UNIVERSITY OF COLORADO DENVER
ANSCHUTZ MEDICAL CAMPUS

27TH ANNUAL STUDENT RESEARCH FORUM

AND

STUDENT RESEARCH AWARDS CONVOCATION

COLLEGE OF NURSING

GRADUATE SCHOOL

SCHOOL OF DENTAL MEDICINE

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DECEMBER 11, 2012
ANSCHUTZ MEDICAL CAMPUS
EDUCATION 2 NORTH/SOUTH

27TH ANNUAL
UNIVERSITY OF COLORADO DENVER
ANSCHUTZ MEDICAL CAMPUS
STUDENT RESEARCH FORUM

Tuesday, December 11, 2012

Poster Sessions
1:00-2:15 pm
2:15-3:30 pm

Awards Convocation
4:00 - 4:30 pm
ED2 South Room1102

ANSCHUTZ MEDICAL CAMPUS
EDUCATION 2 NORTH/SOUTH

The Student Research Forum organizing committee wishes to acknowledge, with gratitude, the financial support for medical student research provided by:

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ABSTRACTS

Ahmed, Isra

Poster Title: FLUORIDE RELEASE AND UPTAKE INTO HYDROXYAPATITE FROM EXPERIMENTAL DENTAL VARNISH

Category: Materials and Methods

Abstract: FLUORIDE RELEASE AND UPTAKE INTO HYDROXYAPATITE FROM EXPERIMENTAL DENTAL VARNISH. I Ahmed (D.D.S., SODM), S Coleman, and CM Carey, School of Dental Medicine, University of Colorado, Denver, CO. Fluoride releasing dental varnishes (F-varnish) typically contain 5% sodium fluoride (NaF) within a resin or rosin base. The concentration NaF that yields optimal fluoride enamel uptake, release, and anti-caries efficacy is unknown. Also, there is controversy on whether the release rate of fluoride into saliva is predictive of the fluoride uptake into enamel. Objectives: measure fluoride uptake (loosely- and tightly-bound) into hydroxyapatite (HAp) discs and fluoride release as a function of NaF concentration in F-varnish. Methods: triplicate sets of F-varnish containing 5.0%, 2.5%, 1.25%, and 0.625% (wt/wt) NaF were prepared. 0.01-0.02 g F-varnish was applied to one side of an HAp disc. Fluoride release into a continuous flow of 30 mmol/L KCl at 1 mL/min was measured over 3 h. The HAp discs were then cleaned and loosely-bound fluoride extracted overnight in KOH (1.0 mL, 1.0 mol/L). Tightly bound fluoride was extracted via serial extractions in HClO4 (1.0 mL, 0.5 mol/L). The extraction solutions were neutralized and analyzed via fluoride ion-selective electrode. Results: the cumulative fluoride release profile increased hyperbolically over 3 h. The total fluoride released at 3 h ([F]180) increased as a function of NaF concentration. The time for 50% (t50) of the fluoride to be released was ≤ 32 min for all varnishes. Loosely- and tightly-bound fluoride increased to 2.5% NaF and plateaued.
[NaF]% [F] Tightly bound [F] Loosely bound [F]180 released t50
(µg/mL) (µg/mL) (µgF/mgVarnish) (minutes) 0.625 0.10(0.03)a
0.09(0.05)c 0.07(0.23)f 4.40 1.25 0.15(0.02)a 0.26(0.12)d
1.87(0.86)g 31.95 2.5 0.25(0.03)b 1.20(0.40)e 2.47(0.47)g 26.10
5.0 0.19(0.05)b 1.18(0.07)e 3.82(0.84)h 19.70 Values in the table are
mean(standard error). Letters indicate groups that are not significantly different in each category
(ANOVA, Newman-Keuls, p

