piercings are increasingly becoming more popular in younger people, making them more socially acceptable. A study is conducted to see how participants view head and neck piercings on dental professionals based off of the location of the piercing and the gender of the professional. The purpose of this study is to determine how head and neck piercings on dental professionals are perceived by the patients, students, and faculty of the West Virginia University School of Dentistry. A survey was administered to the patients, students, and faculty of the West Virginia University School of Dentistry. A paper survey was given to all of the patients, and an electronic survey was given to all of the faculty and students. The survey was 47 questions long and included demographics, locations of different piercings, and the gender of the professional. Each question specifically asked about the ear lobe, eye brow, lip, nose, tongue, and tragus. The Fisher exact test was used for this study to find the statistical data. For the results, there was a statistically significant difference between the gender of the professional and the amount of piercings in a location ($p < 0.001$). A male dental professional was perceived as less professional than a female professional for every piercing presented. Multiple piercings in a single location was also viewed as less professional than a single piercing in a single location. Age was not a factor when determining professionalism in this study. In conclusion, dental professionals whom have a single piercing or are female are viewed as being more professional than those possessing multiple piercings or who are males. The age of the observer does not influence perceptions of professionalism associated with head and neck piercings.

Kang, Jason

140

Medicine, Department of Orthopaedics, Masters

Nanosilver: New Approach towards the Treatment of Extra- and Intracellular Infections

Staphylococcus aureus (*S. aureus*) is the leading cause of bone and joint infection worldwide, with clinical manifestations of osteomyelitis, septic arthritis, and prosthetic joint infection. Currently, antibiotics (along with surgery) are the mainstays of treatment for bone and joint infection. However, the overuse of antibiotics has led to the emergence of antibiotic-resistant strains of bacteria, such as methicillin resistant *S. aureus* (MRSA). Moreover, *S. aureus* has shown the ability to survive intracellularly, further complicating treatment options. Therefore, there is a need for new antimicrobial agents which can combat antimicrobial resistance and treat intracellular bacteria. Due to its unique mode of action, silver has emerged as a treatment option against antibiotic-resistant bacteria, and nanosilver, due to its nano-size associated properties, has recently attracted significant attentions. To our knowledge, there have been no reports regarding the eradication of intracellular infection using nanosilver. The purpose of this study was to elucidate the efficacy of nanosilver as a novel treatment option against extra and intracellular *S. aureus* infection by assessing its concentration, kinetics, and toxicity effects. In addition, potential synergistic effects of conventional antibiotics and nanosilver were examined. Our results show that nanosilver is effective against extracellular *S. aureus* at low concentrations (e.g. 6 µg/mL) with 100% killing efficacy. In addition, synergistic effects were observed with the combination of nanosilver and gentamicin. The treatment of intracellular *S. aureus* with nanosilver plateaued at a killing efficacy of 80% at concentrations as low as 40 µg/mL. The kinetics study revealed that this was achieved within 2 h of nanosilver treatment. The viability assay demonstrated that low concentrations of nanosilver (10 µg/mL-40 µg/mL) were not toxic to human osteoblast cells with a viability above 90%.

Topical Adjuvants Decrease Staphylococcus aureus Biofilm on Orthopaedic Metals: But is it Enough?

Introduction: Failure rates for the treatment of prosthetic joint infection are likely due to biofilm or intracellular bacteria that remain after initial debridement attempts. Adjuvant treatments including washes with betadine, Dakin's solution or hydrogen peroxide have been attempted in an effort to further eradication. The purpose of this study was to evaluate the in vitro abilities of chemical adjuvants to decrease the Staphylococcus aureus biofilm presence on orthopaedic implant materials.

Methods: S. aureus biofilms from a clinical isolate were created on orthopaedic implant grade titanium, stainless steel and cobalt chrome discs. Biofilms were grown for 48 hours at which time discs were evaluated as controls for baseline colony forming units/centimeter squared (CFU/cm²) and compared to treatments with either full strength betadine, sodium hypochlorite (Dakin's solution), hydrogen peroxide, or chlorine dioxide. **Results:** Control discs (n=18) across all metal types had an average of 4.2×10^7 CFU/cm². At both time points, all treatments had a statistically significant reduction in CFU/cm² when compared to each metal's respective control discs ($p < 0.05$). For all metals combined, at each time point, the most efficacious treatments were 10% Betadine and H₂O₂, with an average 98% and 97% reduction in CFU/cm² respectively. There were no significant differences between the reductions seen with 10% Betadine and H₂O₂, but both groups had statistically greater reductions than both Dakin's solution and ClO₂. There was no change in antibiotic resistance patterns after treatment.

Discussion: The use of adjuvant treatment at the time of surgical irrigation and debridement varies among surgeons. Our in vitro analysis of S. aureus biofilms demonstrates a statistically significant reduction in biofilm after a five minute treatment with the modalities. However, the overall concentration of bacteria never decreased below 10^5 CFU/cm². Further development of techniques to eradicate biofilm should be investigated. **Conclusion:** The use of adjuvant chemicals to remove biofilms provides an average 2 log reduction in CFU/cm² from implant materials, but leaves large numbers of CFU's behind.

Kenamond, Mark

101

Medicine, Research was done with the dept. of radiation oncology, Basic Science

The Dosimetric Effects of Limited Elective Nodal Irradiation in Volumetric Modulated Arc Therapy Treatment Planning for Locally Advanced Non-Small Cell Lung Cancer

Introduction: Contemporary radiotherapy guidelines for locally advanced non-small cell lung carcinoma (LA-NSCLC) recommend omitting elective nodal irradiation, given the relatively low regional recurrence rates and benefit of reduced doses to organs at risk (OARs). However, evidence supporting this strategy came primarily from older reports assessing comprehensive nodal coverage using 3D conformal techniques. Herein we evaluated the dosimetric feasibility of the addition of limited elective nodal irradiation (LENI) to standard involved field radiation therapy (IFRT) using volumetric modulated arc therapy (VMAT) planning. Methods: Target volumes and OARs were delineated according to specifications of active NRG clinical trials on CT simulation images of 20 patients with LA-NSCLC. Two VMAT plans (termed IFRT and LENI) were generated for each patient using Eclipse version 11 with calculation algorithm Acuros10. Involved sites were treated to 60Gy in 30 fractions for both IFRT and LENI plans. Adjacent uninvolved nodal regions, considered high-risk based on the primary tumor site and extent of nodal involvement, were also treated to 51Gy in LENI plans using a simultaneous integrated boost approach. Equivalent dose-volume objectives were used in the optimization of all plans. Student's t-tests were used to compare the mean values of dosimetric parameters. Results: All planning objectives for PTVs and OARs were achieved for both IFRT and LENI plans. LENI resulted in significantly higher esophagus Dmean (15.3 vs. 22.5Gy, $p < 0.01$), spinal cord Dmax (34.9 vs. 42.4Gy, $p = 0.02$) and lung Dmean (13.5 vs. 15.9Gy, $p = 0.02$), V20 (23.0 vs. 27.9Gy, $p = 0.03$) and V5 (52.6 vs. 59.4Gy, $p = 0.02$). No differences were observed in heart parameters. On average, only 31.5% of the high risk nodal volume received an incidental dose of 51Gy when untargeted in IFRT plans. Conclusion: The addition of LENI to VMAT plans for LA-NSCLC is feasible, with only modestly increased doses to OARs and marginal expected increase in associated toxicity.

TGF- β 1 mediated lung fibrosis depends on the upstream osteopontin stimulation

Several studies have demonstrated that single-walled carbon nanotubes (SWCNT) exposure caused pulmonary fibrosis with a rapid inflammatory onset and subsequent granulomas formation through mechanisms involving epithelial-mesenchymal transition, myofibroblast ROS-dependent differentiation/recruitment accompanied by the release and interplay of various cytokines/chemotactic factors. The transforming growth factor- β (TGF- β) has been recognized as a central player in the robust pulmonary inflammatory response involved in the development of granulomas and interstitial fibrosis. However, the role of glycoprotein osteopontin (OPN) in TGF- β 1 mediated fibrosis has not been fully explored. We used OPN-knockout (OPN-KO) and wild type (WT) C57BL/6 mice to investigate pulmonary fibrotic response upon exposure to SWCNT (40 μ g/mouse). Reduced release of pro-inflammatory cytokines (MCP-1, TNF- α , IL-6), diminished pulmonary damage markers, and less pronounced neutrophil accumulation were found in broncho-alveolar lavage (BAL) of OPN-KO mice as compared to WT mice. Morphological examination revealed markedly decreased formation of granulomatous lesions along with diminished collagen deposition in the lungs of OPN-KO mice. While a significant increase in the level of TGF- β 1 was found in BAL of WT mice, TGF- β 1 readings in OPN-KO animals remained unaltered. In line with this, significantly reduced levels of TGF- β 1 were detected when RAW 264.7 cells and MLE-15 cells exposed to SWCNT (24 hours, 6 μ g/cm² to 48 μ g/cm²) were pre-treated with an OPN-blocking antibody. To the best of our knowledge, this is the first report to demonstrate that OPN may play a crucial role in TGF- β 1 mediated SWCNT induced lung fibrosis.

Kingsbury, James

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Medicine, Department of Radiology, Resident

TIPS for Refractory Ascites and Variceal Bleeding: A 10-Year Institutional Experience and Literature Review

PURPOSE. We aim to discuss and evaluate the evolution of the transjugular intrahepatic portosystemic shunt (TIPS) technique and stents used at our institution over the 10 year period from 2005-2015 in addition to reviewing literature for the history and development of TIPS placement. The TIPS is a portosystemic shunt created for the management of complications and sequela of portal hypertension. Bare metal stents predominated throughout the 1990s until the mid-2000s when a covered stent became commercially available in the US. **MATERIALS AND METHODS:** The institutional review board approved this retrospective study. We reviewed 157 TIPS procedures that were performed at our institution between 2005 and 2015. Of these, 127 (81%) were a successful first attempt. Thirty (18%) of the procedures were performed as revisions, either for TIPS that were performed at outside institutions or for TIPS we performed prior to 2005. Of the 128 TIPS conducted at our institution between 2005 and 2015, 18 (14%) were subsequently revised due to issues with stent patency. The type of stents used and incidence of revision was evaluated and compared. **RESULTS:** The TIPS technique originated in the 1960s and subsequently refined until the 1980s when the first human procedure was performed. Eventually self-expanding bare metal stents were subsequently used throughout the 1990s, albeit with relatively poor patency rates. In 2003-2004, the Viatorr polytetrafluoroethylene (PTFE) covered stent graft became commercially available. Bare metal stents were exclusively used at our institution until 2009-2010 at which point covered stents were used in greater frequency. During this 10 year time frame, 44 bare metal stents were placed. From 2009 to 2015, 48 Viatorr covered stents were used. The incidence of TIPS revision was almost exclusive to patients receiving the bare metal stents. To date, only one of the TIPS procedures in which a covered stent was used has undergone subsequent revision (2%). **CONCLUSION.** TIPS technique and stents have evolved greatly over the past two decades. It has been established at our institution and throughout the literature that covered stents lead to better control of portal hypertension with a decreased incidence of complications and need for revision.

Kogan, Lisa

139

Other, Mechanical and Aerospace Engineering, Masters

Corticospinal excitability is modulated by limb velocity during locomotion in healthy humans.

The coordination between cortical and midbrain signals involved in the regulation of locomotor drive remains to be a contentious issue in human motor control. Corticospinal excitability (CSE) during different tasks can be directly assessed with noninvasive transcranial magnetic stimulation (TMS). In this study, TMS was used to elicit motor evoked potentials (MEPs) in twelve healthy human volunteers during locomotion on a split-belt treadmill, allowing for CSE to be evaluated throughout four gait tasks. The velocity conditions were limited to two symmetrical tasks, with both belts moving at either 1 m/s or 1.25 m/s, and two asymmetrical tasks, with one belt moving at 1 m/s and the other at 1.25 m/s. Participants were instrumented with wireless EMG sensors to collect activity of ten representative muscles of the right leg, and five muscles of the left leg. Ground reaction forces and moments were collected from force plates in the treadmill. A double cone coil was used to stimulate deep cortical structures corresponding to the area of the primary motor cortex (M1) associated with control of the lower limbs. Two tracking arrays were used to monitor the relative displacement between the coil and the brain of each subject. Brainsight TMS neuronavigation software was used to display and automatically save this relative location to ensure consistency between trials using an outgoing pulse from the TMS hardware for synchronization. For each participant, a target location was found by stimulating around a prior saved location that elicited a response in the right tibialis anterior (TA) during procedural tests, and selecting the target location that elicited the greatest magnitude MEP. The stimulation intensity was chosen as the lowest level that would still evoke an MEP in the right TA active over five stimulations at the target location. The MEP profiles in each episode were detected in EMG signals using the recorded outgoing TMS pulse. MEP magnitude was normalized to the pre-stimulation muscle activity. Normalized MEPs were used to compare CSE across different velocity conditions in representative leg muscles. The results were summarized across subjects. We found that CSE is differentially modulated according to limb velocity during walking.

Ku, Cristy

20

Medicine, Transitional Year Residency, Resident

Detailed clinical phenotype and molecular genetic findings in CLN3-associated isolated retinal degeneration

Importance: There is an increasing trend that mutations in genes traditionally associated with syndromic retinal disease are found to cause non-syndromic inherited retinal degenerations (IRDs). Mutations in CLN3 are classically associated with juvenile neuronal lipofuscinosis (JNCL), a rare neurodegenerative disease with early retinal degeneration and progressive neurologic deterioration have recently also been identified in patients with non-syndromic (IRDs). Objective: To provide detailed clinical, electrophysiologic, structural, and molecular genetic findings in non-syndromic IRDs associated with CLN3 mutations. Design, setting, and participants: A multi-institutional, retrospective case series of 10 patients, age ranging from 16 to 70 years of age, who presented with retinal disease and biallelic mutations in CLN3. Patients had isolated non-syndromic retinal degeneration, without neurological deficits associated with JNCL. Main outcomes and measures: Longitudinal clinical evaluation including full ophthalmic examination, multimodal retinal imaging, perimetry, electrophysiology, and molecular analyses. Results: From the series of 10 patients (7 females, 3 males; mean age at last review 37.1 years [range 16-70 years]), 5 had a progressive late onset rod-cone dystrophy with mean age of onset 29.7 years [range 20-41 years] and 5 with earlier onset rod-cone dystrophy with mean age of onset 11.6 years [range 7-17 years]. Ophthalmoscopic examination revealed macular edema in 4 patients. Macular and peripheral atrophy with significant intraretinal pigment migration occurred late in the disease. Fundus autofluorescence imaging showed central hypoautofluorescence with a hyperautofluorescent ring in 7 patients. OCT imaging demonstrated preservation of foveal ellipsoid zone in 4 patients, despite macular edema in 3 of 4 of these patients. Electroretinography revealed a rod-cone pattern of dysfunction in 6 of 8 patients; ERGs were undetectable in 2 patients. No systemic or neurologic signs or symptoms were present in any patient. Biallelic mutations were present in all patients with 6 novel variants identified. Conclusions and relevance: This report describes detailed clinical, imaging, and genetic features of CLN3-associated non-syndromic retinal degeneration. Six novel disease-causing variants were identified. The age of onset and natural progression of retinal disease differs greatly between syndromic and non-syndromic CLN3 disease, which appears to be related to the associated CLN3 genotype.

Lacy, Frank

115

Medicine, Department of Medical Education, Clinical Sciences/Epidemiology

Comparison of USMLE Step 1 Scores Between PALS Tutors and Non-Tutors

The Peer Assisted Learning Service (PALS) program was established at the West Virginia University School of Medicine in 2012. PALS is a near-peer tutoring service, which is defined as a more senior student teaching a more junior student within the same curriculum. Tutors in the PALS program organize information for tutoring sessions to present information from multiple points of view, prepare for students' inquiries, and help identify students' knowledge gaps. PALS tutors also benefit from the experience. Tutors must review previously learned material. Tutors are also challenged to explain the content, which often results in finding a deeper meaning of the material and enhancing a recall of information. The tutoring responsibilities and duties may position tutors to do well on high-stakes exams, such as the USMLE Step 1 examination. This required licensure exam is an important data point that helps distinguish medical students' applications for residency programs. Residency program directors cite applicant's Step 1 score as a major factor in determining whether applicants will receive an invitation to interview. To our knowledge, no studies exploring the correlation between peer tutoring and national standardized medical exams have been conducted. We compared Step 1 scores of 12 top quartile students tutoring in 3 or more content areas to 12 top quartile students who did not tutor. The tutors' mean Step 1 score ($M = 254.4$) was 10.5 points higher than the mean of non-tutors ($M = 243.9$) ($p < 0.05$). A calculated Cohen's d of 0.87 indicates a large effect size, suggesting that the mean Step 1 difference between tutors and non-tutors is meaningful. These findings are consistent with what is known about learning and memory: those who rehearse and revisit information are able to recall and implement that knowledge more readily. As Step 1 is a multi-subject examination, it also appears that tutoring across multiple subject areas is associated with a significant increase in Step 1 score. These findings provide evidence of the utility of PAL programs in preparing students for standardized examinations and could be used for tutor recruitment.

Lineberry, Kristin

145

Dentistry, Dental Hygiene, Undergraduate

The Influence of pH on Salivary Flow Rates

The pH of consumables may have a direct effect on salivary flow rates. Salivary flow rates may be a critical factor in the progression of xerostomia and dental caries. The purpose of this study was to determine if the pH of consumables have an effect on salivary flow rates. A total of 16 dental hygiene students were presented with a cover letter and consent form; all questions were answered prior to obtaining signatures. Participants were asked to expectorate into a graduated medicament cup. Litmus paper was used to determine the baseline pH of participant's saliva. Participants were given an assigned eight ounce beverage consisting of either water, diluted lemon juice, or 100% lemon juice to be consumed within two minutes. A stopwatch was started once beverage consumption was completed. Participants expectorated into emptied medicament cups at two minute intervals for 20 minutes; salivary volume was measured at each two minute interval. Participants returned on a different day to repeat the above procedure using a different assigned beverage. A total of three sessions were conducted. After the consumption of water, the average pH decrease of participants' saliva was 0.2. After the consumption of diluted lemon juice, the average pH decrease of participants' saliva was 1.8. After the consumption of 100% lemon juice, the average pH decrease of participants' saliva was 2.27. After the consumption of water, the average initial salivary flow volume was 2.683 mL, decreasing to 1.667 after 20 minutes of expectoration at two minute intervals. After the consumption of diluted lemon juice, the average initial salivary flow volume was 3 mL, decreasing to an average of 1.417 mL after 20 minutes of expectoration at two minute intervals. After the consumption of 100% lemon juice, the average initial salivary flow volume was 3.607 mL, decreasing to an average of 1.467 mL after 20 minutes of expectoration at two minute intervals. The average pH change before and after the consumption of the three beverages is not statistically significant ($p=0.001$). Salivary flow rates are significantly different across agents within the twenty minute time frame ($p=0.673$).

Loskutov, Yuriy

78

Medicine, MBRCC, Basic Science

Primary cilium points at LPA signaling as a novel therapeutic target in GBM

The primary cilium is a ubiquitous microtubule based organelle presented on most of human cells. Recently it was noted that loss of primary cilia promotes cell proliferation. Cilium is drastically decreased in cancer cells including glioblastoma, however the mechanism and significance of this event is not understood. Here we report that loss of primary cilia in human astrocytes, potential cell of origin for glioblastoma, stimulate proliferation in lysophosphatidic acid (LPA) dependent manner. LPA is a known mitogen which binds to LPA receptors 1-6 (LPAR). LPAR1 signaling through G-protein coupled receptors like $G\alpha_{12/q}$ was previously reported to be responsible for cancer cell proliferation. We found lysophosphatidic acid receptors 1 (LPAR1) to be accumulated in primary cilia under normal condition and redistribute to the plasma membrane upon loss of primary cilia, meanwhile $G\alpha_{12}$ and $G\alpha_q$ were found only outside of the cilium. Concomitant increase in LPAR1 association with $G\alpha_{12}$ and $G\alpha_q$ upon loss of cilia was noted in co-immunoprecipitation experiments. Thus localization of LPAR1 to cilium limits its interaction with downstream effectors such as $G\alpha_{12}$ and $G\alpha_q$ restricting proliferation signaling. 95-85% of Glioblastoma cells do not have cilium and are highly proliferative. Inhibition of LPA signaling with small molecule compound Ki16425 in glioblastoma cells or patient-derived xenografts drastically suppress their growth both in vitro and in vivo. Moreover, treatment with Ki16425 packed into PEG-PLGA nanoparticles for brain delivery was decreasing tumor progression as monotherapy in intracranial glioblastoma model. Overall our findings indicate that loss of primary cilia is sufficient to increase mitogen signal transduction in normal cells and is critical for maintenance of highly proliferative phenotype in glioblastoma. Clinical application of LPA inhibitors in combination with current standard of care might prove highly beneficial to restrict glioblastoma proliferation and ensure local control of disease.

Lucke-Wold, Brandon

125

Medicine, Neurosurgery, Clinical Sciences/Epidemiology

Traumatic Brain Injury and MicroRNAs: A Novel Approach for Treating Neurotrauma

Background: Traumatic brain injury continues to present a significant clinical challenge in terms of neurosurgical, as well as pharmacologic treatment options. A primary unknown research area is how acute injury alters the underlying biochemical landscape to affect long-term outcomes. Recent evidence suggests that microRNAs are master regulators that control multiple inflammatory and cell injury pathways. We sought to investigate these master regulators following TBI, and whether microRNA levels can be successfully targeted pharmacologically. **Methods:** Serum samples were collected from adult traumatic brain injury patients prior to any intervention (n=12) and compared to controls (n=12). MicroRNA was isolated and quantification was done with rtPCR. An air-acceleration TBI model was used to produce moderate injury (50 PSI) exposure in young-adult male Sprague Dawley rats. A time course of serial blood draws was performed post-injury on the rats. One group was sham (n=7), one group received bryostatin 0.5µg/kg i.p. alone (n=7), one group received bryostatin 0.5µg/kg i.p. post blast (n=7), and the final group received 0.9% saline (n=7). MicroRNA was isolated from the serum and quantified by PCR. Prior to sacrifice, rats were tested on the elevated plus maze. The brains were removed at time of sacrifice and grouped for western blot and IHC. **Results:** A significant increase in the let7 microRNA family was seen in both the human TBI samples as well as the rats exposed to TBI. The let7 microRNAs are master regulators of microglia related neuroinflammation. Interestingly, bryostatin significantly influenced the let7 microRNA family. Bryostatin significantly reduced the biphasic peak in (p<0.01) let7a and (p<0.001) let7f when given five minutes post injury. This was correlated with reduced blood brain barrier disruption assessed with ZO-1 staining and decreased apoptosis activation measured with BCL-2. Furthermore, bryostatin improved behavioral outcomes when given after blast exposure as measured with elevated plus maze by reducing distance traveled (p<0.05). **Conclusion:** MicroRNAs play an important but poorly understood role in neural injury. Understanding how microRNAs regulate cellular cascades following neurotrauma may offer novel approaches for pharmacologically treating patients. Further research is warranted to improve patient outcomes prior to and following intervention.

Ludovici, Dina

94

Pharmacy, School of Pharmacy, Clinical Sciences/Epidemiology

Development of novel oral fast disintegrating strips for use in Parkinson's disease

Objective: Evaluate oral disintegrating strips (ODS) suitable to deliver Parkinson's specific therapeutic agents due to this patient population having trouble swallowing effectively. Methods: ODS strips were designed by quality of design (QD) techniques and following United States Pharmacopoeia standards (USP). ODS strips were formulated using hydroxypropylmethylcellulose (HPMC) and polyvinyl alcohol (PVA). Film casting techniques were used to pour the films. For each batch, the weight, thickness, disintegrating time and stability were evaluated. Results: We found that 15% w/w HPMC was the optimum for forming a ODS which can be used to formulate drugs into. The ODS strips were able to dissolve in less than 60 seconds using a dissolution bath (Vankel) and release tracer compounds effectively. Implications: These strips can be used to treat aging patients who have trouble swallowing. In this study we were able to develop a ODS system that can be easily adapted by the compounding pharmacist to treat elderly Parkinson's patients that face problems swallowing their medication.

Lyons, Kelly

107

Dentistry, Dental, Clinical Sciences/Epidemiology

Efficacy of Three Treatment Modalities for Temporomandibular Joint Disorder (TMD): A Systematic Review

We compared treatment of TMD by botulinum toxin (botox) injection, low level laser therapy (LLLT), and orthotic devices/splints to identify the treatment method most effective in reducing pain as measured by the visual analog scale (VAS). A systematic search of four online databases was conducted, and ten articles met the predetermined inclusion criteria of randomized controlled trial with $n \geq 20$, among other limiters. Studies were reviewed and baseline and final VAS scores were compared among intervention and control groups. The mean reductions in VAS scores were 11 and 14 for two BTX-A treatments, and 2 and 2 for the respective controls; 25.9, 22.5, 29.75, and 50 for LLLT and 27.9, 11.5, 0.75, and 20 for their respective controls; 64.5 and 65.75, 29, 9.8, 37 and 26 for splint treatment, and 18.5, 3.5, 1.22, and 16 for their respective controls. There was a significant time factor present in several studies.

Machi, Anthony

92

Medicine, Emergency Medicine, Clinical Sciences/Epidemiology

Longitudinal Ultrasound Curriculum Incorporation at West Virginia University School of Medicine: A Description and Graduating Students' Perceptions

Introduction: Ultrasound (US) has proven to be a useful clinical tool due to its portability, low cost, noninvasiveness, and absence of ionizing radiation. Medical schools are increasingly attempting to integrate ultrasound education into their curricula. WVU began a longitudinal US curriculum in 2012. We surveyed the first graduating class to assess their experience with the curriculum and its impact. The purpose of this study is to assess our own curriculum and to propose a potential model that could be adapted by other institutions. Methods: In 2016, we conducted a survey of graduating medical students who had finished the full US curriculum. The survey consisted of 12 Likert (1-5) scale questions, demographics, and open ended questions on the successes and areas for improvement in the curriculum. The maximum possible score was 62 if all areas of the curriculum were rated strongly favorable. We regarded any score ³ 42 as favorable and compared scores across campuses and specialties. Results: We received a response rate of >90%. Across all three campuses and specialties, we received a positive survey rate of 92.7% (76/82). Our three campuses had the following positive survey rates: Morgantown – 92.2% (47/51), Charleston – 100% (20/20), and Eastern 81.8% (9/11). Across 16 specialties, we received 6 negative surveys (Emergency Medicine - 1, Family Medicine - 1, Internal Medicine - 2, Pediatrics - 1, and Psychiatry - 1). The open-ended responses were overwhelmingly positive with some students suggesting that US education be made mandatory during the clinical years. The survey results also suggest that the main obstacle for students is facing skepticism from faculty. Discussion: Our survey results suggest that WVU students are engaged and interested in their US education. With such positive open-ended and scaled responses, we are confident that our US curriculum is succeeding, but also realize that there is still room to improve. Although the general consensus acknowledged the benefits of US in medical school education, students addressed frequent barriers preventing them from pursuing continuing US education. These barriers may be resolved by increasing faculty support and/or expanding opportunities for students to incorporate US during required clerkships.

Mandler, Kyle

85

Medicine, Exercise Physiology, Basic Science

Thrombospondin-1 mediates Multi-Walled Carbon Nanotube induced impairment of arteriolar dilation.

Pulmonary exposure to multi-walled carbon nanotubes (MWCNT) and other nanomaterials has been shown to disrupt endothelium-dependent arteriolar dilation in the peripheral microcirculation. The molecular mechanisms behind these arteriolar disruptions have yet to be fully elucidated. The secreted extracellular matrix protein thrombospondin-1 (TSP-1) is capable of moderating arteriolar vasodilation by inhibiting soluble guanylate cyclase activity. We hypothesized that TSP-1 may be a link between nanomaterial exposure and observed peripheral microvascular dysfunction. To test this hypothesis, wild-type C57B6J (WT) and TSP-1 knockout (KO) mice were exposed via lung aspiration to MWCNT or a sham dispersion medium control. Following exposure (24hrs), arteriolar characteristics and reactivity were measured in the gluteus maximus muscle using intravital microscopy (IVM) coupled with microiontophoretic delivery of acetylcholine (ACh) or sodium nitroprusside (SNP). In WT mice exposed to MWCNT, skeletal muscle TSP-1 protein increased > 5-fold compared to sham exposed, and exhibited a 39% and 47% decrease in endothelium-dependent and independent vasodilation, respectively. In contrast, TSP-1 protein was not increased following MWCNT exposure in KO mice and exhibited no loss in dilatory capacity. Microvascular leukocyte activation was measured by assessing third order venular leukocyte adhesion and rolling activity. The WT + MWCNT group demonstrated 223% higher leukocyte rolling compared to WT + SHAM controls. TSP-1 KO animals exposed to MWCNT showed no differences from WT + SHAM control. These data provide evidence that TSP-1 mediates, in part, the systemic microvascular dysfunction in the periphery that follows pulmonary ENM exposure.

Mannan, Rahul

104

Medicine, Neurobiology & Anatomy, Basic Science

What has happened to this hand? An evidence-based case study I

This case is a unique representation of a hand injury in regards to changes in anatomy and function of supporting structures. A case presentation such as this will allow students to gain a greater appreciation for direct functional implications of injury to hand anatomical structures. The injury was sustained in rural Thailand 45 years ago where medical interventions and resources were scarce. Subsequently, only a tetanus shot and four stitches were used in the repair of the injury. From the video images provided, students should be able to determine what tendon(s) of the hand musculature were injured based on the patient's remaining function. The deep cut occurred in Zone II of hand injury, just above the crease at the base of the right 5th finger and the palm. This zone is located between the opening of the flexor sheath (the distal palmar crease) and the insertion of the flexor digitorum superficialis tendon. While flexing her hand to make a fist, she can only flex the metacarpophalangeal joint, but not the proximal and distal interphalangeal joints. This indicates both flexor tendons to that finger were cut, and not properly re-connected while repairing the injury. The muscle bellies in the forearm have atrophied, presenting as a long hollowed-out area on the ulnar side of the distal forearm, proximal to the wrist. The palmaris longus muscle and tendon are more prominent, as part of a compensatory hypertrophy for the loss of other structures. This is a very unique, interesting injury to emphasize the structures and movement of the muscles and tendons in the hand and finger. It can serve as an educational tool used in problem solving cases and learning of the hand anatomy and function.

Marinak, Kristina

60

Medicine, MBRCC, Basic Science

Aurora-A Kinase: a nuclear driver of metastasis.

Aurora-A Kinase (AURKA) is a serine/threonine kinase that is critical for mitosis. AURKA is upregulated in many human cancers, including breast cancer. It has been previously shown that AURKA localizes to the nucleus in breast cancer metastases and especially in metastases of Triple Negative Breast Cancer (TNBC). Our objective is to define the role of nuclear AURKA in breast cancer metastasis in TNBC. Here we report that TNBC cell lines vary in amount of nuclear AURKA and this potentially correlates with their metastatic capabilities. Based on our preliminary findings we hypothesized that nuclear AURKA promotes cell survival and resistance to apoptosis in the metastatic niche. To test this hypothesis we created TNBC cell lines with CRISPR/Cas9 based deletion of endogenous AURKA. We also constructed exogenous AURKA specifically targeted to the nucleus by addition of a nuclear localization signal (NLS) or cytoplasm via addition of a nuclear exclusion signal (NES), respectively. To allow for in vitro and in vivo rescue experiments with exogenous NES or NLS AURKA in sgAURKA expressing TNBC cells, we introduced several silent mutations to avoid sgAURKA targeting. In our pilot orthotopic xenograft study with MDA-MB-231-luc2-Cas9 (TNBC) cells expressing sgAURKA with WT AURKA, NLS-AURKA or AURKA-NES shows an increased metastatic colonization in the AURKA-NLS group. Overall, our results indicate that the amount of nuclear AURKA is increased in metastatic breast cancer cell lines and metastases of TNBC. Our in vivo results show increased metastases in the liver and lymph node in the NLS-AURKA group compared to AURKA-NES, suggesting nuclear AURKA promotes metastasis, but the mechanism of this phenomenon is currently unknown as well as the mechanisms governing AURKA translocation to the nucleus. Elucidation of these mechanisms is critical for development of new therapeutical strategies for control and eradication of metastatic disease.

Somatostatin receptor 2 antagonist, CYN154806, stimulates pulsatile LH secretion in ewes

Administration of somatostatin (SST) or a SST receptor 2 (SSTR2) agonist inhibits pulsatile LH secretion in sheep and humans, respectively, and we recently demonstrated, using an SSTR2 antagonist, that endogenous SST suppresses pulsatile LH secretion in estradiol and progesterone treated ewes. We administered SSTR2 antagonist, CYN154806 (CYN), to ovary intact anestrous ewes and to ovariectomized (OVX) ewes during both seasons. Anestrous ewes (n=8) received an intracerebroventricular injection of 60nmol CYN or saline (SAL); jugular blood samples were collected every 12 min for 2 hrs pre- and 4 hrs post- injection, and was repeated 4 days later using a cross-over design. CYN significantly (P=0.006) increased mean LH concentrations following injection from 1.4 ± 0.2 ng/mL to 4.3 ± 0.7 ng/mL, while SAL did not (pre: 1.3 ± 0.1 ng/mL; post: 2.4 ± 0.4 ng/mL). To test the effects of CYN in the absence of gonadal hormones, the same protocol was performed in OVX ewes (n=6) in anestrous and during the breeding season (n=8). CYN caused a shorter (P=0.015) LH inter-pulse interval (40.3 ± 6.9 min) after injection compared to SAL (71.7 ± 9.6 min) in anestrous but had no effect during the breeding season. To identify possible sites of action we quantified c-Fos co-localization within GnRH and kisspeptin cells. Intact anestrous ewes were euthanized 2 hrs after injection with CYN (n=4) or SAL (n=4). CYN treatment caused an increase (P=0.01) in the percentage of GnRH cells within the mediobasal hypothalamus (MBH) that contained c-Fos (CYN: $25 \pm 3.6\%$; SAL: $7.5 \pm 1.8\%$), but did not alter the percentage of GnRH cells that contained c-Fos within other areas. CYN administration caused a significant (P=0.02), increase in the percentage of kisspeptin cells that contained c-Fos within the caudal arcuate nucleus (ARC; CYN: $9.5 \pm 2.7\%$; SAL: $1.2 \pm 0.5\%$), but not in other regions of ARC. These results demonstrate that endogenous SST acts, at least in part, through SSTR2 to suppress pulsatile LH secretion. Together these data support the hypothesis that endogenous SST suppresses pulsatile LH secretion via inhibition of GnRH and kisspeptin, and are involved in the steroid-independent actions of inhibitory photoperiod in ewes.

McGuire, Joseph

161

Other, Biochemistry, Undergraduate

Functional redundancy of OVOL and GRHL genes in the suppression of the Epithelial-to-Mesenchymal Transition

About 90% of cancers are of an epithelial origin, and metastasis is the main cause of cancer-related deaths. OVOL and GRHL family transcription factors are expressed in epithelial tissues and regulate the epithelial-to-mesenchymal transition (EMT), which is a known process that epithelial cells utilize to metastasize in cancer. We have previously shown that overexpression of individual OVOL or GRHL genes in mesenchymal cells inhibits EMT by repressing a major EMT inducer ZEB1. However, the exact functions and hierarchy of these genes in the maintenance of cell epithelial state are not well understood. To address this, we used the CRISPR/Cas9 system to generate knockouts of OVOL and GRHL family members in epithelial MCF7 breast cancer cells. We found that knocking out individual OVOL or GRHL genes, or double OVOL1&2 and GRHL1&2, is not sufficient to induce an EMT. We have also found that GRHLs regulate OVOL genes, suggesting that OVOLs are downstream of GRHLs. These results suggest that GRHLs and OVOLs play a redundant role in the maintenance of cell epithelial state. We are currently generating sequential (triple/quadruple) knockouts that will allow us to determine if deletion of OVOL1&2 plus GRHL1&2 will be sufficient to reactivate ZEB1 and induce EMT.

Identification of the Structural Loop Element of the Group A Streptococcal Scl1 Adhesin with Binding Capacity for Injured Host Tissue

Background: Group A Streptococcus (GAS) gains access to host tissue via a portal of entry, such as a wound. During wound healing, the host lays a provisional matrix with a unique composition, primarily comprised of cellular fibronectin (cFn), specifically, the isoforms containing extra domain A (EDA/cFn). The streptococcal collagen-like protein 1 (Scl1) is a prominent surface adhesin of GAS, which selectively binds EDA/cFn isoforms. Scl1 is a homotrimeric protein that binds EDA via its N-terminal globular variable (V) domain, composed of three pairs of anti-parallel α -helices connected by flexible loops. We hypothesized that the surface-exposed loops in the Scl1 globular domain are responsible for EDA recognition and binding, enabling GAS for targeted wound colonization. Methods and Results: To test our hypothesis, we studied EDA binding by chimeric recombinant Scl constructs generated by replacement of the loop sequence. We identified that the 22-amino acid loop segment of Scl1 was responsible for binding to recombinant EDA and EDA/cFn by ELISA. Surface plasmon resonance measurements assessed binding affinity of $K_D = 63.3 \mu\text{M}$ between rScl1 and an EDA-derived mimetic peptide. Surface potential maps of Scl1 V-domain homology models revealed a conserved negatively-charged pocket within the V-domain loop segments. To examine tissue colonization, we infected wounded skin-equivalents with GFP-expressing GAS and assessed colonization using standard histopathology and two-photon microscopy. Histopathology of tissue sections revealed bacterial colonization of the exposed dermal surface, as well as bacterial invasion into wound injuries extending deep into the dermal layer. Two-photon imaging revealed the formation of microcolonies within the tissue below wound bed that were encased in a glycocalyx, indicative of biofilm formation. Additionally, GAS infection delayed wound closure and caused epidermal thinning in the surrounding tissue. Conclusions: This work identified a 22-amino-acid structural loop element of the Scl1 adhesin for the capacity to selectively guide group A Streptococcus to damaged tissue and initiate human host infection.

Meigh, Kristin

109

Medicine, Department of Emergency Medicine, Clinical Sciences/Epidemiology

Takotsubo Cardiomyopathy in the Emergency Department: A FOCUS Heart Breaker

Takotsubo cardiomyopathy (TCM) is an important condition for the emergency physician to consider in the differential diagnosis for chest pain. The following report details the case of a 70-year-old woman who presented to the ED with chest pain and nausea following a traumatic event. The patient was found to have an elevated troponin level and a normal EKG. Bedside focused cardiac ultrasound (FOCUS) was performed and showed reduced left ventricular systolic function with mid to apical hypokinesis, both of which are findings consistent with TCM. Cardiac catheterization revealed clean coronary arteries and confirmed the diagnosis of TCM. Maintaining a high index of suspicion for TCM and using FOCUS to narrow the differential diagnosis may improve the management of these patients in the emergency department.

Minor, Emily

61

Medicine, Biochemistry, Basic Science

Dietary Na⁺-depletion stimulates the expression of iron transporters in the rat colon

Iron deficiency anemia is the most common nutrient deficiency worldwide. The majority of non-heme iron absorption occurs in the duodenum via divalent metal transporter-1 (DMT-1) on the apical membrane and ferroportin (FPN) on the basolateral membrane. People with digestive diseases, such as celiac disease, have impaired iron uptake due to decreased absorptive area in the duodenum. Novel therapies to increase iron absorption are needed because current therapies are ineffective or have serious potential side effects. Sprague dawley rats fed a Na-depleted diet for 6 days have increased levels of aldosterone, which has been shown to upregulate various iron transporters, including DMT-1 and FPN. RT-qPCR demonstrates a 4-fold increase in mRNA abundance of DMT-1 and FPN in the duodenum, proximal, and distal colon of rats fed a Na-depleted diet. There was also an increase in protein abundance of DMT-1 and FPN in rats exposed to the same experimental diet. Aldosterone supplementation and/or dietary Na restriction is thus a potential novel therapy to enable colonic absorption of iron in people with digestive diseases that hinder iron uptake in the duodenum.