Ayres, Lauren

Poster Title: Unmet Legal Needs Among Urban Safety Net Clinic Patients

Category: Health Care and Public Health

Abstract: UNMET LEGAL NEEDS AMONG URBAN SAFETY NET CLINIC PATIENTS: LE Ayres, (MD, SOM), MW Miller, MD Díaz, T Farley, P DeWitt, A Melillo, SR Lowenstein. Department of Emergency Medicine, University of Colorado, Aurora, CO. In the United States, there are marked disparities in health outcomes across racial, ethnic and socioeconomic lines; remedying these factors that underlie poor health is critical to improving health outcomes. Because adverse socioeconomic conditions can manifest as legal problems, addressing patients' legal needs may improve health outcomes. This study measured the prevalence of legal needs among patients visiting an urban safety net clinic and whether legal needs were associated with poor health. Over a 2-week period, a 29-question written survey (English and Spanish) was presented to all families in the waiting room of Salud Family Health Center, a safety net clinic in metro-Denver. Respondents were asked if they had experienced any of 12 legal problems in the last year. Questions reflected the National Center for Medical-Legal Partnership's categorization of consequential legal issues: income; insurance; housing; education; employment; legal status; and family safety. Respondents were also asked if they had access to legal services. Respondents who reported at least one legal problem were asked about the impact of the problem(s) on their health. Demographic information was collected, including age, sex, race, ethnicity, English language proficiency, education and health status. Survey responses are reported using proportions and 95% confidence intervals. Surveys were collected from 602 patients (334 in English and 268 in Spanish). The majority of respondents were under age 40 (56%), female (73%) and Hispanic (73%). Overall, 453 (75.2%; 95CI: 71.7-78.7) reported having at least one legal problem in the past year. Of these, 252 (55.6; 51.0-60.2) stated their legal problem(s) caused or exacerbated a health condition; 259 (57.2; 52.6-61.8) reported no access to legal services. This study demonstrates that among patients visiting an urban safety net clinic, unmet legal needs are widespread and may be associated with poor health. Additional studies are needed to ascertain the benefit of routine screening for unmet legal needs in low-income healthcare settings and the efficacy of medical-legal partnerships (collaborations between lawyers and healthcare teams) in resolving patients' legal problems and improving health outcomes.

Baid, Rinku

Poster Title: LEDGF1-326 decreases mutant rhodopsin P23H mediated cell damage potentially by reducing aggregates in human ARPE-19 cells

Category: Vision

Abstract: Purpose: To validate LEDGF1-326(fragment of lens epithelium derived growth factor (LEDGF)) as a potential therapeutic for the treatment of retinal diseases caused by mutant P23H rhodopsin aggregation. Methods: pEGFP-LEDGF1-326 and pP23H-CFP constructs were prepared and assessed in human retinal pigment epithelial cells. Using transient transfection, the aggregation behavior of P23H rhodopsin and its effects on cellular damage were assessed in the presence and absence of various doses of LEDGF1-326 using confocal microscopy and cell viability assays. Western blotting was performed to quantify the aggregation of P23H rhodopsin in the absence and presence of LEDGF1-326. Results: Expression of P23H rhodopsin in retinal pigment epithelial cells indicated distended nuclei, formation of intracellular debris, and a reduction in cell survival. Cellular damage was significantly reduced in cells expressing LEDGF1-326 in dose dependent manner. Additional studies indicated that LEDGF1-326 decreased the oligomers of P23H rhodopsin as well as those of wild type (WT) rhodopsin. Conclusions: LEDGF1-326 decreases the aggregation of P23H rhodopsin and the associated cellular damage in retinal pigment epithelial cells. LEDGF1-326 might be useful in treating cellular damage associated with protein aggregation diseases such as retinitis pigmentosa.