Morris, Allison

132

Other, Human Nutrition, Masters

Wellness Characteristics of College Freshmen at West Virginia University

Objective: To determine baseline wellness characteristics of students participating in a community-based participatory research intervention to reduce obesity among college students. Methods: An online-based survey was offered during the first four weeks of the Fall 2016 semester. The survey was available to all students, however freshmen received a \$5 incentive for taking the survey and their responses were kept for analysis. The survey was distributed through in-person tabling, flyering and requests to faculty members to share with students. The survey included questions to determine fruit and vegetable consumption, physical activity level, stress score, and sleep hours. BMI was determined through self-reported height and weight. Each student received their results in a personalized wellness report card that documented their health scores compared with the campus average and general recommendations, as well as health improvement tips. Results: Total respondents (n=360) were 69% female and ethnic diversity (83% Caucasian, 6% African American, 4% Asian, 3% Hispanic, 4% other) was similar to the total university population. Respondents had an average fruit and vegetable consumption of 3 serving per day (2.71 ± 2.25 SD), a physical activity level (IPAQ) of 3224 ($3.224.40 \pm 2652.6$ SD), a stress score of 25 (24.92 ± 7.91 SD) out of 50, averaged 7 hours of sleep (6.95 ± 1.13 SD) and the campus have an average BMI of 24 (24.22 ± 4.41 SD). Participants were asked if they identified themselves as being from the Appalachian region (n= 114). Those who self-identified as Appalachian had a FV consumption of 3 servings per day (2.97 ± 2.24 SD), a PA level of 3381 (3381 ± 2755.3 SD), a stress score of 25 (24.54 ± 8.40 SD), an average of 7 (6.99 ± 1.41 SD) sleep hours and a BMI of 24 (24.12 ± 4.41 SD). Scores of self-identified Appalachian students' health behaviors were not statically significant different than the general student population. Conclusion: Survey results provide insight into the health behaviors of college students. As Appalachian populations are often at higher risk of health disparities, having Appalachian students with similar health behaviors to the general population suggest a possible protective factor of high educational attainment.

Senior Dental Hygiene Student's Abilities to Properly Utilize the Buccal-Object Rule

The buccal-object rule is utilized by dental professionals to locate a foreign object in the oral cavity. The buccal-object rule determines whether an object is located on the buccal or lingual side of the tooth; this rule can be used to locate objects such as, unerupted supernumerary teeth. Improper utilization of the buccal-object rule may result in inaccurate charting on a patient's odontogram. This study was conducted by evaluating West Virginia University (WVU) senior dental hygiene student's abilities to properly utilize the buccal-object rule. Clinicians may lack competence when utilizing the buccal-object rule, therefore, the purpose of this study was to determine if senior dental hygiene students can accurately identify the surface location of buccal and lingual restorations. For this study, forty-seven amalgam restorations were placed on five dentoforms. A series of four radiographic images were obtained per side of each dentoform and eighteen senior dental hygiene students viewed each radiographic series on computer monitors and charted surface restorations choosing from mesial, occlusal, distal, mesioocclusal, distoocclusal, mesioocclusodistal, buccal, or lingual. The students' surface charting accuracy was reported using frequencies. Furthermore, comparison of surface charting accuracy with the hypothesized minimum competency level of 74% were compared using a directional t-test, and comparison of buccal and lingual surface charting accuracy were compared using a non-directional t-test. On average, students correctly charted buccal and lingual restorations at a 49.54% accuracy level; students correctly charted buccal restorations an average of 66.67% and correctly charted lingual restorations an average of 32.41%. In conclusion, students were more able to accurately identify buccally located restorations as compared to lingually located restorations.

Moye, Abigail

76

Medicine, Biochemistry, Basic Science

ARL2BP, a ciliary protein, controls the growth of photoreceptor microtubular axonemes, organ positioning, and sperm motility.

Photoreceptor neurons are specialized cells that possess elaborated outer segments (OS) containing disc like structures which are anchored by connecting cilia (CC). The delineation of the OS proteins involved in the conversion of light to electrical signal has been extensive, nevertheless little is known about the mechanisms that control the growth and maintenance of the photoreceptor cilia and OS. A recent study revealed a link between ARL2BP and blindness in humans, yet the function of ARL2BP is unknown. Furthermore, patients with mutations in ARL2BP display situs inversus (organ reversal), indicating a syndromic affect, which is commonly seen in ciliopathies. Using a novel animal model lacking ARL2BP, our goal is to identify the role of ARL2BP in the development and function of photoreceptors. We observed normal laminar development of the retina at post-natal day 16 (P16) in the absence of ARL2BP, yet the photoresponse as assessed by electroretinograms (ERGs) were reduced by 50% (n=4, all experiments used littermate controls). As animals aged, the ERG responses progressively declined, which is directly related to degeneration of photoreceptor nuclei. Furthermore, at P16 ultrastructural analysis using transmission electron microscopy revealed dysmorphic photoreceptor outer segment discs (longitudinal instead of horizontal). We also consistently observed reduced photoreceptor axonemal length in ARL2BP KO's as early as P10. Based on this data, we believe abnormal OS development is due to defective growth of axonemes. Additionally, KO mice displayed situs inversus and sperm immotility, further indicating the importance of ARL2BP in ciliated organs. In this study, we show that ARL2BP is involved in maintaining the structure of photoreceptor outer segments and alignment of discs. We hypothesize that ARL2BP is involved in regulating the growth and stability of axonemal microtubules, and is therefore essential for photoreceptor disc organization. Alternatively, ARL2BP may control the localization of ARL2, a small GTPase involved in tubulin biosynthesis. We are currently testing these hypotheses using mouse embryonic fibroblast (MEF) isolated from ARL2BP KO animals, which provides us with an easily tractable system. These experiments will shed light on the function of ARL2BP and ultimately contribute to our understanding of cilia development, photoreceptor structure, and associated ciliopathies.

Mullens, Cody

103

Medicine, Medicine, Clinical Sciences/Epidemiology

Titanium Hardware Complications in Pediatric Cranioplasty

Cranioplasty is performed in infants to address congenital and traumatic anomalies. Multiple approaches for cranioplasty exist, many of which employ different approaches and utilize different types of grafts to cover the defect and permit normal calvarial growth, while protecting the underlying neural tissue. Titanium hardware has been used in this patient population. Aging pediatric cranioplasty patients with titanium implants are a population at risk for scalp breakdown and implant extrusion. While complications from titanium implantation in adult cranioplasty patients are well documented in the medical literature, reports of complications in pediatric populations are sparse. This case series illustrates four examples of negative sequela associated with titanium utilization in infant cranioplasty and our treatment strategy for each case.

Myles, Samantha

156

Dentistry, Dental Hygiene, Undergraduate

Anxiety and Comfort Levels of the Simulated Sensory Impaired Dental Patient

Sensory impairment is a common disability seen in the world; providing dental treatment to patients with visual or auditory impairments requires alterations from regular appointments such as differences in explaining procedures, oral hygiene instruction, and chairside manner. Research has been done in order to further our knowledge of treating patients with disabilities, but not enough has been done to assess the concerns and oral health care needs of the sensory impaired patient. Patients from the School of Dentistry were asked to participate in a sensory impairment simulation in order to assess their comfort levels while undergoing either visual, auditory, visual and auditory, or no sensory impairment through the use of blacked out goggles and/or noise-cancelling ear-muffs. The results showed no significant feelings of discomfort at any points in the procedures; majority of the patients felt comfortable before, during, and after the simulations took place. There were no differences in comfort levels between the different sensory impairment groups. Comfort levels from the beginning to the conclusion of the procedures were assessed using an ANOVA test, and no differences were found. Although the results were not significant, it is in the best interest of the patient to monitor their comfort and anxiety levels throughout the dental appointment, especially in a sensory impairment situation.

Naimo, Marshall

73

Medicine, Exercise Physiology, Basic Science

Methylation Alters Skeletal Muscle Apoptosis Transcription and Myonuclei Morphology Following Resistance-Type Training in Old Rats

Previously, our lab has shown that modifying the frequency of resistance-type training using stretch-shortening contractions (SSCs) from 3 to 2 days/wk attenuates age-dependent maladaptation. Evidence suggests a link between nuclei morphology and epigenomics, but the precise mechanisms of these responses on myonuclei is unknown. Therefore, the purpose was to quantify gene expression and methylation for apoptosis in old versus young skeletal muscle following training at different frequencies, and report concurrent status of nuclei morphology. Tibialis anterior (TA) muscles of young (3 mo) and old (30 mo) male Fischer 344xBN rats exposed to 80 SSCs for 3 or 2 days/wk for 1 month were harvested 3 days post-training. Gene expression and methylation were quantified via RT2 Profiler and Methylation Arrays. Frozen TA sections were stained for β -dystroglycan and DAPI to perform total nuclei and myonuclei morphology via total particle analysis and manual tracings using Image J. Young rats adapted to 3 and 2 days/wk training and differentially ($p < 0.05$) expressed 21 and 7 apoptotic genes, respectively. Old rats maladapted to 3 days/wk training and only expressed 1 apoptotic gene; however, old 2 days/wk expressed 8 apoptotic genes. Methylation increased in SSC trained relative to non-trained control muscles only in old 3 days/wk (0.8 ± 0.004 vs $2.2\% \pm 0.02$, $p < 0.05$). For old 2 days/wk there was no difference in methylation compared to non-trained (0.70 ± 0.004 vs $1.0 \pm 0.01\%$). An age effect ($p < 0.05$) was shown by a higher total count in old relative to young non-trained controls for both total nuclei ($7,708 \pm 181$ vs $6,695 \pm 171$ nuclei per mm^2) and myonuclei ($1,943 \pm 78$ vs $1,483 \pm 74$ nuclei per mm^2). A training effect ($p < 0.05$) resulted in decreased myonuclei count in old 2x/wk relative to both old 3 days/wk and old non-trained ($1,590 \pm 86$ vs $1,888 \pm 86$ vs $1,943 \pm 78$ nuclei per mm^2). Reduced SSC training frequency positively influences aged muscle by decreasing methylation of apoptotic genes, thereby increasing gene expression concomitant with decreases in myonuclei count, which may influence adaptation with aging by eliminating dysfunctional myonuclei, thus aiding in improved muscle size and function.

Nawar, Nariman

12

Medicine, Pathology, Resident

Acute Myeloid Leukemia with Secondary BCR-ABL1 Rearrangement following Allogeneic Bone Marrow Transplant: A Rare Event Possibly Associated with a Poor Prognosis

The acquisition of BCR-ABL1 rearrangement as a secondary cytogenetic abnormality in acute myeloid leukemia (AML) is a rare event of uncertain clinical and therapeutic significance. To further investigate this phenomenon, a 10-year retrospective review of bone marrow cytogenetic data was performed to identify AML patients that acquired BCR-ABL1 on follow-up. A single case of AML with secondary BCR-ABL1 rearrangement was identified among a total of 530 cases of AML diagnosed at our institution. We report a case of a 23-year-old female who first presented with AML accompanied with FLT3 mutation and normal female karyotype. The patient underwent two cycles of induction chemotherapy with a FLT3 inhibitor, but did not achieve remission, having 7% residual myeloblasts after the second cycle. Given the refractory nature of her disease, the patient opted for allogeneic bone marrow transplantation. At three months post-transplant, the patient achieved remission with 100% engraftment. Following brief remission, the patient relapsed, was re-induced and subsequently went into remission. Approximately 1 year later, the patient relapsed again and, on bone marrow evaluation, showed a BCR-ABL1 rearrangement. She was therefore re-induced with a tyrosine kinase inhibitor (TKI) resulting in bone marrow aplasia and undetectable levels of the BCR-ABL1 transcript. However, within two months, the patient's disease recurred with reappearance of the BCR-ABL1 abnormality and the additional development of TP53 mutation. Following two years of therapy, the patient is currently alive but has recently relapsed with periorbital myeloid sarcoma, as well as sustained significant complications of her disease including intracranial hemorrhage and cardiac tamponade. Secondary acquisition of BCR-ABL1 rearrangement in AML is a rare event, occurring late in the evolution of refractory disease. While further studies are needed to more completely characterize this abnormality, secondary BCR-ABL1 in AML appears to portend a poor prognosis with lack of response to TKI therapy.

Neeley, Brandon

98

Medicine, Emergency Medicine, Clinical Sciences/Epidemiology

Prognostic Utility of Alkaline Phosphatase Isoenzyme Levels in Emergency Department Sepsis Admissions in Appalachia

Sepsis is the 8th leading cause of death in West Virginia (WV) and the 10th leading cause of death in the US. The annual fiscal burden associated with inpatient and after care costs for sepsis survivors exceeds \$22 billion nationally, or \$110 million in WV. The clinical syndrome of sepsis is characterized by systemic inflammation and widespread tissue injury due to infectious processes. Recent data suggest that alkaline phosphatase (AP) activity is essential for preserved mitochondrial function, cellular bioenergetics, and endothelial barrier integrity in sepsis models and pathogenesis. It has been suggested that elevated AP levels in sepsis patients may be associated with worse outcome. However, the degree to which AP isoenzyme levels correlate with illness severity, mortality, or serve as a risk stratification tool remains unclear. To determine whether AP isoenzyme activities and levels correlate to sepsis severity in emergency department (ED) patients, we conducted a prospective observational single-center study in a tertiary care academic ED with the following inclusion criteria: (1) age \geq 18 years, (2) diagnosed with probable sepsis (\geq 2 SIRS + infection), (3) provided informed consent. Patients with known acute or chronic hepatitis were excluded. Serum (10 mL) and EDTA plasma (10 mL) were collected from patients within 12 hours of ED registration. Serum total and isoenzyme AP activity levels were quantified by gel electrophoresis and densitometry. Concentration (IU/L) and relative percentage were reported for the following AP isoenzymes: liver 1 (L1), liver 2 (L2), bone, intestinal, and placental, as mean \pm SEM. Total and isoenzyme concentrations between sepsis patients and controls were compared using the Mann-Whitney test with significance determined as $p < 0.05$. Forty-nine patients were enrolled; sepsis ($n=44$), controls ($n=10$), exclusions due to hemolyzed sample ($n=20$). L2 isoenzyme concentrations were significantly elevated in sepsis patients vs. controls (15.3 ± 2.2 vs. 4.8 ± 0.8 , $p=0.004$), while total AP or L1, intestinal, bone, and placental isoenzyme concentrations did not differ significantly. These results provide novel insights into the role of AP and its isoenzymes in the pathophysiology of sepsis. Specifically, the L2 isoenzyme warrants further investigation as a potential ED sepsis biomarker.

BMI- and Gender-Specific Increase of MAP2K3/p38 Activity in Human Cardiac Hypertrophy

Introduction MAP2K3 is a stress-induced kinase and its role cardiac hypertrophy has been controversial: while in vitro studies have displayed a positive correlation in activity with hypertrophy, in vivo studies have shown a negative association. Its direct downstream target, p38 α MAPK, has been shown to be activated in hypertrophic and failed hearts, but this has not been explored with regard to gender or BMI. **Hypothesis** Early activation of p38 MAPK in hypertrophy is influenced by gender and BMI. **Methods** Human heart samples were grouped into non-failed (NF), left ventricular hypertrophy (LVH), and NF without LVH (control). BMI < 25 was considered "lean", 25 < BMI < 30 was considered overweight, and BMI > 30 was considered "obese". RNA-Seq was used to generate cardiac gene expression profiles. Immunoblots were used to examine protein expression of MAP2K3, p38, and activated p38 (pp38; phospho-T180 and Y182). **Results** We found that MAP2K3 mRNA levels were increased in obese males by 134% with LVH compared to non-LVH controls (FPKM: LVH = 19.2 \pm 3.5, n=3; non-LVH = 8.2 \pm 1.9, n=3; FPKM = Fragments Per Kilobase of transcript per Million mapped reads), without statistical significance (p>0.05). MAP2K3 protein expression was 5-fold higher in LVH (1.24 \pm 0.20, n=9) versus non-LVH hearts (0.25 \pm 0.03, n=15) (p<0.0001). Within all LVH hearts sampled, MAP2K3 protein expression is higher only in male overweight or obese (1.21 \pm 0.22, n=7) over lean (0.52 \pm 0.04, n=6) (p<0.05). No differences were detected in gene expression profiles of the four isoforms of p38 and total p38 protein expression levels between LVH and NF groups (p>0.05). Activated-p38 was detected in LVH without failure. Levels of p38 activation are higher in overweight/obese than in lean male group (pp38/p38 ratio: M_BMI>25 = 0.63 \pm 0.03 (n=7), M_BMI<25 = 0.41 \pm 0.12 (n=3), p<0.05). For BMI>25, levels of activated p38 are also higher in male (0.63 \pm 0.03, n=7) than in female (0.08 \pm 0.01, n=3) (p<0.0001), independent of LVH. **Conclusions** We found increased protein expression of MAP2K3 and phosphorylation of p38 in cardiac hypertrophy positively associated with male obese human hearts.

Nguyen, Elena

10

Medicine, Transitional Year, Resident

Evaluating Patients with Known or Suspected Orbital Tumors with Visual Fields: Practice Patterns among Oculoplastic Surgeons

Background/ Rationale: Orbital tumors are a common problem presenting to the oculoplastic surgeon which may be evaluated by visual field testing. Although changes in visual fields are commonly reported with many different orbital tumors, the specific rates and types of visual field defects associated with specific tumor types is not well described. Because of this, we hypothesize that there are variances in the practice patterns of oculoplastics surgeons in obtaining visual fields for the diagnosis and follow up of patients with orbital tumors. **Methods:** A survey was developed using www.surveymonkey.com and a link to the survey was sent electronically to all members listed in the American Society of Ophthalmic Plastic & Reconstructive Surgeons (ASOPRS) member directory with available contact information. A 2-week timeline was given to complete the survey on an anonymous basis. Descriptive statistical analysis was performed on the data collected based on the respondents' answers. **Results:** One hundred seventy ASOPRS members (25%) responded. Most practiced primarily in private (59%) or academic (35%) settings. Humphrey visual fields (HVF) were the preferred modes of visual field testing; 24-2 HVF and 30-2 HVF at 45% and 43%, respectively. Although most respondents would not obtain visual fields on new patients with orbital masses (73%), 25% would repeat visual field testing or neuroimaging every year if the orbital mass was stable. In the context of clinical findings, visual field testing was most often obtained for loss of peripheral vision by confrontation (92%), followed by optic nerve edema or excavation (89%), relative afferent pupillary defect (86%), loss of central visual acuity (85%), and loss of color vision (82%). In the context of neuroimaging findings, visual field testing was most often obtained for mass effect on the optic nerve (94%), followed by intraconal location posterior to the globe equator (74%). **Conclusion:** Although visual field testing is not routinely used for evaluation of patients with new diagnoses of orbital masses, it is most commonly implemented if potential damage to the optic nerve is suspected based on clinical or radiographic findings.

Nickerson, Andrew

33

Medicine, Biochemistry, Basic Science

Forskolin (cAMP) Promotes Insertion of Large Conductance Potassium (KCa1.1) Channels into Apical Membranes of Rat Distal Colon

The mammalian colon contributes significantly to overall K⁺ homeostasis. In contrast to the small intestine, where K⁺ transport is exclusively paracellular, the colon participates in active K⁺ transport. Colonic K⁺ secretion occurs mainly in crypt enterocytes via basolateral uptake through the Na⁺/K⁺ pump and Na⁺/K⁺/2Cl⁻ co-transporter (NKCC1), followed by apical exit through large conductance, Ca²⁺-activated (BK) channels. K⁺ absorption is mediated by a P-type H⁺/K⁺-ATPase on apical membranes of surface enterocytes, and basolateral exit through either BK or intermediate conductance (IK) channels. K⁺ flux studies were performed in distal colonic mucosal tissues obtained from male Sprague-Dawley rats (200-225g). Unidirectional K⁺ fluxes, utilizing ⁸⁶Rb as a tracer, and short-circuit current (ISC) were simultaneously measured under voltage-clamped conditions in the Ussing chamber technique. Results indicate that the BK channel opener BMS 204352 (BMS, 10M) and the adenylate cyclase activator forskolin (FSK, 10M) induced a net K⁺ secretion of 0.083 ± 0.04 and 0.274 ± 0.05 Eq/cm²*hr, respectively (n=4, p<0.05). Immunofluorescence (IF) studies performed on the same tissues used in flux experiments showed markedly increased apical staining of BK channels in tissues exposed to FSK, but not in those exposed to only BMS. Taken together, these data suggest that while BMS may only open BK channels already present on apical membranes, FSK may cause further K⁺ secretion by triggering the insertion of more BK channels into the apical membrane.