Balk, Daniel

Poster Title:

Category: Health Care and Public Health

Abstract: Study Objectives: Recently there has been increased attention to “distracted driving” from cell phone use or texting while driving; population estimates suggest that 25% of drivers regularly talk on cell phones while driving and 18% regularly text or email while driving. Less is known about the driving habits of emergency department (ED) patients, who may be a group more prone to high-risk behavior. We sought to describe the beliefs and self-reported behaviors of ED patients concerning distracted driving. Methods: Research staff invited consecutive patients aged 18-64 visiting an urban ED to self-complete a pilot-tested, confidential survey regarding their beliefs about driving risk and their self-reported driving patterns and crash experiences. Non-English speaking patients, those who did not currently drive, and those with cognitive impairment or a critical illness were excluded. We calculated proportions and 95% confidence intervals (CI) to describe the beliefs and behaviors of drivers by age group (18-24, 25-34, 35-44, 45-54, and 55-64 years), and we used Fisher exact tests to examine differences among age groups. Results: Overall, 201 patients completed the survey (participation: 82%). Slightly more than half were female (60%) with a median age of 42 (interquartile range: 23).

Most respondents drove everyday or almost every day (83%; 95% CI 77-88) and rated themselves as good drivers (88%, 95%CI 83-92). Most patients reported always wearing seat belts while driving (88%; 95%CI 83-92) and as passengers (85%; 95%CI 80-90), without significant differences by age group. More patients thought a driver is likely to be hurt if texting (94%) than if talking on a cell phone (84%) while driving, and more patients reported sometimes or always talking on a cell phone (39%) than texting (13%) while driving, with some differences by age groups (Table). In the past 12 months, 26% of respondents reported having been stopped by the police while driving and 13% reported having been involved in a motor vehicle crash as the driver, without differences by age group, gender, or texting or cell phone behavior. In this small sample, beliefs about the likelihood of being hurt by texting or cell phone use while driving were not associated with the self-reported behaviors themselves. Neither beliefs nor self-reported behaviors differed significantly by gender. Conclusion: Although most responding ED patients believed a person is likely to be hurt if talking on a cell phone or texting while driving, many reported doing these things themselves, especially talking on a cell phone, at rates higher than general population estimates. Younger patients, who appeared to have a lower perceived risk of cell phone use and texting while driving and a higher incidence of texting while driving, may be a particularly high risk group in need of targeted prevention messages.

Berlinberg, Adam

Poster Title:

Category: Metabolism and Endocrinology

Abstract: Purpose of Study: Nuclear factor-κB (NFκB) is activated in many cancers and plays a key role in promoting cell proliferation, survival, and invasion. This pathway has also been shown to play a role in resistance to chemotherapy and radiotherapy in some cancers. Most patients with advanced thyroid cancer are fairly resistant to standard chemotherapy. We hypothesize that inhibition of NFκB signaling (bortezomib) will sensitize thyroid cancer cells to standard chemotherapy (docetaxel). Methods: One anaplastic thyroid cancer cell line (8505C) and one papillary thyroid cancer cell line (BCPAP) were used to study the effects of bortezomib and docetaxel in combination or alone. An SRB-based growth proliferation assay was used to assess cell growth inhibition (3 days; 0-20 nM docetaxel, 0-10 nM bortezomib), while a Matrigel based invasion assay was used to assess invasion (18 hours; 0.31 nM docetaxel, 1.25 nM bortezomib). Apoptosis was studied using the Promega 3/7 Caspase Assay kit (24 hours; 0-10 nM docetaxel, 0-100 nM bortezomib). Summary of Results: Bortezomib and docetaxel act synergistically to inhibit cell proliferation, decreasing cell growth more than either drug alone (8505C Bliss Index: -0.145, BCPAP Bliss Index: -0.362;). Invasion is inhibited by combination treatment more than either drug alone (8505C: 16% invasion combo, 84% bortezomib, 73% docetaxel; BCPAP: 38% combo, 125% bortezomib, 91% docetaxel). The combined drug treatment activates the apoptosis pathway as indicated by Caspase activity, while only bortezomib activates the Caspase pathway alone (5 nM docetaxel, 50 nM bortezomib; 8505C:

6.48 fold Caspase increase bortezomib, 1.07 docetaxel, 6.89 combo; BCPAP: 7.90 bortezomib, 1.30 docetaxel, 8.63 combo). Conclusions: These data indicate that the combination of bortezomib and docetaxel is an attractive therapy for advanced thyroid cancer. Global decreases in growth and invasion with bortezomib and docetaxel in combination using clinically achievable IC50 values are encouraging for preclinical in vivo studies.

Blanchard, Ashley

Poster Title: Direct Admissions Are Not an Independent Risk Factor for Unplanned ICU Transfers from an Inpatient Unit within 12 Hours of Admission

Category: Health Care and Public Health

Abstract: DIRECT ADMISSIONS ARE NOT AN INDEPENDENT RISK FACTOR FOR UNPLANNED ICU TRANSFERS FROM AN INPATIENT UNIT WITHIN 12 HOURS OF ADMISSION. Ashley Blanchard, MD candidate University of Colorado School of Medicine. Jennifer Reese, MD1 (faculty sponsor); Lalit Bajij, MD, MPH1; S Deakyne, MPH1; T Neubrand, MD1; M Cunningham, MD1. 1Pediatrics, University of Colorado, Aurora, CO, United States. Background: Appropriate patient placement at the time of admission to avoid unplanned transfer to ICU and codes outside of the ICU is an important safety goal for many institutions. Patients directly admitted to the hospital are thought to be at increased risk of unplanned transfer to the ICU. Objective: To determine if direct admission is an independent risk factor for unplanned transfer to the ICU within 12 hours of admission. Design/Methods: A retrospective review of all of unplanned ICU transfers within 12 hours of admission to an inpatient unit at a tertiary care children's hospital from January 2010-July 2011. Records were reviewed by the Patient Disposition Review Committee and cases were categorized as preventable or non preventable based on certain clinical criteria. Proportion of preventable unplanned transfers from each portal of entry were calculated and compared to overall admissions. Results: 166 unplanned ICU transfers occurred during the study period, 71 (43%) were preventable. The most common cause was misplacement based on illness acuity (37, 53%), followed by miscommunication (27, 39%), high ICU census (6, 8%), missed diagnosis (4, 6%) and other (4, 6%) (multiple selection was allowed). The proportion of patients with preventable unplanned transfers that were directly admitted, admitted from the ED or the OR were not different from these proportions of all patients admitted to the hospital ($p = 0.3088$) Conclusions: The most common causes of unplanned ICU transfers were misplacement for illness acuity and miscommunication. Admit source of unplanned transfers did not differ from overall hospital admissions. Interventions to prevent unplanned transfers should be focused within inpatient departments, specifically on improving communication and properly placing patients at the time of admission. Next steps include further specific clinical analysis of diagnosis, interventions and outcomes in our population.

Burneikis, Dominykas

Poster Title:

Category: Surgery

Abstract: INFLAMMATORY MARKER MCP-1 ELEVATED IN RAT BRAIN FOLLOWING TRAUMA HEMORRHAGIC SHOCK . D Burneikis (MD, SOM), L Lee, J Stringham, M Fragoso, F Gamboni, A Banerjee, Deparment of Surgery, University of Colorado School of Medicine, Aurora, CO. Systemic inflammatory response syndrome (SIRS) following severe trauma with hemorrhagic shock (T/HS) contributes to increased morbidity and mortality in resuscitated patients. Though T/HS and SIRS have been studied extensively in liver, lung and kidneys, the inflammatory status of the brain following T/HS remains largely undefined. Elevated concentrations of monocyte chemotactic protein-1 (MCP-1) and interleukin-1 beta (IL-1b), as seen after systemic infection-induced inflammation, have been established as reliable markers of neuroinflammation. We hypothesized that MCP-1 and IL-1b concentrations in the brain would be elevated in rats subjected to trauma and hemorrhagic shock. Rats were subjected to T/HS (laparotomy, hypovolemic shock to MAP of 30 mmHg for 45 minutes) and resuscitated with shed blood. Brains were dissected and homogenized in their entirety. Plasma fraction of whole blood was collected from each animal. MCP-1 and IL-1b concentrations in whole brain homogenate were determined by ELISA and normalized to total protein concentration in the sample. Significance was tested using Student's t-Test. MCP-1 concentration significantly increased in plasma ($p=.04$) and whole brain homogenate ($p=.009$) from the T/HS group when compared to controls. There was no significant difference in whole brain homogenate IL-1b concentration between T/HS and control groups. Animals in the T/HS group sustained sufficient injury to cause systemic inflammation as evidenced by elevated plasma MCP-1 concentration. Furthermore, elevated whole brain homogenate MCP-1 concentration in the T/HS group suggests the presence of neuroinflammation as early as three hours post shock. Additional study including other markers and multiple time points for comparison will define the neuroinflammatory peak following T/HS.