Niemann, Michael

100

Medicine, Medicine, Clinical Sciences/Epidemiology

Occult Iliac DVT in 2nd Trimester Pregnancy: Clues on Bedside Ultrasound

Isolated pelvic DVTs are rare and difficult to diagnose, but are more common in pregnant women and carry an increased risk of embolization. Pulmonary embolism (PE) is the most common non-obstetric cause of death in pregnancy. Compression ultrasound is the first-line imaging test for suspected lower extremity DVT, but it cannot usually directly visualize or easily diagnose isolated pelvic DVT.

Nonetheless, Point of Care Ultrasound (POCUS) may provide valuable clues to help rule in pelvic DVT and expedite initiation of anticoagulant therapy. Such findings include increased venous diameter, increased resistance to compression, visible venous reflux, and blunted phasicity. This case presents an example of how these findings on POCUS led the emergency physician to make the difficult diagnosis of pelvic DVT at the bedside within seconds.

LEUKOCYTE INDUCED ALTERATIONS IN BEHAVIOR AND SENSORY MODALITIES IN SEPTIC MICE

Sepsis is a life threatening syndrome as evidenced by a systemic inflammatory response evoked by a local infection. Central nervous system (CNS) impairment (i.e. cognitive decline, sensorimotor dysfunction, delirium, mood disorders) is one of the many clinical presentations in ~70% of sepsis patients. The mechanisms through which sepsis initiates and exacerbates acute and chronic brain dysfunction that influence behavioral outcomes are unclear. We hypothesized that sepsis injury would increase leukocyte extravasation across the blood-brain barrier and alter behavioral outcomes in injured mice compared to controls. Male mice were subjected to sub-lethal cecal ligation and puncture (CLP, n=12), an animal model of experimental sepsis, or sham-injured, (n=7.). Following induction of sepsis at Day 0, sickness behavior in mice was assessed daily. The total mortality in this study after surgery across both experiments was 24% in the CLP mice and 0% in the sham mice. Additionally, cognition, thermal nociception, motor activity and anxiety-like behaviors were evaluated over a 7-day period. Perfused brains were harvested on Day 7 for isolation of leukocytes and quantification of microglia (CD45^{lo}/CD11b⁺/CD11c^{+/-}), infiltrating monocyte (CD45^{hi}/CD11b⁺/CD11c⁻), neutrophil (CD45^{hi}/Ly6G⁺), dendritic cells (CD45^{hi}/CD11b⁺/11c⁺) and T helper cells (CD45^{hi}/CD4⁺) populations by flow cytometry. Our results show that T helper cell populations in the brain were elevated in CLP mice (88.20%) compared to sham mice (79.74%). The infiltrating monocytes populations also increased in CLP mice (78.15%) compared to sham mice (70.64%). CLP mice exhibited a decreased horizontal and vertical spontaneous locomotion. Thermal nociception was also altered in CLP mice compared to sham mice as exhibited by increased latency of response to thermal stimuli and fewer nociceptive behaviors. This result suggests that extravasation of certain leukocyte populations across the blood brain barrier could correlate to the observed behavioral changes exhibited by the septic mice. These studies will provide a functional understanding of this process to establish therapeutic interventions that will prevent CNS impairment in sepsis survivors.

Nye, Maya

95

Public Health, Occupational and Environmental Health Sciences, Basic Science

Use of Trace Metals for Estimating Community Exposure to Marcellus Shale Development Operations

Since 2009, unconventional natural gas drilling (UNGD) has significantly increased in the Appalachian region of the United States with the exploration of the Marcellus Shale gas formation. Elevated concentrations of particulate matter $<2.5 \mu\text{m}$ (PM_{2.5}), have been documented in areas surrounding drilling operations during well stimulation (otherwise known as hydraulic fracturing or “fracking”). As such, many Appalachian communities are experiencing increased industrial activities and possible air pollutant exposures from nearby shale gas extraction activities. Recent epidemiological studies have associated emissions from UNGD with health effects based on distances from the well pads though little progress has been made in targeting the exposure agent(s). In this study, we collected samples of PM_{2.5} on PTFE filters at three points downwind (1, 2 and 7 km) of a Marcellus Shale gas well pad in Morgantown, West Virginia during an 8-day hydraulic fracturing stimulation process. The filters were analyzed for trace metal content via inductively coupled plasma mass spectrometry (ICP-MS). Further analysis was conducted using an experimental model incorporating wind patterns to determine which metals could be traced downwind of the UNGD site. Previous studies of UNGD operations indicated that 1km might be the extent of measurable emissions from the well pad. Results of this study seem to indicate that well pad emissions may be measurable at distances of at least 7 km. Magnesium (Mg) concentrations, in correspondence with wind patterns, were consistently proportional to other elements (barium, strontium, vanadium) at each sampling site. These data suggest that Mg may be a good trace element to detect the reach of emissions from UNGD point sources in the Marcellus Shale region allowing even complex topographic and meteorological conditions to be modelled and confounding sources of similar emissions to be discounted. Additionally, the data appear to lend credence to recent epidemiological studies showing effects of UNGD as far out as 15 km and suggest that UNGD air emissions may be an exposure agent to communities living even some distance from UNGD facilities. Future studies are needed to further explain the off-site reach of UNGD emissions and to characterize their potential toxicity.

Obeng, Joyce

59

Medicine, MICB, Basic Science

Desmoplakin expression induced by the novel prolyl hydroxylase-3 inhibitor AKB-6899 suppresses breast cancer cell migration and promotes aggregation

The purpose of this study is to: 1) determine the ability of a novel small molecule inhibitor of prolyl hydroxylase-3, AKB-6899, to induce mRNA and protein expression of Desmoplakin (DSP) in metastatic human breast tumor cells; 2) evaluate DSP function in regulating tumor cell migration and aggregation; 3) assess toxicity on both normal mammary epithelial and breast tumor cells; and 4) in ongoing work, assess its potential as a treatment for metastatic breast cancer using patient-derived xenografts (PDX) in vivo. DSP is a member of the plakin family and major protein component of the desmosome. It serves as the anchoring protein for keratin cytoskeletal filaments intracellularly and cadherin proteins extracellularly to maintain strong adhesive junctions between cells. Clinically, DSP expression is reduced as breast cancer progresses and its loss predicts a poor prognosis and increased risk of metastasis. We demonstrate that AKB-6899 augments DSP mRNA expression in both mouse and human breast cancer cells by qRT-PCR and DSP protein expression using immunofluorescence microscopy. More importantly, we show that this up-regulation of DSP induces functional changes in tumor cells by significantly increasing tumor cell aggregation and decreasing cell migration on a Radius 2-D Cell Migration plate and on a 3D nanofiber-coated matrices. These effects are observed using concentrations of AKB-6899 that are not toxic to the cells as shown by XTT and Trypan Blue exclusion assays. In summary, our pre-clinical data supports the potential for AKB-6899 as a novel therapy for metastatic breast cancers which lose DSP expression as they progress.

O'Dell, Deidre

37

Medicine, Neuroscience, Basic Science

Beyond Neuronal Track Tracing with HSV1 H129

Transynaptic viral tracers have been used as a tool in neuroscience for many years. These viruses are capable of traveling through the nervous system by infecting neurons with direct synaptic contacts. These techniques have been used to not only map the neuroanatomical pathways of various circuits but also manipulate the cells infected with virus. However, we do not know how functional neurons are once they are infected with specific viral strains. H129 is an encephalitic herpes simplex virus 1 (HSV1) obtained from a clinical isolate. This neurotropic transynaptic virus enters neurons through the dendrites, replicates in the nucleus, and then travels to the axon terminal via anterograde axonal transport. Once the virus reaches the terminal, it is released at the synapse onto the dendrites of an uninfected neuron. Initially, we used H129 to label the synaptically linked neurons from the trigeminal nerve (V1) to the deep cerebellar nuclei (DCN), especially in the anterior interpositus nucleus (AIN), that underlie learning in the eyeblink conditioning paradigm. Eyeblink conditioning is the development of a conditioned eyeblink response to a conditioned stimulus (tone) that is paired with an unconditioned stimulus (periorbital shock). Indirect evidence suggests this behavioral paradigm involves modulation of the neurons in the cerebellum, particularly in the AIN, of the eyeblink conditioning circuit (EBCC). Eventually, we planned to locate individual, virally-labeled neurons in the EBCC to compare the synaptic and electrophysiological properties of cells from conditioned animals with cells from animals that received explicitly unpaired presentations as controls or were naïve. While H129 allowed us to map the EBCC from the trigeminal nerve to the AIN, functional studies of the cells comprising the pathway were deemed to be next to impossible. The attributes of this transynaptic virus that enables it to travel from neuron to neuron may limit its applicability for uses other than track tracing. By the time H129 reaches the AIN, cytotoxicity and other host defenses have rendered the neurons unusable for further study. Viral-infected neurons have either died from necrotic cell death or have become stripped of synapses by the time H129 reaches the AIN.

Overholt, Tyler

111

Medicine, School of Medicine, Clinical Sciences/Epidemiology

Female Sexual Dysfunction: A West Virginia University Clinical Experience

Introduction: 40% of women in the United States experience concern with regard to sexual function. Female sexual function (FSF) can be broken down into different categories based on the domain involved, including desire, arousal, orgasm, and pain. There are multiple causes for FSF including physical, hormonal, and psychological etiologies, and patients may have additional risk factors that contribute to the dysfunction experienced including depression, obesity, and hypertension. This is especially relevant in West Virginia, which ranks among the highest for several of these risk factors. The presence of sexual dysfunction in patients with interstitial cystitis (IC) is significant and well documented. Herein, we report the data on 362 subjects indexed by the presence or absence of IC and compare the degree of sexual dysfunction associated with the disease. **Methods:** Domain values were obtained by employing the Female Sexual Function Index (FSFI), developed by Rosen, et. al,. This 19-item questionnaire evaluates FSD in six domains. Data was analyzed on an item-for-item basis and by the six domains of sexual dysfunction for our patients and compared to two control groups. The first consisted of 131 healthy volunteers (Rosen, 2000) and the second consisted of 127 patients with Female Sexual Arousal Disorder (FSAD). Statistical significance was determined with one-way ANOVA testing ($P < 0.05$). **Results:** WVU patients with IC scored the lowest in arousal, lubrication, and orgasm, and had the lowest scores in each category compared with all other groups ($P < 0.001$). WVU patients without IC scored the lowest in arousal and desire, and had worse scores than the control in all categories. **Conclusion:** This study is the first exploration of the Urologic patients in West Virginia with regard to FSF, and it highlights a vastly significant amount of sexual dysfunction within this population. West Virginia in 2015 had the 47th worst health ranking in the United States, with especially high prevalence of smoking, obesity, physical inactivity, heart disease and diabetes. Understanding the physical and psychological causes of female sexual dysfunction as well as the category of sexual function affected is critical for properly treating patients for their specific need.

Papenberg, Brenen

70

Medicine, Neurobiology & Anatomy, Basic Science

Novel Functions of 11q13 Transcripts in Invasive Late Stage Appalachian Head and Neck Squamous Cell Carcinoma

Incidence and mortality rates for head and neck squamous cell carcinoma (HNSCC) vary geographically. Appalachian residents consume tobacco products to a greater extent than national averages, a risk factor known to promote HNSCC through increased genomic instability. The most common genomic abnormalities in HNSCC is amplification of the chromosome 11q13 region. 11q13 amplification enhances tumor progression and poor outcome due to protein overexpression. Transcriptome analysis of HNSCC with 11q13 amplification indicates that 13 out of 17 amplified genes are overexpressed, including the oncogenic cell cycle gene *CCND1* (cyclin D1). Recently, 3'UTRs of select mRNAs have been shown to function as positive regulators of cancer progression by sequestering tumor suppressive microRNAs (miRs) or by interacting with 3'UTR AU-rich sequence element (ARE) binding proteins (ARE-BPs) responsible for transcript regulation. Thus, the 3'UTR regions of elevated 11q13 transcripts may accelerate HNSCC progression by titrating tumor suppressive elements required for effective oncogenic progression normally present in non-amplified cancer. The purpose of this project is to determine if the 3'UTR regions of transcripts produced by 11q13 amplified genes contribute to HNSCC progression. The overall hypothesis is that 11q13 amplification contributes to poor HNSCC outcome by increasing cytoplasmic 11q13-derived transcripts that serve as competing endogenous (ce)RNAs to collectively sequester tumor-suppressive miR and ARE-BPs. Predictive algorithms and secondary TCGA data analysis indicates that the *CCND1* 3'UTR contains multiple miR response elements expected to bind known tumor-suppressive miRs. Patient outcome data indicates that *CCND1*-amplified patients with 3'UTR containing transcripts have poorer overall survival than patients with cyclin D1 overexpression, but lacking the 3'UTR. In addition, the 11q13-amplified gene *PPFIA1* (PTPRF interacting protein alpha 1) 3'UTR regions contain numerous AREs that interact with ARE binding proteins (ARE-BPs). 11q13 amplified patients with *PPFIA1* transcript overexpression also have a worse prognosis. Functional assays designed to evaluate the effect of the *CCND1* and *PPFIA1* 3'UTR on HNSCC cell cycle, proliferation, migration are in progress. Identification of a tumor-promoting effect from 11q13 transcripts provides alternative avenues for therapeutic intervention in this most aggressive form of HNSCC by potentially identifying novel druggable transcription targets, in addition to protein-based precision medicine strategies.

Patterson, Jessica

41

Medicine, Neuroscience, Basic Science

Roles for Dendrites in Neural Circuit Formation

The proper formation and morphogenesis of dendrites is critical for the establishment and regulation of network connectivity. The development of a new model system for studying dendrite geometry has led to the view that axons and dendrites work in concert to define mature innervation topology. Characteristic of other developing neural systems, calyx of Held (CH) innervation of principal neurons of the medial nucleus of the trapezoid body (MNTB) bears the hallmarks of initial growth and elaboration of synaptic connections followed by strengthening and pruning. Using 3D ultrastructural analysis, we demonstrate that the growth and particular shapes of dendrites are intimately tied to competition between presynaptic inputs during neural circuit assembly. To quantify the growth dynamics of mice neural structures from postnatal day (P) 2 to 9, serial block-face scanning electron microscopy (SBEM) was used to collect nanoscale resolution three-dimensional representations of neurons and their synaptic inputs. Morphological maturation of dendrite architecture was quantified by Sholl analysis, Stahler order, surface area, and proximal dendrite count. Quantification of synaptic contacts and apposed surface area between dendrites and axons indicated the integral and dynamic relationship between dendrite growth and the formation of connections in the nervous system. Dendritic structure and innervation was found to vary with the state of competition between terminals, and axon-dendrite association and axodendritic synapses may be a critical step in the innervation of the cell body via the calyx of Held. Data showed the convergence of multiple inputs onto large elaborate dendrites at P2, followed by a significant decrease in dendrite branching, number, surface area, and axodendritic synapses as competition resolved and neurons matured. These findings suggest that dendrites grow and branch, perhaps to capture passing axons, and then may direct axons to the soma even as branching is diminishing and entire dendrites are removed.

Petrisko, Tiffany

55

Medicine, Neurobiology and Anatomy, Basic Science

Peripheral viral challenge triggers hippocampal synthesis of inflammatory proteins

Peripheral viral infections increase seizure propensity and intensity in susceptible individuals. We have modeled this comorbidity by demonstrating that the acute phase response (APR) induced by intraperitoneal injection (i.p.) of the conventional viral mimetic, polyinosinic-polycytidylic acid (PIC), renders the brain hypersusceptible to kainic acid (KA)-induced seizures. In a quest to identify molecular substrates of this hypersusceptibility, we profiled gene expression in the hippocampus, the ictal site of KA-induced seizures. This analysis revealed upregulated expression of a plethora of inflammatory genes at the message level. Here, temporal changes of the most upregulated species were determined at the protein level. Briefly, eight-week old female C57BL/6 mice were i.p. injected with 12 mg/kg of PIC and inflammatory proteins were quantified by ELISA over the time frame encompassing seizure hyperexcitability (0-94 h). We found a robust generation of three chemokines. CXCL10 showed the highest increase reaching ~800 pg/mg of protein 6-12 h after PIC challenge. CXCL1 and CXCL2 were elevated to ~90 and ~14 pg/mg of protein, respectively. While CXCL1 and CXCL2 levels rapidly dwindled by 24 h, the decrease in CXCL10 level was protracted up to 72 h post PIC. The hippocampus also featured a modest increase in the synthesis of complement proteins, i.e., Cfb, C3, C8 and C9. Moreover, there was ~3 fold increase in the levels of anaphylatoxins C3a and C5a, indicating the activation of the complement cascades. The levels of the canonical neuromodulatory cytokines, TNF α and IL1 β , were not changed. Our results indicate that the production of CXCL10 might drive the development of seizure hypersusceptibility induced by peripheral viral challenge.

Pilkerton, Courtney

127

Other, Medicine/Epidemiology, Clinical Sciences/Epidemiology

Influence of individual and community socioeconomic factors on cardiovascular health in the United States

Introduction: Despite advances in treatment and decreases in risk factors, cardiovascular disease remains the cause of 1 in 3 deaths in the United States. A thorough understanding of health determinants requires inclusion of factors at multiple levels of proximity to individuals. The objective of this study was to identify the characteristics of individuals and the areas in which they live that promote cardiovascular health. Methods: 2011 Behavioral Risk Factor Surveillance System survey data were used to calculate American Heart Association's cardiovascular health index (CVHI) for individuals. County variables were abstracted from Area Health Resource File. Poisson regression was used to determine the association between individual/county characteristics and CVHI. Results: Females had a 12.0% (12.0, 13.0) higher CVHI than males. Individuals identifying as non-Hispanic black had a 7.0% (6.0, 8.0) higher CVHI than non-Hispanic whites. An individual's education and income had a dose response association with CVHI. A 10% increase in the number of college graduates in a county was associated with 4.0% (4.0, 4.0) higher CVHI. There was a significant interaction ($p < 0.01$) between an individual's income level and the median household income of the county lived in and ($p < 0.01$) between an individual's race/ethnicity and the ethnic density of the county in which they live. Conclusion: Both individual and county demographic characteristics were associated with individual-level CVHI and county demographic characteristics can modify the relationship between individual factors and CVHI. This information can assist public health and government agencies in developing priorities and evaluating the potential effectiveness of policies and programs.

Pinti, Mark

21

Pharmacy, MBRCC, Basic Science

Role of NEDD9 in Mammary Tumor Formation and HER2+ Breast Cancer

Neural Precursor Cell Expressed, Developmentally-Downregulated 9 (NEDD9) is a key scaffolding protein overexpressed in several cancer types. NEDD9 is involved in receptor tyrosine kinase signaling and has been implicated in migration, invasion, and metastasis. Previous work has shown that deletion of NEDD9 (KO) in a MMTV-neu(erbB2/her2) mouse model of her2-driven tumorigenesis decreases spontaneous tumor formation up to 90% when compared to MMTV-her2 mice with wild type NEDD9. To further elucidate the role of NEDD9 in HER2+ breast cancer initiation we developed a conditional Cre-dependent NEDD9 overexpressing transgenic mouse strain. This strain was crossed with MMTV-Cre to produce specific upregulation of NEDD9 only in mammary epithelium followed by crossing with MMTV-neu/her2 overexpressing line. The resultant mouse strains: MMTV-Cre/her2/NEDD9, MMTV-Cre/NEDD9 and MMTV-her2 were assessed for the rate of spontaneous tumor initiation and progression. Our findings indicate that Cre/her2/NEDD9 mice develop tumors twice faster than Cre/her2 mice and succumb to disease earlier. Interestingly, nearly all MMTV-her2 tumors have significantly elevated levels of endogenous NEDD9 when compared to non-transformed mammary epithelial cells from the same animal, suggesting that upregulation of NEDD9 is required for her2 driven tumor initiation. It has previously been shown that MMTV-her2-NEDD9 KO mice have a lower luminal to basal progenitor cell ratio than MMTV-her2 mice. We hypothesize that the ratio of luminal to basal progenitor cells in Cre/her2/NEDD9KI mice compared to Cre/her2 mice will be significantly higher and potentially correlate with earlier onset of spontaneous tumor development. Additionally, to examine the impact of NEDD9 expression on sensitivity of breast cancer cells to HER2+ -targeted therapy we depleted NEDD9 in the BT474 HER2+ breast cancer cell line and treated with increasing doses of lapatinib. Preliminary data suggests that NEDD9 depletion drastically decreases the LD50 of lapatinib from 0.8uM to 0.1uM. Depletion of NEDD9 alone did not significantly change the cell viability. Thus combination of NEDD9 depletion/targeted therapy with lapatinib, and potentially Herceptin, might provide significant therapeutic benefit in treatment of HER2+ breast cancers.