Burrack, Adam

Poster Title:

Category: Immunology and Autoimmune Diseases

Abstract: AUTOIMMUNE DESTRUCTION OF AN ISLET ALLOGRAFT IS DELAYED BY CO-STIMULATION BLOCKADE THERAPY. A Burrack (PhD, GS) M Coulombe, KS Beard, and RG Gill, Department of Immunology, Univ. of CO, Aurora, CO. Type 1 diabetes (T1D) results in hyperglycemia due to an autoimmune attack on insulin-producing beta cells within the pancreatic islets. Islet allografts can restore euglycemia in T1D patients; however these grafts do not survive. Non-obese diabetic (NOD) mice develop insulitis and autoimmune beta cell destruction requiring CD4+ T cells, CD8+ T cells, and B cells. We study islet allograft destruction by the NOD mouse as a system to interrogate concurrent autoimmune and alloimmune T cell responses. In the NOD recipient, islet allograft destruction is more rapid than isograft destruction, despite the fact that NOD mice harbor self-MHC-restricted memory T cells specific for islet-derived peptides. Regulatory T cells delay diabetes onset in NOD mice. We hypothesized that depletion of CD25+ regulatory T cells would accelerate isograft destruction – which we have observed. T cell co-stimulation blockade via anti-CD154 antibody significantly delays isograft destruction in the NOD recipient. We observed an approximate 10-fold decrease in the percent of graft-infiltrating CD4+ T cells that co-produced IFN-gamma and TNF-alpha upon ex vivo polyclonal re-stimulation. CD154 blockade had less effect on islet allograft rejection. We hypothesize that a sub-population of autoimmune memory T cells will cross-react with graft cell MHC. We will test this hypothesis by sorting graft-infiltrating CD8+ T cells at the time of transplant destruction with MHC class I tetramers (IGRP206-214) followed by re-stimulation with allogeneic cells and quantification of IFN-gamma production. We predict a preponderance of graft-infiltrating IGRP tetramer-binding CD8+ T cells will respond to graft cell MHC. We do not expect to observe this allograft-specific response from isograft-infiltrating T cells. Because (1) Foxp3-expressing CD4+ regulatory T cells are thought to be required for both self tolerance and transplantation tolerance, (2) CD8+ T cells specific for IGRP206-214 can damage/destroy beta cells, and (3) anti-CD154 treatment had less effect on CD8+ T cells, we will test transient CD8+ T cell depletion in combination with anti-CD154 treatment. We predict this treatment will promote long-term isograft survival and prolonged allograft survival.

Canastar, Mehtap

Poster Title: AFFECT OF CRIZOTINIB ON THE PROTEIN EXPRESSION PROFILE AND ANCHORAGE INDEPENDANT PROLIFERATION OF 3T3 CELLS TRANSFECTED WITH EML4-ALK VARIANTS.

Category: Hematology and Oncology

Abstract: AFFECT OF CRIZOTINIB ON THE PROTEIN EXPRESSION PROFILE AND ANCHORAGE INDEPENDANT PROLIFERATION OF 3T3 CELLS TRANSFECTED WITH EML4-ALK VARIANTS. MD Canastar, (M.D., SOM), RC Doebele, Department of Medicine, University of Colorado, Denver, CO. Background: Small subset of non-small cell lung cancer (NSCLC) patients carry an inversion -inv(2)(p21p23)- that results in the fusion gene of echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK). EML4 portion of the fusion protein enables constitutive dimerization and thus deregulated activation of ALK and PI3K-AKT and RAS-MAPK signaling cascades resulting in proliferation of NSCLC cells. Patients with EML4-ALK fusion gene who are being treated with Crizotinib (TKI) show improvement. Inversion of small arm of chromosome 2 can occur at different locations contributing different EML4 fragments to the fusion proteins. Behavior of cells, such as proliferation, drug sensitivity and intracellular signaling events downstream of ALK, harboring different variants has not been investigated in detail, which is the focus of current project. Material and Methods: NIH 3T3 cells transfected with four different EML4-ALK variants were used: exons 6, 13, 18 and 20 (E6;A20, E13;A20, E18;A20 and E20;A20 respectively) of EML4 fuse to exon 20 of Alk in a lentiviral plasmid were introduced into NIH3T3. Puromycin selected cells were assayed for activation of Alk, Erk, Akt, and Stat3 in response to Crizotinib by western blotting. Soft agar assay was performed on NIH 3T3 cells with the different EML4-ALK variants to determine the effect of crizotinib on anchorage independent growth. Results: Western blotting showed that NIH 3T3 cells with the E6;A20 variant had reduced phosphorylated Alk, Erk, Akt and Stat3 in response to Crizotinib, cells with E13;A20 showed Alk and pAlk band at a lower than expected molecular weight. E18;A20 and E20;A20 showed very low levels of Alk. Only detectable affect of Crizotinib treatment on cells with E13, E18, E20 was reduced phosp Stat3 levels. RT-PCR showed no EML4-ALK mRNA for variants E13 and E18. Soft agar assays revealed different anchorage dependant growth in response to Crizotinib. Conclusions: Crizotinib has been showed to be an effective inhibitor of Alk and downstream signaling pathway in NIH 3T3 cells with the variant E6. Crizotinib effect was only detectable in Stat3 levels in cells with variants E13, E18, and E20. Further investigation is necessary to conclude if the low to undetectable levels of Alk in cells with variants E13, E18, E20 is due to ineffective transfection or due to variant effect.

Chandler, Joshua

Poster Title: NEBULIZED THIOCYANATE IMPROVES LUNG INFECTION OUTCOMES IN MICE

Category: Pharmacology and Physiology

Abstract: NEBULIZED THIOCYANATE IMPROVES LUNG INFECTION OUTCOMES IN MICE. JD Chandler (PhD, GS), E Min, J Huang, DP Nichols, BJ Day. Nebulization of isotonic and hypertonic saline solutions is used in the treatment of a number of pulmonary diseases including cystic fibrosis, asthma, and COPD. The benefits of these therapies include improved lung function, phlegm clearance, and fewer lung infections. Thiocyanate (SCN) is a normal component of the airway epithelial lining fluid (ELF). Pulmonary epithelia secrete SCN onto their apical surface as a mechanism to mitigate both oxidative and pathogenic stress. We observed that SCN acts as an antioxidant by protecting lung epithelial cells from both hypochlorous acid (HOCl), a major product of neutrophil myeloperoxidase (MPO), and MPO-mediated toxicity. We then exposed C57BL/6 mice to nebulized isotonic SCN (0.5% w/v) in saline and characterized its pharmacokinetics. Nebulized SCN increased ELF SCN levels approximately 20-fold after 30-minute treatment (Cmax=2.3 mM) and cleared rapidly (t1/2=4.4 h) with similar kinetics in the plasma (Cmax=1.2 mM, t1/2=5.1 h). We then nebulized mice infected with Pseudomonas aeruginosa with either SCN or saline control starting 24 hours post-infection and then twice daily up to 72 hours. Infected mice nebulized with SCN rapidly regained body weight lost prior to intervention and had significantly less bacterial burden and neutrophilic inflammation than control. SCN also enhanced reduced glutathione in the airway compared to control. SCN is a strong candidate for therapy in patients suffering from lung infection and the associated inflammation and oxidative stress as observed in cystic fibrosis and other infectious diseases of the lung.