Metabolic monitoring and cage activity in mice exposed to 7-months of electronic cigarette vapor

Introduction: Nicotine is a central nervous system stimulant that increases heart rate and metabolism. Electronic cigarettes (E-cigs), also known as electronic-nicotine-delivery systems (ENDS), are growing in popularity and include flavorings and chemical by-products that may have deleterious consequences. Little is currently known about the long-term effects of E-cig exposure, particularly in the context of wholebody metabolism. We hypothesize that E-cigs would increase basal metabolism similar to that with regular tobacco cigarettes. Methods: C57BL/6 female mice were randomly assigned to 3R4F tobacco-cigarette (N=13), cappuccino flavored E-vapor (18 mg/ml nicotine, N=12), or filtered air (N=13) exposed groups. Animals were exposed 4-h/day, 5-d/wk for total of 8-months. Wholebody metabolic gas exchange and cage activity was measured after the 7-month of exposure using a home-cage chronic laboratory animal monitoring system. Food and water were administered ad libitum. Results: Oxygen consumption (VO₂) during the day was significantly increased in E-cig and 3R4F by 16% and 12%, respectively ($p < 0.05$) compared to Air exposed mice. VO₂ was not different between groups at night. Carbon dioxide production (VCO₂) during the day was also increased in E-cig by 17% ($p < 0.05$) and tended to increase in 3R4F by 14% ($p = 0.06$) compared to Air group, and also was not different at night. Respiratory exchange ratio (RER) was not different between any of the groups during day or night, however heat production (kcal/hr) during day was significantly greater in E-cig mice by 15% and 16% compared to 3R4F and Air groups, respectively ($p < 0.01$). Heat at night also tended to be greater in E-cig mice by 7% and 8% compared to 3R4F and air, respectively, but did not reach significance ($p = 0.18$). Cage movement and activity was not different between groups during the day or at night. Conclusion: Exposure to E-cigs increased VO₂, VCO₂ and heat production, resulting in higher basal metabolism during the day, but not at night. A similar, but slight lower increase in VO₂ and heat during the day, was observed with 3R4F tobacco reference cigarettes. These data suggest chronic E-cig exposure increases basal metabolic activity, but does alter spontaneous cage activity or metabolism when the animals are physically active.

Porter, Keyana

53

Pharmacy, Pharmaceutical Sciences, Basic Science

Long-term administration of hormonal therapy: progestins within three classes

Sex-specific risk factors in AD research are not extensively known; however, recent research shows that allopregnanolone, a metabolite of progesterone, may be involved in the development of AD. Both clinical evidence and experimental animal models show that allopregnanolone is decreased in AD and in vivo, administration of allopregnanolone can alleviate cognitive dysfunction in AD. In summary, researchers have recently demonstrated that allopregnanolone is critical to the targeting of the regenerative response in the brain. As hormonal contraceptives elicit significant decreases in allopregnanolone levels, and reduced allopregnanolone levels are implicated in AD pathogenesis, our long-term goal is to understand how exogenous administration of progestins impacts cognitive function. Our central hypothesis of this project is that long-term administration of hormonal contraceptives, more specifically progestins, will accelerate the development of cognitive dysfunctions and exacerbate AD neuropathology in a triple transgenic (3xTg-AD) mouse model of AD. The rationale for the proposed research is that, once gender-specific risk factors for accelerating the progression of AD are known, they may facilitate innovative approaches to the treatment or the delay of disorders such as AD. My thesis project has three specific aims. Aim 1 will assess the effects of three commonly used progestins, Levonorgestrel (LNG), Medroxyprogesterone Acetate (MPA), and Norethindrone Acetate (NETA), on prosurvival and apoptotic signaling pathways and mitochondrial function, in vitro, using a neuronal cell line and primary culture from 3xTgAD mice; Aim 2 will assess these same progestins on cognitive decline in the 3xTgAD mouse, assessed by behavioral assays; and Aim 3 will assess the ability of exogenous allopregnanolone (ALLO) to antagonize these effects of progestins. Collectively, these studies will substantially advance our knowledge on the role of and mechanisms by which contraceptives may influence age-related cognitive decline. Such knowledge is needed to improve hormonal therapy of millions of women.

Povroznik, Jessica

48

Medicine, Physiology & Pharmacology, Basic Science

Locomotor Effects of a Low-frequency Fire Alarm on C57BL/6 Male Mice

Maintaining appropriate acoustic conditions for animal welfare and data collection is of paramount importance in biomedical research facilities. Negative impacts of disruptive sound are known and can include auditory damage, changes in immune system function, and alterations in behavior (i.e., freezing behavior in response to an aversive/startling auditory stimulus). One type of disruptive sound occurring in animal research facilities is that of fire alarms. To attenuate this issue, many facilities have incorporated the use of low-frequency fire alarms that emit warning tones outside of the rodent audible range; the impact of tones emitted by these devices on laboratory animals has been assumed to be negligible. However, this has not yet been methodically tested in the context of animal behavior outcomes. Thus, our objective was to investigate the impact of low-frequency fire alarm deployment on rodent locomotor behavior using the open field, a test known to be sensitive to disruption by acoustic stimuli. To accomplish this, adult male C57BL/6 mice (n=19) were randomized to one of three alarm exposure groups (No Alarm; 1-min Alarm During Trial; 1-min Alarm 15-min Before Trial), placed in individual, photobeam-activated locomotor chambers, and allowed to explore the arena for a 10-min trial. Results showed that animals who experienced alarm exposure during the trial displayed significantly reduced horizontal locomotion and showed a trend towards reduced vertical locomotion. These data suggest that a brief auditory alarm tone can temporarily disrupt movement in male mice, a valuable insight should an alarm be deployed during behavioral assessment. Further, findings support close collaboration between scientists, husbandry/veterinary staff, and institutional facility staff to ensure appropriate acoustic conditions for research animals are maintained whenever possible.

Cadherin-mediated radio-sensitization in GBM involves down-regulation of anti-apoptotic Bcl-2.

Cadherin-mediated radio-sensitization in GBM involves down-regulation of anti-apoptotic Bcl-2. Walid Radwan MD, Himaly Shinglot MS, Christopher P. Cifarelli MD, PhD; Department of Neurosurgery, West Virginia University, Morgantown, WV Background: Resistance to chemo-radiotherapy in residual GBM remains an obstacle in achieving disease stability following maximal surgical resection. Although molecular characterization of gliomas has emerged as a means of classification/prognostication, few, if any, molecular determinants of glioma are used as a basis for treatment. In our GBM model, we developed a strategy for increasing radio-sensitivity via manipulation of cadherin-mediated cell adhesion. Prior studies demonstrated an increase in radiation-induced cell death in U87MG and U251MG cells in culture following exposure to a recombinant E-cadherin protein, while in vivo studies in NSG mice using the E-cadherin-Fc resulted in increased overall survival following radiation. In the current study, we have delineated some of the downstream effectors of cadherin-mediated radiation sensitization, including members of Bcl-2 family of apoptotic proteins in both normoxic and hypoxic conditions representative of the tumor microenvironment. Methods: Utilizing recombinant E-cadherin-Fc fusion proteins in the U87MG cells, a 2X 100 paired run RNA-sequencing analysis was performed on the Illumina-HiSeq1500 in conjunction with the WVU and Marshall University Genomics facilities. Hypoxic cells cultures were maintained at 1%O₂ and semi-quantitative RT-PCR for Bcl-2 according to MIQE guidelines. Results: E-cadherin-Fc treatment results in a significant reduction of BCL2 (log₂ - 0.76749; p=0.003) compared to control, while hypoxic culture conditions result in a dose-dependent increase in Bcl-2 in radiation resistant U87MG cells following external beam radiation. In addition, there was a dose-dependent increase in BCL2 under hypoxic conditions (log₁₀ 0Gy = 0.617, 4Gy = 1.06, 8Gy = 1.131, 20Gy = 1.754, p = 0.003) in radiation resistant U373MG cells following external beam radiation Conclusion: Increased radiation-induced cell death following E-cadherin-Fc exposure in U87MG cells is associated with a decrease in the expression of anti-apoptotic Bcl-2, normally upregulated following radiation in hypoxic conditions. There is increased expression of anti-apoptotic Bcl-2 in a dose-dependent manner under hypoxic conditions in U373MG cells following external beam radiation.

Raeisi, Nasim (Holly)

116

Pharmacy, Pharmacy, Clinical Sciences/Epidemiology

Retrospective review of Time in Therapeutic Range (TTR) for inpatients receiving warfarin at a large, academic medical center

Retrospective review of Time in Therapeutic Range (TTR) for inpatients receiving warfarin at a large, academic medical center N. Holly Raeisi, PharmD Candidate; Megan Bodge, PharmD, BCOP; Kara Piechowski, PharmD, BCPS Warfarin is an oral anticoagulant that has the longest history of use to prevent thromboembolic disorders. Warfarin has a complex dose-response relationship, which makes it difficult to use safely and effectively. International normalized ratio is a standardized laboratory measurement providing information about a patient's blood clotting tendency. High INR indicates risk of bleeding and low INR correlates with risk of thromboembolism. Therefore, it's critical to keep the INR in an effective therapeutic range based on the indication for use. Time in therapeutic range (TTR) is a tool used to assess how well INR is managed. Higher TTR is correlated with less major bleeding and other thromboembolic complications. Since warfarin has many drug-drug and drug-food interactions and has the potential to cause adverse effects which may be life threatening to patients, it is important to monitor closely. Historically, warfarin has been managed primarily by physicians, especially in an inpatient setting. However, pharmacists' knowledge of drug-drug interactions, pharmacology, and pharmacokinetics makes them ideal candidates to manage warfarin therapy. Our objectives in this project are to identify the TTR for inpatients managed per usual care and identify correlating factors in poor warfarin management. This will be a retrospective chart review of 100 patients who received warfarin at WVU Ruby Memorial Hospital starting October 2016. Patients who are continued on warfarin from home, ≥ 18 years of age, and who are admitted to WVU Ruby Memorial Hospital will be included for review. Anyone newly started on warfarin during the hospitalization will be excluded. . The goal of this project is to establish a baseline for warfarin management as an institution and identify areas of improvement for future management.

Rai, Pragya

112

Pharmacy, PSP, Clinical Sciences/Epidemiology

The association of dipeptidyl peptidase-4 inhibitors use with joint pain among United States adults with type-2 diabetes mellitus

OBJECTIVES: Few recent studies have reported that the use of dipeptidyl peptidase-4 inhibitors (DPP4Is), a class of antidiabetic agents, may be associated with joint pain. The purpose of this study was to examine the association of DPP4i use with joint pain in Type 2 Diabetes Mellitus (T2DM) patients.

METHODS: This was a retrospective cross-sectional study, pooling data from 2012 and 2014 Medical Expenditure Panel Survey. The sample consisted of T2DM patients (n=4,559) over the age of 40 years with (n=3,185) or without (n=1,306) joint pain. DPP4Is were identified from prescription drug files and joint pain was identified from medical conditions files using ICD9CM codes. Chisquare test and logistic regression were used to examine the association between DPP4I use and joint pain.

RESULTS: Among adults with T2DM, 69.9% reported physician-diagnosed joint pain and 7.4% were DPP4I users. There was no significant difference in DPP4I use among those with and without joint pain (7.8% vs 6.3%). Even after adjusting for other factors that may affect DPP4I use, there was not a statistically significant difference in DPP4I use among T2DM adults with and without joint pain (AOR= 1.04, 95% CI= 0.74, 1.48). Adults with prescription insurance (AOR= 1.76, 95% CI= 1.01, 3.04) and public health insurance (AOR= 1.76, 95% CI= 1.02, 3.03) were significantly more likely to use DPP4I as compared to those with no prescription insurance and private health insurance, respectively. Adults who had a heart disease were significantly more likely to use DPP4Is as compared to those who did not have heart disease (AOR= 1.59, 95% CI= 1.18, 2.15).

CONCLUSIONS: DPP4I use was not affected by the presence of joint pain. However, we found that adults with heart disease were more likely to use DPP4I, despite studies reporting an association between DPP4I use and heart failure.

Rellick, Stephanie

170

Medicine, Physiology/ Pharmacology, Basic Science

Evaluation of Hydraulic Fracturing Chemicals on Neuronal Cell Mitochondrial Function

There is concern among residents living near well sites as to whether or not hydraulic fracturing can impact drinking water by releasing chemical additives into the surrounding ground, potentially contaminating both ground water and drinking water. We evaluated the effects of both acute and chronic exposure BTEX on neuronal cells. The chemical we are currently investigating consists of components of raw petroleum products, collectively referred to as BTEX (benzene, toluene, ethylbenzene and xylene), to determine its effects on neuronal cell viability and mitochondrial function in a neuronal cell culture model using the XFe96 Extracellular Flux Analyzer and Calcein AM assays. We will also expand our studies to a murine model of ischemic stroke. We observed that low concentrations of BTEX that are not toxic to neurons leads to an increase in mitochondrial activity. In a pilot animal experiment, we observed that animals will drink water containing BTEX, and can drink the water for 7 days with no visible health effects. Preliminary data suggest that mice receiving an IP injection of BTEX have increased infarction in the cortex and striatum. The increase in mitochondrial activity with low concentrations of BTEX may increase mitochondrial activity initially, but a secondary insult or injury may prevent cells from being able to respond to this damage, resulting in enhanced cell death. We intend to chronically expose mice to low concentrations of BTEX in drinking water, and then induce a transient middle cerebral artery occlusion to see if exposure to BTEX leads to a worse outcome.

Rickards, Allen A

106

Medicine, Neurobiology and Anatomy, Clinical Sciences/Epidemiology

Improving the selection of ideal cartilage grafts during facial reconstruction through morphometric analysis of commonly grafted costal cartilages

Costal (rib) cartilage grafting is a commonly used procedure by otolaryngologists and plastic surgeons in facial reconstruction. In fact, costal cartilage is harvested, shaped, and grafted for aesthetic reconstruction of the nose, auricle, temporomandibular joint, midface, or larynx. Despite the wide utilization of costal cartilage grafts, there is little agreement regarding which cartilage level and which particular portion of each costal cartilage is the most optimal for grafts of varying sizes. Furthermore, there have been few studies dedicated to understanding the shapes of costal cartilage. Therefore, the aim of this cadaveric study was to provide salient measurements that will aid in the selection of optimal costal cartilage harvests. This study aimed to detail the average shapes of the most commonly grafted cartilages (i.e., the 5th, 6th, and 7th rib cartilages). The 5th costal cartilage was determined to have the straightest shape and would therefore be particularly suitable for nasal dorsum onlay grafting. The lateral portions of the 6th and, particularly, the 7th costal cartilages have the most acute curvature. Therefore, the lateral portions of the 6th and 7th costal cartilages, would lend themselves to the 'C'-shaped graft utilized in the reconstruction of the auricle. The data presented in this study represent the geometric morphometric analysis of 96 cadaveric costal cartilages and provide a starting-point for the development of an algorithm that will enable selection of optimal cartilage for facial reconstructive surgery based upon the desired graft size.

Roach, Katherine

57

Pharmacy, PPS, Basic Science

Variations in Nickel Oxide Nanoparticle-Induced Pulmonary Toxicity and Exacerbated Allergic Response Following Acute Respiratory Exposure

Particle size and morphology play critical roles in nanomaterial-induced lung inflammation, but the relationship of these factors to augmentation of allergic response in the respiratory tract is largely unknown. To address this concept, two different sizes of nickel oxide (NiO) particles were characterized and investigated *in vivo*. Dynamic light scattering showed the average particle sizes (APS) were 27 nm for NiO-1 and 190 nm for NiO-2. NiO-1 particles were spherical while NiO-2 particles were more irregular and plate-like. The goal of the study was to assess effects of the different NiO particles on augmentation of allergic response using an ovalbumin (OVA) model. Effects of NiO on the lung were also assessed at critical time points correlating to the OVA model in the absence of OVA. Female BALB/c mice were given a single dose of 40 μ g of NiO-1, NiO-2, or dispersion medium (DM; vehicle control) by oropharyngeal aspiration (OPA) and euthanized at 1, 10, 19, and 29 d post-exposure in the absence of OVA. In the OVA allergy model, mice were similarly exposed to particles or DM on day 0, sensitized to OVA via *i.p.* injection at 1 and 10 d, challenged with OVA at 19 and 28 d via OPA, and euthanized at 29 d. In the absence of OVA, only NiO-2 induced significant and persistent increases in lung injury and inflammation in the lung, but both NiO-1 and NiO-2 increased mediastinal lymph node (LN) size as compared to controls. In the OVA allergy model, the smaller nanoparticles (NiO-1), resulted in an exacerbated airway response following OVA challenge, and increased serum OVA-specific IgE levels as compared to vehicle and allergy controls. Differentially, exposure to NiO-2 significantly increased LN size, yet reduced OVA-specific IgE levels. Overall, results demonstrate that size, and possibly particle morphology, contributed to nickel-based particle-induced pulmonary inflammation and modulation of immune responses in the lung. The larger plate-like particle was capable of inducing a greater degree of pulmonary inflammation; however, the smaller NiO particle exacerbated the allergic response to OVA to a greater degree. Further studies are need to elucidate the mechanisms related to these findings.

Rottgen, Trey

72

Medicine, Biochemistry, Basic Science

Large conductance potassium (KCa1.1) channel mediated potassium secretion provides the driving force for water secretion in organoids from rat distal colon

Organoid culture has been adapted as a method to recapitulate colonic physiology, especially epithelial electrolyte transport in an in vitro model. We tested the hypothesis that K⁺ secretion can provide a novel pathway for water secretion. Colonic crypts, containing Lgr5⁺ cells, were isolated from male Sprague-Dawley rats (n=4) and plated in an extracellular support (Matrigel) supplemented with crypt culture media containing specific niche factors necessary for proliferation and organoid formation. Utilizing an activator (BMS-204352, 10 μ M) of large-conductance of potassium (KCa1.1) channels, we were able to induce swelling of organoids and increase the luminal to total volume ratio that was significantly different from controls (63.3 \pm 4.7 vs. 33.5 \pm 5.2, α <0.05). Paxilline (KCa1.1 blocker, 1 μ M) completely inhibited the BMS-204352 induced swelling and was not significantly different from unexposed organoids (34.4 \pm 3.8 vs. 33.5 \pm 5.2, ns). CFTR-172 inhibitor did not prevent BMS-204352-induced swelling, which was not significantly different from BMS-204352 alone (55.8 \pm 5.6 vs. 63.3 \pm 4.7, ns). We conclude from these data that large conductance of potassium (KCa1.1) channels mediate potassium secretion that contribute to a novel mechanism of water secretion that could be clinically impactful in certain pathophysiological states.

Russell, Ashley

71

Medicine, Physiology/Pharmacology, Basic Science

The Effects of TNF- α on Mitochondrial Function and Alzheimer's Disease Progression: A Vicious Cycle

Both the cause of late onset Alzheimer's disease and the driving force behind its progression are not well understood. Inflammation within the central nervous system, termed neuroinflammation, is a promising candidate for the responsibility of disease progression. Cytokines are a category of small signaling proteins, secreted by many cell types, which act as immunomodulators in response to immune activation. One cytokine of particular interest is tumor necrosis factor-alpha, TNF- α , as it is elevated in both the peripheral blood and cerebrospinal fluid of patients suffering from Alzheimer's disease. TNF- α receptor activation can lead to a number of outcomes, particularly the activation of the transcription factor, NF κ B. Our lab has recently identified a NF κ B binding site on the promotor region of the microRNA-34a gene. MicroRNAs (miRs) are small, non-coding RNA molecules that can repress protein translation by base-pairing with mRNA. miRs function in a one to many ratio, in that one miR can bind to several different mRNAs, and one particular mRNA can be paired with many different miRs. miR-34a has been found to bind to several key mitochondrial electron transport chain mRNAs. If miR-34a is suppressing translation of proteins for these mRNAs, replacement during normal protein turnover will not occur, and the electron transport chain will collapse. We tested the hypothesis that TNF- α exposure increases exosomal secretion of miR-34a. After a 24 hour exposure period, exosomes collected from the media of TNF- α treated HT-22 cells contained significantly higher levels of miR-34a than non-exposed controls. We also tested the hypothesis that TNF- α exposure induces mitochondrial dysfunction. After a 24 hour exposure period, HT-22 cells showed significant decreases in ATP production, spare capacity, and maximum respiration. These data support the hypothesis that TNF- α exposure leads to increased expression of miR-34a, and subsequent mitochondrial dysfunction after a 24 hour exposure period.

Sanchez, Cristina L.

171

Medicine, Microbiology, Immunology and Cell Biology, Postdoc

PERK-dependent regulation of IL-6 family of cytokines during ER stress

The endoplasmic reticulum (ER) plays a critical role in the cell. During neurodegeneration, misfolded proteins accumulate within the lumen of the ER, and perturb homeostasis. In response to misfolded protein stress, or ER stress, the cell initiates the highly-conserved unfolded protein response (UPR). The ER stress-sensor PERK regulates one of three signaling branches that promotes adaptation to ER stress. Sustained PERK activation, however, is associated with the neuroinflammatory events that may facilitate neurotoxicity. IL-6 production, which is increased in neurological diseases, has been linked to PERK signaling through a JAK1-dependent mechanism in astrocytes. Nevertheless, how PERK regulates other members of the IL-6 family of cytokines, including OSM, IL-11, CNTF and LIF, during ER stress remains to be elucidated. To understand this interplay, we have analyzed the expression of the IL-6 family of cytokines in vitro in primary murine astrocytes. Additionally, we compared the differential expression of the IL-6 family members between astrocytes and macrophages following ER stress induction. Interestingly, our results suggest a divergent PERK-dependent regulation of both the IL-6 family of cytokines and between these cell types. Overall, this study provides mechanistic insight into how ER stress coordinates inflammatory signaling in different cells types involved in neuroinflammatory and neurodegenerative diseases.

Saralkar, Pushkar

23

Pharmacy, Pharmaceutical Sciences, Basic Science

Sparing of brain tissue by the mitoNEET agonist NL-1 in cerebral reperfusion injury after stroke

Ischemic stroke affects a significant number of patients each year. Based on the finding that the antidiabetic drug pioglitazone is neuroprotective in stroke, we evaluated a novel mitoNEET (CISD1) ligand (NL-1) devoid of peroxisome proliferator-activated receptor gamma (PPAR- γ), in a murine t-MCAO (transient middle cerebral artery occlusion) model of ischemic stroke. Mice were treated with NL-1 (10 mg/kg, i.p.) 30 minutes before reperfusion injury and allowed to recover for 24 hours. We found that NL-1 reduced the infarct volume by 43% and reduced edema by 58%. A kinase panel screen indicated that NL-1 does not inhibit directly any kinases significantly with only a modest inhibition of the WNK lysine deficient protein kinases (WNK3>WNK2>WNK1). NL-1 was additionally found to decrease reactive oxygen species production with an IC50 of 5.95 μ M. Taken together with respiration data on isolated mitochondria our findings suggest that NL-1 protects against the reperfusion injury in stroke via direct interaction with mitochondria. This is the first report showing the mitoNEET ligand NL-1 as neuroprotective in cerebral reperfusion-injury.

Schroer, Adam

63

Medicine, Physiology and Pharmacology, Basic Science

Novel insights into the role of Regulator of G Protein Signaling-21 in perception of taste

The gustatory system is key in regulating the intake of spoiled foods, toxins, and nutrients. Understanding the physiological regulation of taste should enhance our ability to alter the palatability of therapeutics and other nutrients, thus facilitating intake of substances to promote overall health. Bitter, sweet, and umami (savory) tastes are detected by T1R or T2R family G protein-coupled receptors (GPCRs) that associate with heterotrimeric G proteins and initiate intracellular signaling cascades after activation by tastant binding. 'Regulators of G protein Signaling' (RGS proteins) act as $G\alpha$ -directed GTPase-accelerating proteins (GAPs) and are known to regulate this underlying G protein activity and, thus, the timing and amplitude of GPCR-initiated signaling events. RGS21, among the most recent members of the RGS protein superfamily to be cloned, is expressed selectively in taste receptor cells of the taste bud. We recently reported the creation of an *Rgs21::RFP* BAC transgenic reporter mouse, which confirmed that *Rgs21* expression is highly enriched in the chemosensory cells of the taste bud with minimal expression in other tissues. By measuring the separate effects of RGS21 over- and under-expression in a tastant-responsive epithelial cell line, we have recently shown that RGS21 regulates bitter tastant signaling through acute changes in cAMP and Ca^{2+} second messengers. To investigate the role RGS21 plays in taste sensitivity *in vivo*, we have now created *Rgs21^{fl/fl}* mice and bred them with *CMV::Cre* driver mice to generate constitutive RGS21-null mice. To ensure that loss of RGS21 did not affect the viability of taste cells, we assessed the morphology and number of taste buds in the circumvallate papilla. RGS21-null mice have no alterations in taste bud morphology or number as compared to wild-type mice. These mice were further tested in two-bottle preference studies. In the absence of RGS21 expression, mice were found to have blunted aversion to the bitterant denatonium and a blunted preference to the sweetener sucrose (metabotropic responses), whereas aversion to the sour tastant HCl (ionotropic response) was unchanged. Future experiments are needed to determine if RGS21 operates solely within the taste receptor cell, and if RGS21 directly modulates signaling by T1R / T2R tastant receptor agonists.

Sechrest, Emily

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Pharmacy, Pharmaceutical and Pharmacological Sciences, Basic Science

The β 2-subunit of the Na⁺,K⁺-ATPase is palmitoylated in retinal neurons

Maintenance of Na⁺ and K⁺ gradients by the Na⁺,K⁺-ATPase pump is crucial for proper cellular function and survival. The Na⁺,K⁺-ATPase is a heterodimer, made up of one α - (catalytic) and one β - subunit, which is integrated into the plasma membrane. To date, four α - (α 1, α 2, α 3, α 4) and three β - (β 1, β 2, β 3) subunit isoforms have been identified and have been shown to be expressed in a tissue-specific manner. In photoreceptor neurons, the Na⁺,K⁺-ATPase maintains the photocurrent required for transduction of visual signals to downstream neurons (bipolar cells, ganglion cells). In photoreceptors, the Na⁺,K⁺-ATPase is comprised predominantly of ATP1 β 2 and ATP1 α 3. Previous research demonstrates that genetic ablation of *Atp1b2* results in rapid degeneration of photoreceptors, and loss of retinal ATP1 α 3 expression. Interestingly, this phenotype is not rescued by substitution of ATP1 β 2 with ATP1 β 1, highlighting a unique requirement for ATP1 β 2 in photoreceptor function and survival. Nevertheless, the specific role of ATP1 β 2 in photoreceptor neurons remains unclear and is the focus of this study. Using acyl resin-assisted capture (acyl-RAC), our lab has determined that ATP1 β 2 undergoes S-palmitoylation, a reversible, post-translational lipid modification. Our prediction analysis software, CSS-Palm, predicts the 10th amino acid (Cys-10) in ATP1 β 2 to be palmitoylated, which is unique to the β 2 isoform. Palmitoylation was further confirmed in mammalian cell culture by metabolic labeling with 17-ODYA, a palmitoyl chemical analog. From these data, we observe loss of palmitoylation of ATP1 β 2 following a cysteine to serine (C10S) mutation. Furthermore, we see that wild-type ATP1 β 2 and ATP1 α 3 are enriched at the plasma membrane, while mutant ATP1 β 2 and ATP1 α 3 mislocalize to the cytosol in cell culture studies. Based on these results we demonstrate that palmitoylation of ATP1 β 2 plays a major role in its association and ATP1 α 3, as well as proper trafficking of this heterodimeric enzyme to the plasma membrane. Understanding the importance of palmitoylation of ATP1 β 2 is crucial in elucidating the role of this enzyme in maintenance of proper visual function and structure of the retina.

FpvA Peptide Vaccine Confers Protection against *P. aeruginosa* Infections in Acute Murine Pneumonia.

Pseudomonas aeruginosa is one of the major opportunistic pathogens responsible for hospital-acquired infections associated with high morbidity and mortality. The ability to adapt to different environments and multi-drug resistance make this bacterium a major health concern. Vaccination against *P. aeruginosa* could provide a solution against these infections. However, despite all the research efforts, there is still no licensed vaccine available. Efficient iron uptake is important for *P. aeruginosa* to colonize and sustain its growth in the host. In order to produce a vaccine against *P. aeruginosa*, we developed a synthetic peptide vaccine targeting one of its major siderophores, ferripyoverdine receptor (FpvA), which is highly conserved between different isolates and upregulated during the acute infections. In order to increase the immunogenicity, we conjugated the peptide antigens to the keyhole limpet hemocyanin (KLH) as a carrier protein. We used a murine vaccination/infection model to evaluate the effectiveness and immunogenicity of FpvA peptides and KLH-conjugated FpvA peptides vaccines compared to heat-killed *P. aeruginosa* and adjuvant only vaccinated groups. CD1 mice received a primary vaccine followed by a booster intranasally with curdlan as an adjuvant. Blood samples were collected by tail bleeding every week and by cardiac puncture after challenge for ELISA serum antibody detection assays. Lung tissue lysates and nasal washes were serially diluted and plated for CFU counts. Vaccination with FpvA-KLH peptides significantly decreased bacterial burden in nasal cavities and lung. The lung weight increased in adjuvant only group compared to other vaccinated groups, which suggest vaccination reduced inflammation and edema. IgG antibody titers against FpvA were detected in the sera of FpvA-KLH peptides vaccinated groups which indicates that KLH conjugation increased the recognition of the peptides by the immune system. We further analyzed lung homogenates of each mouse by flow cytometry analysis. The results showed differences in lymphoid and myeloid cell recruitment between the different vaccine groups. Altogether, these observations suggest that KLH conjugation increased overall immunogenicity and recognition of the FpvA peptides, which provided protection against *P. aeruginosa* acute pneumonia infections.

Trends in Utilization of Smoking Cessation Agents before and after the Passage of FDA Boxed Warning in the United States

Background: Despite lack of robust evidence on the adverse neuropsychiatric effects of bupropion and varenicline, the two commonly prescribed smoking cessation agents, in 2009, the FDA required a black box warning (BBW) for these two medications. We investigated if there was a decline in use of bupropion and varenicline after the BBW by comparing the percent using these medications before and after BBW. Methods: We conducted a retrospective observational study using data from the Medical Expenditure Panel Survey from 2007 to 2011. The study sample consisted of adult smokers, who were advised by their physicians to quit smoking. Unadjusted analysis using chi-square tests and adjusted analyses using logistic regressions were conducted to evaluate the change in bupropion and varenicline use before and after the BBW. Secondary analyses using segmented regression were conducted to assess significant differences in the use of these medications over time. Results: Among users of varenicline, we observed a statistically significant decline from 10.6% in year 2007 to 2.3% in 2011 (p value <0.05). In the logistic (Adjusted Odds Ratio=0.35, 95% CI= 0.22-0.57) and segmented regressions (Odds Ratio =0.51, 95% CI=0.31-0.82) smokers who were advised to quit smoking by their physicians were less likely to use varenicline in the post-BBW period as compared to pre-BBW period. We did not observe significant differences in bupropion use between the pre- and post-BBW periods. Conclusion: The passage of the FDA boxed warning was associated with a significant decline in the use of varenicline, but not in the use of bupropion.

Shah-Khan, Sardar

15

Medicine, Department of Internal Medicine/Digestive Diseases, Resident

Using the Plan-Do-Study-Act Approach to Improve Inpatient Colonoscopy Preparation

In-patient colonoscopies with poor preps provide challenges to gastroenterologists performing the procedure. Poor preps can make the procedure difficult to perform, and can require repeat procedures to be performed. The aim of this project is to increase the quality of inpatient colonoscopy preparations. The plan-do-study-act approach will be used to implement this quality improvement project. Inpatient colonoscopies from November, December, and January will be evaluated to determine the quality of preps. An intervention program will then be conducted to improve the quality of these preps. This intervention program will be three fold: #1) the implementation of an Epic order set to standardize the process of ordering colonoscopies. 2) distributing a patient education handout explaining why a good prep is important 3) direct education to physicians (hospitalists, residents) and nursing staff on the prep process and its importance. After the intervention phase, the quality of preparations over a couple month period will be re-evaluated, and the effects of the intervention will be determined. This intervention will hopefully improve the quality of preps, which will lead to better outcomes, reduced length of stay, and better patient satisfaction.

Shapiro, Scott

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Medicine, Otolaryngology-Head and Neck Surgery, Resident

Total Malleus Removal During Cholesteatoma Surgery: An Analysis of Residual Disease and Hearing Outcomes

Background: Cholesteatoma is a destructive and expansile focus of ectopic keratinizing squamous epithelium in the middle ear and mastoid space. It is the most common cause of disruption of the ossicular chain, the bones of the middle ear which conduct sound from the eardrum into the cochlea. Cholesteatoma often causes hearing loss, chronic drainage from the ear, and intracranial complications due to its propensity to erode and destroy the bones of the middle ear and skull base. A tympanomastoidectomy is a surgical procedure performed to remove cholesteatoma and reconstruct the ossicular chain, but despite surgery residual disease is common and even expected in extensive cases. The removal of middle ear bones such as the malleus to increase exposure of the middle ear cavity during surgery is controversial, as it is thought that it may worsen hearing loss. Objective: Determine the effect of complete removal of the malleus on rate of residual disease and hearing outcomes. Methods: We reviewed 286 operative records and their corresponding clinic and audiogram reports of all patients who underwent surgery for cholesteatoma between 2009-2016 at Ruby Memorial Hospital. We performed multivariate logistic regression to model the rate of residual disease and degree of hearing improvement based on whether malleus was removed or left intact while controlling for extent of disease, type of reconstruction, and number of previous surgeries. Results: The adjusted odds ratio for residual disease when the malleus was removed was 0.285 (0.074-1.14) which approached but did not meet statistical significance ($p = 0.076$). The adjusted odds ratio for post-operative conductive hearing loss of less than 20 decibels when the malleus was removed was 1.748 (0.434-7.04), which was a not a statistically significant difference ($p = 0.431$). Conclusions: The increased exposure of the middle ear provided by removal of the malleus may decrease the rate of residual disease. As it does not compromise hearing outcomes, it should be considered during surgical removal of cholesteatoma.

JAK1 Regulates ER Stress-Induced Gene Expression in Astrocytes

Many diseases including neurodegenerative disorders such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are associated with the accumulation of misfolded proteins in the endoplasmic reticulum (ER). ER stress occurs when the protein folding capacity of the ER is overwhelmed, resulting in the initiation of the Unfolded Protein Response (UPR) in attempts to regain homeostasis. However, unresolved UPR activation leads to cell death and inflammation. The UPR is initiated, in part, by the trans-ER membrane kinase PKR-like ER kinase (PERK). Recent evidence indicates that ER stress and inflammation are linked, and we have shown that this involves PERK-dependent Janus Kinase (JAK) 1 signaling. This signaling provokes the production of inflammatory genes such as Interleukin-6 (IL-6) and chemokine (C-C motif) ligand 2 (CCL2). Here, siRNA knockdown and RNA-seq reveals JAK1 regulates approximately 20% of ER stress-induced gene expression. JAK1 traditionally is associated with cytokine receptors and mediates inflammatory signaling by stimulating Signal Transducers and Activators of Transcription (STATs) to influence immune-associated gene transcription. However, of the over 500 JAK1 dependent genes identified in this study, less than half contained STAT binding motifs within the gene promoters. This suggests JAK1 mediates additional, unconventional signaling during ER stress. By using JAK1 siRNA knockdown and a JAK1/2 kinase inhibitor, AZD1480, we have shown that JAK1 modulates gene expression using discrepant kinase-dependent and independent mechanisms when stimulated with ER stress and cytokines in astrocytes. Oncostatin M (OSM) and ER stress-induced induction of inflammatory genes such as IL-6, CCL-2, and cyclooxygenase-2 (COX-2) was dependent on JAK1 kinase activity while expression of stress related genes NUA family SNF1-like kinase 2 (NUAK2) and Growth Arrest and DNA Damage Inducible Alpha (GADD45 α) were independent of JAK1 kinase activity. This implies JAK1 is a major driver of transcriptional adaptation in response to ER stress and JAK1 may have uninvestigated kinase-independent roles in controlling gene expression.

Sivaneri, Mona

133

Medicine, Health Sciences, Masters

Dental Student Forensic Knowledge and Skills

Background Dental forensics is an area of dental research and knowledge in which students receive limited exposure. The purpose of this research was to evaluate dental student knowledge about dental forensics and to evaluate dental student skills in comparing radiographs. **Methods** Dental students (N=152) were provided 10 radiographs of extracted teeth. One of the radiographed teeth was heat-altered to 600°C for 15 minutes. The students were asked to match the heat-altered tooth's radiograph to one of the 10 radiographs. A 10-question survey concerning dental forensics was also presented to the students. **Results** There were 92.1% of dental students who were able to correctly identify a heat-altered tooth's radiograph from the 10 radiographs provided. Of the 10 questions provided, 5 had a correct response rate above 70%. **Conclusion** Dental students were successful in matching a dental radiograph of a heat-altered tooth and its original radiograph. However, there is a need for current and emerging information about dental forensics.

Smith, Catherine

30

Medicine, Neurobiology and Anatomy, Basic Science

Investigating the in vivo function of Map3k12 binding inhibitory protein (Mbip) during mammalian development

Effective cortical circuit activity relies on a balance of excitation and inhibition, which is regulated by the modulatory effects of GABAergic inhibitory interneurons. Perhaps not surprisingly, many neuropsychiatric disorders such as epilepsy, autism, and schizophrenia, are thought to result from the dysregulation of interneuron function in cortical circuitry. Our lab has shown that the c-Jun N-terminal kinase (JNK) signaling pathway is necessary for the organized and timely entrance of interneurons into the cortex. We have extended our study of JNK signaling throughout development using novel genetic knockout mice to study Map3k12 binding inhibitory protein (Mbip). Mbip is a protein that can regulate JNK signaling by directly binding and inhibiting Map3k12 in the cytosol and enhancing or repressing the expression of JNK genes in the nucleus. We hypothesize that Mbip plays an essential role in proliferation, differentiation, and migration of interneurons during development, because this gene is expressed in the medial ganglionic eminence (MGE), where most cortical interneurons are born. We have created two mouse lines with alleles designed to either constitutively or conditionally ablate Mbip in vivo. Global Mbip knockout is lethal by embryonic day 12.5, indicating that Mbip is essential for mammalian development. Overt morphological abnormalities are observed by e8.5. We intend to assess developmental abnormalities by comparing patterns of proliferation, differentiation, and migration using both in vivo immunohistochemical and molecular analyses and in vitro embryo culture methods at e8.5 and earlier ages. To study the effects of Mbip on cortical inhibitory interneuron development, we have used an MGE-specific driver line to conditionally delete Mbip from cortical interneuron precursors. Using this model, we can assess the role of Mbip during interneuron development, differentiation, and function. This work will provide novel insight into the intracellular signaling mechanisms controlling early embryonic development, and to how those intracellular mechanisms affect the migration of cortical interneurons, which will contribute to a better understanding the formation of cortical circuitry and may aid in elucidating the etiology of developmental and neuropsychiatric disorders.