CHANG, KUN-CHE

Poster Title: BETA-GLUCOGGALIN SUPPRESSES LIPOPOLYSACCRIDE-INDUCED INFLAMMATORY MARKERS BY ALDOSE REDUCTASE INHIBITION IN MURINE MACROPHAGES AND OCULAR TISSUES

Category: Health Care and Public Health

Abstract: BETA-GLUCOGGALIN SUPPRESSES LIPOPOLYSACCRIDE-INDUCED INFLAMMATORY MARKERS BY ALDOSE REDUCTASE INHIBITION IN MURINE MACROPHAGES AND OCULAR TISSUES. KC Chang1, 2(Ph.D., GS), B Laffin1, J Ponder2, A Enzsoly3, J Nemeth3, DV LaBarbera2 and JM Petrash*1, 2, 1Department of Ophthalmology, School of Medicine; 2Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Science, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA; 3Department of Ophthalmology, Semmelweis University, Budapest, Hungary.
Aldose reductase (AR) reduces toxic lipid aldehydes and mediates inflammatory signals triggered by lipopolysaccharide (LPS). β-glucogallin (BGG), a recently described AR inhibitor,

was purified from extracts of the Indian gooseberry (Emblica officinalis). In this study, we found BGG shows low cytotoxicity in Raw264.7 murine macrophages and effectively inhibits AR activity as measured by suppression of sorbitol accumulation. In addition, BGG-mediated inhibition of AR prevented LPS-induced cytokines release, activation of JNK, p38 and lowered ROS levels, which could inhibit LPS-induced apoptosis. Uveitis is disease of the eye associated with chronic inflammation. In this study, we also demonstrated that BGG suppresses the infiltration of inflammatory cells into the ocular media of mice with experimental uveitis. To understand why AR inhibition suppresses LPS-induced uveitis, we investigated the morphology and migration of macrophages. We demonstrated that BGG attenuates LPS-induced cellular morphological change and migration. We further proved that BGG inhibits LPS-induced MMP-9 activation, which plays an important role for macrophages to migrate to the site of inflammation. Accordingly, these results suggest BGG is a potential therapeutic for inflammatory diseases.

Cho, Eun

Poster Title: ASSOCIATIONS OF BODY SITE AND SEX WITH MOLE GROWTH IN A 1998 BIRTH COHORT OF COLORADO CHILDREN: A PILOT STUDY ANALYSIS OF CHANGE IN MOLE SIZE BETWEEN THE AGES OF 12 AND 13

Category: Health Care and Public Health

Abstract: Any change in size, shape, color, or feel in a mole is a warning sign for melanoma. Faster growing moles are associated with greater risk, and larger moles are more likely to develop into melanoma. The aims of the study were to describe the magnitude of mole size change over a one-year period during adolescence and to compare changes in mole size on the face vs. the back between boys and girls, and to determine if there is an interaction between sex and body site. A random sample of 50 children from a Colorado birth cohort was used for a pilot study examination of changes in mole size over one year across body site (face and back) by sex. Three moles per site were measured on each child at ages 12 and 13. Linear mixed models were used to account for correlation in change in size across moles within a child and to adjust for phenotypes. Each mole on a child was used as the unit of analysis, clustered by location on the body within each child. In both years, moles on the back were significantly bigger than moles on the face. The average change in mole size was 0.05mm on the face and 0.32mm on the back. Change in mole size on girls' backs was significant after adjusting for phenotypes (0.42mm, p