Snodgress, Michelle

153

Medicine, Medical Laboratory Sciences, Undergraduate

A Comparison of Consistency in Glucose Testing Results Between the Pointe 180 Analyzer™ and the Abbott Architect™

Incidence of diabetes, most notably Type 2, has been increasing tremendously in recent years. Approximately 8% of adults in the United States have been diagnosed with diabetes making it the most common carbohydrate metabolism disorder.¹ Due to the severity of complications patients with uncontrolled glucose levels are at risk for, it is crucial that tests measuring glucose are precise. Requesting laboratory analysis of glucose levels is typically the route physicians take to diagnose and monitor progression of diabetes. Glucose testing is the most widely used test of blood chemistry and the main tool for diagnosing the disease.⁴ The purpose of this experiment was to compare how consistent the results from a Pointe 180 Analyzer™, used in the student laboratory of the Medical Laboratory Sciences program at WVU, measuring glucose levels are compared to the Abbott Architect™, used in the Ruby Memorial Hospital Clinical Laboratory. The Pointe 180™ is not approved by the FDA for clinical use in the USA, only for use in research or educational settings.⁸ The results of the Pointe 180 Analyzer™ will be compared to the results of the Abbott Architect™ currently in use at Ruby Memorial Hospital and CLIA standards to see if it could potentially be deemed substantially equivalent to another glucose analyzer and approved by the FDA.

Sprenkle, Neil

25

Medicine, Neuroscience, Basic Science

Endoplasmic Reticulum Stress Transmission among Cells of the Central Nervous System

Improper protein folding and trafficking are common pathological events observed in various cell types in neurodegenerative diseases. If the protein quality control mechanisms of the endoplasmic reticulum (ER) fail to re-establish proteostasis, misfolded proteins accumulate within the lumen of the ER and perturb normal cellular processes. While low-level stimulation of the unfolded protein response (UPR) is considered a beneficial physiological response to acute insult, sustained UPR activation resulting from prolonged ER stress can promote neurotoxicity. Nevertheless, there still remain unanswered questions regarding the cell-extrinsic role of the UPR under normal physiology and how this mechanism is compromised in diseased states. To address this conundrum, we evaluated whether transferring supernatants from ER stressed astrocytes to different cell types could modulate their functional characteristics. Here we demonstrate that ER stressed astrocytes secrete protein mediator(s) which regulate both inflammatory and ER stress responses in other astrocytes and neurons in vitro. Initial exposure to this stress factor(s) confers resistance against subsequent ER stress to neurons by engaging the adaptive signals of the neuronal UPR. However, persistent exposure to this unidentified mediator(s) suppresses the initial protective effect and becomes cytotoxic. Overall, these findings provide insight into the cell-nonautonomous influence of ER stress on cells of the central nervous system. Further understanding the molecular mechanisms underlying this mode of intercellular communication would present novel therapeutic opportunities to treat neurodegenerative diseases.

Sprowls, Samuel

26

Pharmacy, Pharmaceutical Sciences, Basic Science

Radiation induced CNS Damage in Normal Brain During Treatment of Brain Metastases

BACKGROUND: With increased survival achieved by advances in primary cancer treatment, brain metastasis is an ever-growing issue. Standard treatment of brain metastases from primary breast tumors utilizes differing methodologies of radiotherapy and/or adjunctive systemic chemotherapies, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and neurosurgery. Acute side effects from radiation include fatigue, alopecia, headache, and nausea, vomiting, with cognitive impairment developing 2-4 months post-treatment. Herein we hypothesize that radiation treatment may increase permeability in normal brain tissue. **METHODS:** Athymic female nude mice were exposed to a one-time dose of 20 Gray of radiation using the Xstrahl XenX small animal radiation research platform. Radiation was localized to a single 1x1 mm² beam through the right hemisphere, as to provide the contralateral hemisphere as control. At 14 days post-irradiation, animals were perfused with 10 μ Cu 14C-aminoisobutyric acid (14C-AIB). Concentration of 14C-AIB was determined in the region of interest in irradiated brain and in non-irradiated brain using MCID software for autoradiography. **RESULTS:** Analysis of brain regions demonstrated significant permeability increases in irradiated normal brain tissue as compared to untreated tissue. **CONCLUSIONS:** Radiation induced unsought damage in normal brain tissue upon simulated treatment of CNS metastases. While this procedure revealed radiation-induced increases in permeability, the mechanistic aspect as to how changes in permeability have transpired remains undiscovered. Imaging techniques such as immunofluorescent microscopy could help to elucidate potential mechanism(s). **FUTURE DIRECTIVES:** Experiments utilizing ionizing radiation to simulate treatment of CNS metastases could reveal better adjunctive chemotherapeutic regimens and or provide targetable pathways to reduce the injurious response that occurs during radiotherapy.

Temporal Neutrophil and Lymphocyte Dynamics Following Acute Ischemic Stroke

Introduction: An improper immune response has been shown to increase mortality following acute ischemic stroke (AIS). Targeting the immune system may offer a critical, new treatment options in AIS. Recently, several immune-modulating agents, such as neutrophil inhibitory factor (UK-279, 276) showed promise in preclinical AIS models; however, either failed or were detrimental in clinical trials. One potential reason for their failure may be incorrect timing of administration due to a lack of characterization of a healthy versus a detrimental peripheral immune profile following AIS. The aim of this study is to characterize the pattern of peripheral neutrophil and lymphocyte expression and neutrophil-lymphocyte ratio (NLR) following AIS. **Methods:** We analyzed data from 101 patients for this study (Control (n=25), good outcome (n=30), and poor outcome (n=46)). White blood cell differentials were used to record neutrophil and lymphocyte counts at three time points post AIS: 0-24, 24-48, and 48-96 hours. AIS patients were grouped by severity using their National Institutes of Health Stroke Score (NIHSS) and functional outcome using their Modified Rankin Scale (MRS) at discharge **Results:** Regardless of severity or outcome, patients have an elevated neutrophil counts from 0-48 hours following AIS. From 48-96 hours following AIS, patients with mild AIS or good outcome have a significant decrease in neutrophil count; with a concordant increase in lymphocyte count compared to severe AIS patients. Further, NLR at discharge is significantly higher in severe AIS patients or patients with poor outcome ($p=0.015$). **Conclusion:** In conclusion, our study is the first to describe the distinct patterns of peripheral neutrophil and lymphocyte expression in the acute phase of AIS, comparing AIS patients with good versus poor outcome. These findings may provide insight into the failure of neutrophil inhibitors in clinical trials. This study also provides support for the use of the NLR as a prognostic marker, especially 48-96 hours or at discharge, compared to the traditional assessment at admission.

HIF-1 α , but not HIF-2 α , Regulates the Tie2 Receptor on Tie2-Expressing Monocytes in PyMT Breast Tumors and Augments Angiogenic Function and Metastatic Potential

Tie2-expressing monocytes (TEMs) are a distinct subset of pro-angiogenic monocytes selectively recruited into tumors in breast cancer patients. Due to the hypoxic nature of the tumor microenvironment, we investigated if oxygen regulates the trafficking of these cells into tumors or if these monocytes differentiated to TEMs once inside the tumor proper. To delineate involvement of the hypoxia inducible factor- α (HIF- α) subunits in this process, we derived macrophages from bone marrow of LysM-Cre control, HIF-1 α -floxed/LysM-Cre, or HIF-2 α -floxed/LysM-Cre mice and found that the population of F4/80+/Tie2+ TEMs from wild type and HIF-2 α -deficient macrophages increased when exposed to hypoxia while no such increase was observed in HIF-1 α -deficient macrophages. To understand if HIF-1 α regulates F4/80+/Tie2+ cell chemotaxis into the tumor or if HIF-1 α drives the differentiation of F4/80+/Tie2- cells to Tie2-positivity, we orthotopically implanted PyMT breast tumor cells into the mammary fat pads of LysMcre control, HIF-1 α -floxed/LysM-Cre, or HIF-2 α -floxed/LysM-Cre mice and evaluated TEM infiltration, tumor angiogenesis, and metastatic potential (circulating tumor cells and micrometastases to the lung). There was no difference in the percentage of TEMs in the bone marrow (CD45+/Tie2+) or peripheral blood (CD11b+/CD31-/Gr-1o/Tie2+) compartments among the mouse groups. In contrast, HIF-1 α -floxed/LysM-Cre mice had a significantly smaller percentage of TEMs in tumors compared to wild type or HIF-2 α -floxed/LysM-Cre mice even though the percentage of total F4/80+ macrophages was unchanged. Further, this observed loss of TEMs in the HIF-1 α -floxed/LysM-Cre mice correlated with significantly less tumor angiogenesis as measured by CD31. Finally, the percent of TEMs in the tumors better correlated with the amount of circulating tumor cells and pulmonary micrometastases than the percent of total tumor F4/80+ macrophages.

Stephens, Benjamin

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Medicine, Ophthalmology, Resident

Comparing Monocular and Binocular Performance on Chart Tests of Acuity, Contrast Sensitivity and Reading in Normal Subjects

Purpose: To compare monocular and binocular performance of normal subjects on near chart measures of basic visual function and reading (speed and acuity) as a preliminary study comparing functions in visually impaired patients. Methods: Subjects were patients or employees at the West Virginia University Eye Institute with near acuity of 20/25 or better in each eye ($\log\text{MAR} < 0.1$). Their average age was 36 years. Eight of the 20 were male and 12 female. We assessed each subject's performance on 5 vision chart tests, ETDRS, Pelli-Robson (Precision Vision), Smith-Kettlewell Low Luminance Acuity (SKLL), and MN Read. Subjects were tested on each test monocularly and binocularly at a distance of 16 inches (40 cm). Subjects' stereopsis was tested using the Titmus Test. Testing was performed in a well lit room (252 lux). ETDRS and MN Read charts were black type on white backgrounds (contrast > 0.9). Binocular summation was evaluated by comparing binocular values to the mean monocular value or to the best monocular value. Results: Best monocular acuity was the best predictor of reading acuity ($p < 0.0005$, $r^2 = 0.497$) and reading speed ($p < 0.0005$, $r^2 = 0.49$). Statistically significant binocular summation ($p < 0.008$) was observed for all tests except reading speed. However, binocular summation was considerably less than the theoretical value of 1.4 ($\log 0.15$). For comparisons to the average monocular acuity the binocular advantage averaged -0.068 and compared to the best monocular acuity -0.035 . When binocular reading speed was compared to the average monocular speed there was a gain of only 1.6 words/min ($p = 0.696$). However, the faster monocular speed was 11.643 words/min greater than binocular reading speed ($p = 0.005$). Conclusion: In our sample, binocular summation did not approach the theoretical and often observed square-root of 2 for acuity or contrast sensitivity. The present results are consistent with prior reports that the best monocular acuity can serve as a good surrogate for binocular acuity and with reports that reading speed in subjects with normal vision shows little if any binocular advantage. In fact, we observed that binocular speed was less than the fastest monocular speed.

Sundar, Jesse

67

Medicine, Biochemistry, Basic Science

Alternative splicing of mRNA regulated by Musashi is crucial for photoreceptor development and function

We have recently delineated a splicing program specific to vertebrate photoreceptor cells that is controlled by the Musashi proteins, MSI1 and MSI2. This program produces photoreceptor specific variants of several proteins involved in primary cilia biogenesis and vision. We hypothesized that the Musashi proteins are required for photoreceptor morphogenesis and function due to their predicted regulation of photoreceptor-specific splicing variants of ubiquitously expressed genes. The objective of this study is to determine if the production of splicing variants guided by Musashi is essential for photoreceptor development and function. To achieve our objective, we generated knockout mice in which either Musashi-1 (Msi1), Musashi-2 (Msi2), or both genes were ablated in the retina. After validating these models by western blot, we analyzed their photoreceptor function by electroretinography and their morphology by immunocytochemistry. The splicing of photoreceptor-specific exons in mature transcripts was determined by reverse transcriptase PCR. Photoreceptor function was absent in the Msi1/Msi2 double knockout mice at postnatal day 16 (PN16). The loss in function correlated with disrupted OS development in double knockout mice. In agreement with the established role of the Musashi proteins in controlling splicing in photoreceptors, the splicing of 13 out of 14 photoreceptor-specific exons we tested was blocked in the double knockout mice. In contrast to the double knockout, the photoreceptor function was mostly preserved at PN16 in the single Msi1 or Msi2 knockouts. The Msi1 but not Msi2 single knockout had a moderate effect on exon inclusion of some of the alternative exons tested. Our results show that the Musashi proteins are required for normal photoreceptor development and likely control the photoreceptor-splicing program. We also observed a functional redundancy of the two Musashi genes in photoreceptor cells which explains why no mutations within the Musashi genes have been found to cause blindness in humans.

Tallman, Rachel

165

Pharmacy, Pharmaceutical Sciences, Undergraduate

Efficacy of NKTR-102 against conventional chemotherapy in treating two models of breast cancer brain metastases

Background: Brain metastases are one of the leading causes of death in advanced breast cancer. Post diagnosis, mean survival time is between two and sixteen months, with approximately 80% mortality within one year. Treating brain metastases presents a challenge since commonly-used chemotherapeutic agents inadequately permeate the blood-brain and blood-tumor barriers. NKTR-102 is a novel agent comprised of irinotecan conjugated to polyethylene glycol (PEG) polymers capable of crossing these barriers. NKTR-102 aims to increase survival in patients with triple negative and HER2+ breast cancer metastases. Methods: Female athymic nude mice were injected via intracardiac injection with triple negative MDA-MB-231-BrLuc or HER2+ JIMT1-BrLuc cells. Gemcitabine (60 mg/kg) and eribulin (1.5 mg/kg) were dosed via intraperitoneal injection every 4 days, while NKTR-102 (50 mg/kg), irinotecan (50 mg/kg), paclitaxel (6 mg/kg), vinorelbine (10 mg/kg), docetaxel (10 mg/kg), and vehicle (200 μ L) were administered via tail vein every 7 days starting on day 21 in the 231-BrLuc cohort. NKTR-102 (50 mg/kg) and vehicle (200 μ L) were administered via tail vein every 7 days, while lapatinib (100mg/kg) was given orally twice daily starting on day 14 in the JIMT-BrLuc cohort. Bioluminescence images were captured biweekly, and survival data was collected. With the 231-BrLuc model, a terminal injection of 14 C-NKTR-102 was used to see irinotecan distribution in the brain. Results: In the triple negative model, median survival for NKTR-102 was 86 days, with 40% of mice surviving to study completion. Median survival for docetaxel, vinorelbine, eribulin, gemcitabine, irinotecan, paclitaxel and vehicle were 39 days, 43 days, 40.5 days, 48 days, 35 days, 42 days, and 39 days respectively. In the HER2+ model, median survival for NKTR-102 (10% survival to completion), lapatinib, and vehicle was 31 days, 29 days, and 28 days respectively. In both models, NKTR-102 showed increased efficacy against conventional chemotherapy for the treatment of brain metastases. Autoradiographic data showed 14 C-NKTR-102 accumulated preferentially in 231-Br tumors compared to normal brain. Conclusion: NKTR-102 is a promising chemotherapeutic agent to prolong survival in triple negative and HER2+ breast cancer brain metastases when compared to conventional therapies.

Taylor, Matthew

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Medicine, Exercise Physiology, Masters

Relationship between changes in Body Mass Index (BMI) and circulating albumin levels in breast cancer patients from West Virginia

Background Cachexia is the loss of weight and muscle atrophy that is all too common in cancer patients. Low albumin levels are correlated with weight loss in cancer patients. There is discrepancy in the literature as to the degree of cachexia experienced in patients with breast cancer and changes in circulating albumin. Our group received data from WVCTSI's Integrated Data Repository (IDR) on height, weight, and blood albumin levels of over 5,000 West Virginia women diagnosed with breast cancer so that we may test our hypothesis that there would be an association between low albumin levels and reduction in body mass index. **Methods** We calculated the patients' BMI and identified the greatest change from the day of their diagnosis. The greatest positive or negative percent change was paired with the albumin level for that date if it was available. 1,971 patients had associated albumin levels to their largest change in BMI. We then examined the data using regression analysis. We also received data from a separate cohort of 22 patients with known breast tumor subtype: ER+/PR+ (n=9); Triple+ (n=8); Triple- (n=3); Her2+ (n=1); control (n=1). We superimposed their results on the regression analysis graph of the initial 1,971 patients in an attempt to find a relationship among subtypes. **Results** Surprisingly, we found little to no relationship between albumin levels and the changes in BMI ($R^2 = 0.0137$). In fact, of the 1,971 patients analyzed, nearly the same number of patients that had lost weight had gained weight, resulting in a median BMI change of zero. Additionally, nearly 50% of the patients analyzed had subnormal albumin levels (Mean=3.6; Median=3.5). Also, no relationship between BMI and albumin was observed in the separate cohort of patients with known breast tumor subtypes. **Conclusion** Albumin levels, despite tending to be lower than average in breast cancer patients ($<3.5\text{mg.dL}^{-1}$), were not an indicator of whether or not patients were likely to have lost weight. These findings did not support our hypothesis, and suggest no association between reduced BMI and circulating albumin levels in West Virginia women with breast cancer.

Thornton, James Doulgas

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Pharmacy, Pharmaceutical Systems and Policy, Clinical Sciences/Epidemiology

Health-Related Quality of Life in Patients Receiving Long-Term Opioid Therapy: A Systematic Review With Meta-analysis

Purpose: Over 25 million Americans reported having daily pain and between 5 and 8 million Americans used opioids to treat chronic pain in 2012. This is the first systematic review with meta-analysis to determine the effects of long-term opioid use on the Physical Component Summary (PCS) score and Mental Component Summary (MCS) scores of a Health-Related Quality of Life instrument in adults without opioid use disorder. Methods: The a priori eligibility criteria for the PubMed (MEDLINE), Scopus, and PsylNFO searches were: (1) randomized controlled trial, (2) at least one opioid intervention group, (3) minimum of four-week duration of opioid use, (4) comparative control group, and (5) adults ≥ 18 years that do not have dominant disease. The unit of analysis was the standardized mean difference effect size (Hedges's g). All results were pooled using random-effects models. Results: Of the 340 non-duplicate citations screened, 19 articles comprising 26 treatment comparisons and 6,168 individuals (treatment $n=3,160$; comparators $n=3,008$ with duplicates removed) met the inclusion criteria for the systematic review. Thirteen treatment comparisons were available for the meta-analysis. Across all PCS analyses, small, statistically significant improvements were observed (opioid versus opioid only: $g=0.27$, 95% CI=0.05-0.50, opioid versus placebo only: $g=0.18$, 95% CI=0.08-0.28, and all studies combined: $g=0.22$, 95% CI=0.11-0.32). There were small but not statistically significant changes on the MCS scores. Overall, high heterogeneity was present. Conclusions: PCS scores improve with no change in MCS scores. However, long-term opioid trials are rare and only two trials included lasted longer than one year.

Verna, Nicole

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Public Health, Undergraduate Program, Undergraduate

School Climate, Basic Psychological Needs, & Risk of Academic Failure: A Whole Child Model

Purpose: Prior research suggests students whose basic psychological needs are being met using pro-social means are less likely to participate in risky behaviors related to academic failure. This study examined school climate as a pro-social source of meeting the basic psychological needs of early and late adolescents and a means of reducing risk. **Procedures:** Two thousand four hundred and five students ($n=2,405$; 2, 43% female, 89% white) from 6 mid-Atlantic middle and high schools completed paper and pencil surveys (RR=88.2%). Structural equation modeling was used to describe the associations between variables and groups. Three models were developed for each grade level. All models included factors related to school climate and developmental needs. Models varied by outcomes related to school dropout, substance use, and teen parenting. Comparisons were made between high school and middle school groups by outcome. **Measures:** School Climate Measure (Zullig, et al., 2010); Basic Psychological Needs Satisfaction (Deci & Ryan, 2000); Achievement: Self-reported, averaged Math & English GPA; Substance Use: Log natural of the sum score for tobacco, alcohol, and drug use; Sexual risk: number of sexual partners. **Analysis:** Structural Equation Modeling (Mplus Version 7.3). Model controls for: Grade level (middle/high), Race (White/non-white), Maternal education (income), and Household configuration. **Findings:** All six models indicated a strong fit (minimum CFI=.96) and evidence supported school climate as a means of meeting student developmental needs and reducing risk. **Conclusions:** Evidence suggests positive school climates can be a pro-social source of meeting student developmental needs and reducing risks related to academic failure.

Vo, Quynh

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Medicine, Neurology, Basic Science

Continuous Levodopa Dosing Improves REM Behavioral Disorder Associated With Parkinsonism

Rapid eye movement sleep behavior disorder (RBD) is frequently present in Parkinson's disease (PD) and is characterized by excessive motor activity during sleep and REM sleep without atonia. We developed reliable behavior based criteria to identify RBD in the well-established 6-hydroxydopamine lesioned rat model of PD and tested the effects of continuous levodopa (LD) administration on this dysfunction. Using blinded raters, video recordings of normal and hemiparkinsonian (HP) rats were analyzed to develop a composite score consisting of six behavioral signs that occurred during polysomnographically confirmed epochs of sleep-wake stages. HP rats were then treated with 2 mg/kg and 4 mg/kg of LD doses on intermittent (twice or thrice a day) and continuous (every 4 hours for 48 hours) schedules. The abnormal sleep slouch, one of the six behavioral signs included in our criteria was indicative of REM sleep onset in the rat. There was good agreement between the behavior based criteria and polysomnographic criteria for all sleep-wake stages in normal rats and for REM in HP rats (concordance correlation coefficients (CCC)>0.8). Continuous LD dosing at 4mg/kg showed a significant decrease in REM behavior disorder and limb deficits when compared to baseline ($p<0.05$). We demonstrate that the phenomenological correlates of RBD can be reliably characterized and rated in the HP rat. We also show that continuous LD administration round the clock ameliorates RBD while maintaining therapeutic benefits for parkinsonism without any deleterious consequences, suggesting that similar interventions may have benefits in PD patients.

Voronkova, Maria

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Medicine, West Virginia University Cancer Institute, Basic Science

SOX9 regulates cancer stem-like cells in non-small cell lung cancer

Lung cancer is the leading cause of cancer death worldwide in both men and women, every year killing more people than breast, prostate and colon cancers combined. Drug/radiation resistance and tumor relapse contribute to low patient survival, which has largely been attributed to the acquisition of cancer stem-like cells (CSCs) or tumor initiating cells. Moreover, conventional therapies are not effective against CSCs. This signifies the need to identify mechanisms of CSC regulation which could lead to the discovery of CSC-specific drug targets and the development of more effective anticancer therapies. An embryonic transcription factor SOX9 has been implicated in CSC regulation in a number of cancer types, but little is known about its role in non-small cell lung cancer (NSCLC). We demonstrated that high SOX9 expression correlates with poor survival in NSCLC patients by analyzing The Cancer Genome Atlas (TCGA) data. We hypothesized that SOX9 plays a key role in lung cancer progression and chemoresistance by upregulating CSCs. To test this hypothesis, SOX9 was stably or transiently knocked down or ectopically overexpressed in various NSCLC cells, and their effects on CSC formation, biomarkers, and drug resistance were investigated using molecular and immunological techniques. Our results showed that SOX9 knockdown decreased the number of tumor spheres in NSCLC cells. We also showed for the first time that SOX9 knockdown dramatically downregulated the expression of a functional CSC regulator ALDH1A1. Consistent with this finding, an overexpression of SOX9 in non-cancer lung epithelial cells promoted tumor sphere formation, supporting the role of SOX9 in CSC regulation. Soft agar colony formation assay substantiated the effect of SOX9 knockdown on anchorage-independent growth. Likewise, SOX9 knockdown inhibited the proliferation of NSCLC cells, and more importantly, it increased cell sensitivity to the chemotherapeutic drug cisplatin, whereas SOX9 overexpression decreased it. Together, our results indicate an important role of SOX9 in the regulation of CSCs in NSCLC. Since CSCs are a key driver of chemoresistance and relapse, our findings may have important implications in the development of novel therapeutic strategies for chemoresistant lung cancer

Watson, Joseph

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Medicine, Emergency Medicine, Clinical Sciences/Epidemiology

Fiberoptic Nasotracheal Intubation in the Emergency Department for Severe Upper Airway Obstruction

Angioedema of the upper airway can pose a challenge for Emergency Department physicians when attempting to intubate. The semi-awake fiberoptic nasotracheal intubation is an underutilized procedure that allows for the establishment of a definitive airway without removing the patient's airway reflexes, protecting against the cannot intubate, cannot ventilate scenario. Although a common teaching in emergency medicine, fiberoptic nasotracheal intubations are rarely performed. We report a case of a successful fiberoptic nasotracheal intubation in a patient with an acute upper airway obstruction later found due to angioedema. Emergency physicians should have routine training and access to equipment for fiberoptic privileges to provide optimum patient care.

Adaptive neural mechanisms in individuals with autism when processing multisensory vs. unisensory real-world stimuli

Autism is now being diagnosed in 1 in 68 children in the United States according to the CDC. Sensory processing dysfunction is a pervasive aspect of autism in which every-day sounds, sights, smells, etc., can be overwhelming or conversely may fail to register in the brain at the appropriate levels. Often this impacts a person's ability to participate in every-day activities such as going to the grocery store or sitting in a classroom. The world is inherently a multisensory environment in which our brain must process multiple types of sensory inputs simultaneously. Precise integration across the senses improves performance on tasks involving reaction time and accuracy and is critical for language development. While individuals with autism do integrate multiple sensory inputs, many tend to do so over a wider timeframe. Most studies investigating sensory integration in autism utilize artificial stimuli such as pure tones and simple shapes. However, relatively little is known about sensory integration in this population in regards to processing real-world sensory information. This study utilized functional magnetic resonance imaging (fMRI) to investigate differences in sensory integration in high-functioning adolescents and young adults with autism (n=27) compared to their peers without autism (n=28; matched for age, IQ, gender, and handedness) using real-world stimuli. While in the MRI, participants watched a video of someone bouncing a basketball. Their task was to press a button when they perceived the ball to impact the floor. Sometimes the video had synchronous audio of the basketball bouncing sound (the multisensory condition) and sometimes there was no auditory information (the unisensory, visual only task). fMRI Results indicated that individuals with autism were utilizing different brain regions across these two conditions compared to their peers without autism, which may reflect adaptive cortical mechanisms in the high-functioning autistic group. The psychometric data indicate that the addition of sound in the multisensory condition differentially impacted the task accuracy between the two groups. The fMRI results add to our understanding of adaptive cortical development in individuals with high-functioning autism while the behavioral data is significant for considerations regarding targeted interventions and modifications to school and workplace environments.

Werner, Zachary

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Medicine, Orthopedics, Basic Science

Does a tissue-specific stem cell favor a lineage-specific differentiation? A donor-matched study

Mesenchymal stem cells (MSCs) offer an attractive resource given their ease of availability, lack of ethical issues, and potential application to a wide range of therapeutic scenarios. Given the various types of MSCs, a study of the differentiation capabilities of each lineage in a donor-specific setting, including adipose-derived stem cells (ADSCs) and synovial-derived stem cells (SDSCs), was warranted to examine the proper culturing methods to stimulate directed differentiation. We hypothesized that each type of MSC would differentiate best towards its natural lineage, with SDSCs having better capabilities than ADSCs in terms of osteogenic differentiation. Populations of rabbit ADSCs and SDSCs were first expanded in plastic flasks. They were subsequently reseeded on a plastic substrate and stimulated towards adipogenic, osteogenic, and chondrogenic differentiation. Alizarin Red Staining, q-PCR, and differentiation specific analyses were conducted to confirm the differentiation inductions. As expected, q-PCR revealed SOX-9 expression to be significantly higher in SDSCs at day 0 of chondrogenesis compared to ADSCs. ADSCs showed significantly greater levels of each adipogenic mRNA marker, denoting their greater adipogenic differentiation capabilities. Alazarin Red Staining indicated significantly greater osteogenic differentiation of SDSCs in two out of four rabbits. However, q-PCR analysis of osteogenic markers indicated ADSCs exhibited greater mRNA levels for SPP1, with the remaining markers showing insignificant differences between ADSCs and SDSCs. Ongoing investigations using Western Blots may provide clarity with regards to which has greater osteogenic differentiation. These findings indicate that each type of MSC has differentiation tendencies, which might provide important data for stem cell-based tissue engineering and regeneration.

Werwie, Nicole

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Medicine, Department of Surgery, Clinical Sciences/Epidemiology

Examining the Prognostic Significance of Select Inflammatory Cytokines Using an Open-Source Genomics Platform Reveals Novel Expression Patterns Across Breast Carcinoma Subtypes

Introduction: Given the high rates of obesity and aggressive breast cancers in rural Appalachia, it is paramount to understand how adipose supports the tumor microenvironment. We previously found that adipose-derived stem cells cultured with triple-negative tumor cells promote the expression of pro-inflammatory cytokines. This finding is significant as it could explain, in part, how obesity contributes to worse outcomes in breast cancer. Methods: Cytokines and growth factors were measured in co-cultures of adipose stromal cells and MDA-MB-231 lines. To validate their clinical significance, we compared cytokine mRNA expression profiles using the Cancer Genome Atlas (n = 1,005) and evaluated them for indices of tumor progression. Results: FGF7 and CCL5 overexpression was evident in in vitro arrays and showed a significant impact on survival within TCGA data. FGF7, CCL5, CCL2, IL6, and IL6R were analyzed for expression across molecular subtypes of breast cancer. IL6R, CCL5, and CCL2 expression varied significantly, with mean expression highest in triple-negative tumors. After dichotomizing the samples for estrogen receptor status, IL6R, CCL5, and CCL2 showed significantly higher mean expression in ER negative tumors. Ingenuity Pathway Analysis indicated IL6, IL6R, CCL5, and CCL2, but not FGF7, cooperate through many pathways to promote tumor progression. Conclusions: Genomic data analysis support in vitro findings that IL6R, CCL5, and CCL2 overexpression may predict a worse prognosis in breast cancer. For adipose-driven, hormone receptor negative breast tumors commonly found in our Appalachian population, these cytokines and growth factors could serve as novel therapeutic targets. (Supported by NIH P20GM103434 and NIGMS U54GM104942)

Wiseman, Brian

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Medicine, School of Medicine, Basic Science

Altered Hip Neuromechanics During a Jump Task Between Ankle Instability, Copers, and Healthy Controls

Ankle sprains often lead to ankle instability (AI). However, some individuals (copers) who have sprained their ankles do not go on to develop chronic nature of ankle instability. Using copers as a comparison group will help us understand movement neuromechanics that underlie chronic ankle instability.

PURPOSE: To examine sagittal plane hip angle, moment, gluteus maximus activation, and medial hamstring activation during a max jump task. **METHODS:** 66 subjects (M=42, F=24; 22.2±2 yrs, 173.8±8 cm, 71.4±11 kg) consisted of 22 ankle instability (81.9±7.3% FAAM ADL, 60.9±11.6% FAAM Sports, 4.1±2.8 sprains), 22 Copers (100% FAAM ADL & Sports, 2.0±1.1 sprains), and 22 healthy controls. Subjects performed 5 jumps, consisting of a max vertical jump, landing on a force plate, and transitioning immediately to a side jump, while the dependent variables were collected during stance (initial foot-contact to toe-off). Functional linear models ($\alpha=.05$) were used to detect mean difference between groups. If functions and corresponding effects sizes (95% confidence intervals) did not cross the zero, then significant differences existed ($P<.05$). **RESULTS:** Figure 1 shows that while copers demonstrated similar sagittal plane hip angle, moment, and gluteus maximus activation, AI subjects demonstrated up to 5° greater hip flexion, 0.5 Nm/kg hip extension moment, and 15% less gluteus maximus activation compared to normals ($P<.05$). A significant difference was not found in medial hamstring activation ($P>0.05$). **CONCLUSIONS:** Increased hip flexion angles and extension moments suggest that AI subjects adopt altered hip neuromechanics, compared to copers and normals. Reduced gluteus maximus activation as opposed to greater hip flexion angles and extension moments suggest that sagittal-plane trunk motion may play a role in these altered hip neuromechanics in AI subjects.

Perianal Dermatitis and Perianal Skin Care in Newborn Infants

Background: Perianal dermatitis (PD) is characterized by inflammatory reaction in the perianal area with poor functioning of skin barrier. It is commonly described as “butt breakdown” in neonatal intensive care (NICU) setting. Its incidence is unknown, and no written guidelines specifically for perianal skin care currently exist. Many neonates frequently have more than one over-the-counter diaper product applied to their perianal area without proper documentation of diagnosis or outcome. The true cost and efficacy of these products has not been evaluated. Objectives: 1) To identify the incidence of PD among neonates admitted to WVUH NICU. 2) To determine the usage pattern and cost efficacy of commonly used diaper products for PD. Methods: A retrospective chart review of patients admitted to WVUH NICU from January 1, 2013 to December 31, 2014 was conducted to identify neonates with at least one order of Aquaphor, BagBalm, Desitin, Flanders or Nystatin. Diagnosis of PD or diaper dermatitis/rash was identified based on primary diagnosis at the time of product ordered. Various demographic and clinical parameters were recorded. Usage patterns of these five products were analyzed, and associated costs estimated. Results: Of 1241 NICU admissions, 56.2% (n=698) had at least one diaper product ordered during their stay while 8.9% (n=62) had multiple products ordered. However, only 23.0% (n=161) had appropriate documentation of PD. The most common product ordered first was Aquaphor (64.3%), followed by Desitin (19.2%), Flanders (6.5%) and BagBalm (3.3%). Only 2.4% (n=17) with a formal PD diagnosis had documented rash improvement following product usage. Only 2.4% were discharged home with one of these products. The estimated cost of these products was \$14,139 over 2 years, averaging \$20.26 per patient per hospital stay. Conclusion: Over half of the NICU neonates were exposed to one or more “butt products”, but usually without documented diagnosis or product efficacy. The cost of these products was significant, and possibly underestimated due to the lack of documentation. Creating standardized diagnostic tools and preventive guidelines may decrease incidence of PD and overuse of these products.

Wolfe, Stanley

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Medicine, WVU Trauma and Critical Care Institute, Basic Science

Prevalence of Biofilm Attachment on Explanted Surgical Mesh

Objective: Biofilm have been identified as a source of chronic and recurrent infection in many medical devices. Furthermore, standard culture techniques only sample the planktonic bacteria on the biofilm surface. The objective of this study was to evaluate explanted abdominal mesh for the presence of biofilm. **Methods:** 15 explanted meshes were collected and evaluated using confocal light microscopy and electron microscopy to identify and stage the biofilm. Cultures of the planktonic and sessile species were performed. Demographic data including age, BMI, smoking status, and comorbidities were collected. **Results:** Seven of the operations were classified as clean, 8 contaminated. 13/15 meshes were positive for biofilm. Biofilms were found to be 2 stage I, 3 stage II, 3 stage III, and 5 stage IV. There was a correlation between biofilm stage for infected cases, but not for clean. Of the samples in which there was bacterial growth there was no correlation between the surface sample and the biofilm sample. **Conclusion:** Biofilms are present on abdominal wall meshes and there is a clear discordance between the bacteria on the surface vs within the biofilm. Therefore, therapies that impact the surface only (i.e. antibiotics) are likely to fail. Larger studies are warranted to understand the role of biofilm on infected and non-infected meshes.

Wolford, Logan

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Medicine, Medicine, Clinical Sciences/Epidemiology

Utilization of Internet search engine data for determining inflammatory eye disease patterns

With over 88 million adults in the United States searching for medical information online annually, “infodemiology” or information epidemiology is becoming a valuable tool for public health research. Application of methodology has been limited in ocular diseases. We herein describe the use of internet-based search engine data as a novel complementary source for better understanding the epidemiologic factors of inflammatory eye diseases. Using Google Trends, search frequency of disease-related terms for stye and multiple sclerosis during the last 5 years were obtained. Data were grouped into five cohorts of ten states based on average yearly temperature, and temporal patterns of Google web search data were correlated with temperature variation. Temporal pattern of Google search volumes for stye and multiple sclerosis - the former having a peak in the warmer months, and the later having a bimodal peak in March and September correlated strongly with variation of average temperature in states with moderate climates. Temporal pattern of relative Google search volumes for stye and multiple sclerosis further corroborated existing knowledge of heat sensitivity as a risk factor for these conditions. The utilization of internet-acquired data represents a resource to study variation in disease based on temperature and seasonality and may be a viable epidemiological surveillance system that could help alert health-care providers to better equip them for rising healthcare concerns in the community.

Yadav, Vishal

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Medicine, Physiology and Pharmacology, Postdoc

Role of Adenosine receptors in Angiotensin II dependent hypertension in mice.

Our recent finding showed that acute angiotensin (ANG) II stimulation enhanced A1 adenosine receptor (AR) dependent cytochrome P450 (CYP) 4A mediated contraction in mouse mesenteric arteries (MA). In addition, A2BAR dependent and partly KATP channel mediated relaxation was also reduced with ANGII stimulation. These data suggest a possible interaction between ANG II and ARs at vascular level which may play a role in ANG II dependent hypertension. In ANG II (1000 ng/kg/min, 21 days) infused hypertension mouse model, tail cuff was used to measure blood pressure. Aorta as a conduit and MA (second order) as a resistance artery were chosen for muscle tension studies. Protein expressions in aortas and MAs were analyzed by western blot. Infusion of ANG II increased systolic arterial blood pressure (SAP) in mice. Particularly, in ANG II infused mice, SAP (in mmHg, mean \pm SD) at day 0 was 101.6 ± 6.675 which increased to 156.7 ± 15.68 on day 21 ($p < 0.05$) while in saline control mice, SAP was 100.8 ± 6.753 (day 0) and changed to 105.4 ± 7.620 (day 21). Higher expression of A1AR (~155% over 100%) and CYP4A (~50%, ~0.6 over 0.3, ratio to actin) was present in MAs in hypertensive compared to control mice. Expression of A1AR and CYP4A was comparable in aortas of hypertensive and control mice. CCPA (A1AR agonist) -induced concentration dependent contraction was significantly reduced in aorta of hypertensive mice compared to control. NECA (non-selective AR agonist) produced a significantly higher relaxation in aorta of hypertensive mice. In MAs, CCPA-induced contraction was reduced in hypertensive mice. NECA induced relaxation was comparable in MAs. Pinacidil (KATP channel opener) induced relaxation was significantly lower in MAs of hypertensive mice. In conclusion, our data reveal important role for A1AR dependent signaling in ANG II induced hypertension. Higher A1AR and CYP4A may reduce KATP channel dependent relaxation of MAs aiding vascular contraction and blood pressure. Further studies involving ARs pharmacological inhibitors and genetic models are required to fully understand the relationship between ANG II and ARs in the development of hypertension. (Supported by NIH grant HL 027339)

ASSOCIATION BETWEEN CHRONIC HEPATITIS B AND METABOLIC SYNDROME

Background. The association between chronic hepatitis B (CHB) infection and metabolic syndrome (MetS) remains inconclusive. This study was designed to determine the association between CHB infection and MetS among the US population with updated data and adjustments for a comprehensive set of risk factors. **Methods.** Adults aged 18 years or older who were clinically assessed for Hepatitis B and MetS from the National Health and Nutrition Examination Survey (NHANES) 2003-2004, 2005-2006, 2007-2008, 2009-2010, and 2011-2012 cycles were included in the study (n=29,906). MetS was defined according to NCEP/ATP III guideline. CHB was identified by the seropositivity of Hepatitis B surface antigen and core antibody in the absence of Hepatitis B surface antibody. Rao-Scott χ^2 test and logistic regressions were employed in the analyses. **Results.** MetS was significantly less prevalent among adults with CHB compared to adults without CHB (9.6% vs. 18.6%, $p = 0.037$). In adjusted analyses, adults with CHB were less likely to have MetS compared to those without CHB with an adjusted odds ratio (aOR) of 0.12 and 95% CI: (0.02-0.85). Regarding individual component of MetS, CHB was inversely associated with high waist circumference (aOR = 0.10, 95% CI: 0.03-0.41) and dyslipidemia (aOR = 0.42, 95% CI: 0.21-0.84). No association between CHB and other metabolic components were found. **Conclusions.** A significantly inverse association between CHB and MetS was found in the study.