Crunk, Amanda

Poster Title:

Category: Metabolism and Endocrinology

Abstract: DYNAMIC REGULATION OF HEPATIC LIPID DROPLET PROTEOME BY DIET. AE Crunk 1,2 (Ph.D., GS), J Monks2, A Murikami1,2, M Jackman3,4,5,7, PS McLean3,4,5,7, M Ladinsky8, ES Bales2, S Cain5, DJ Orlicky6,7, JL McManaman1,2,4,5,7Program of Molecular Biology1, Division of Basic Reproductive Sciences2, Division of Endocrinology and Metabolism3, The Center for Human Nutrition4, The Colorado Obesity Research Initiative5, Department of Pathology6, University of Colorado School of Medicine, 7 and The Department of Molecular Developmental Biology, University of Colorado Boulder8 Obesity affects nearly 30% of the population in the United States. Health consequences of obesity include cardiovascular and kidney diseases, type II diabetes, and non-alcoholic fatty liver disease. Although there are many causes of liver steatosis, the excess accumulation of cytoplasmic lipid droplets (CLD) account for almost 70% of all liver steatosis cases. How CLD affect metabolism, and how nutritional status impacts CLD function, are essential elements in understanding steatosis and its associated pathophysiological manifestations. CLD contain specialized proteins that mediate their formation and function. Because information about the properties of hepatic CLD proteins is limited, and the role diet plays in regulating hepatic CLD formation is unknown, we set out to investigate the effects of dietary fat CLD protein composition. Livers from mice fasted and re-fed a low fat diet (LFD) or high fat diet (HFD) were analyzed by HPLC-MS/MS, western blot, immunofluorescence microscopy (IFM) biochemical and metabolic analysis. The proteome of the HFD-CLD contained more proteins from pathways in β-oxidation, lipid metabolism, steroid and cholesterol synthesis, carbohydrate synthesis and transport. LFD-CLD had increases in amino acid metabolism, nucleotide metabolism, carbohydrate catabolism, and lipid synthesis proteins. Perilipin 2 (Plin2), a critical regulator of CLD formation was the most abundant protein on HF-CLD. IFM demonstrated that Plin2 specifically localized to both LF- and HF-CLD, and quantitative immunoblot showed that relative abundance on HF-CLD was about 4x that of LF-CLD. Immunoelectron microscopy documented that HF feeding increased the Plin2 surface density. Taken together these data point to clear effects of diet on the hepatic CLD proteome and suggest that Plin2 surface density may be a physiological determinant of CLD function.

Daily, Sarah

Poster Title: TRANSITIONAL CARE MODELS' IMPACT ON MINORITIES AND RURAL POPULATIONS

Category: Health Care and Public Health

Abstract: TRANSITIONAL CARE MODELS' IMPACT ON MINORITIES AND RURAL POPULATIONS. SE Daily (BSN, CON), DD Cline, Ph.D., College of Nursing, University of Colorado | Anschutz Campus, Aurora, CO. Purpose: To review literature on two care transition models, the Care Transitions Intervention and the Transitional Care Model, focusing specifically on each models' impact on underserved racial/ethnic minorities and rural populations. Background: Readmission of patients recently discharged is costly and often unnecessary. Efforts to avoid readmissions have focused on transitional care models. Little is known about the impact of these models on racial/ethnic minorities and rural populations. By 2042, the US Census Bureau predicts that minorities will make up a majority of the US population. It has been shown that racial/ethnic minorities experience significant healthcare disparities and have increased rates of hospital readmissions. Rural communities, another underserved population, also face known disparities such as fewer healthcare resources and a lack of healthcare providers. Given the expected demographic changes and known disparities, it is important to assess the impact of transitional care models on racial/ethnic minorities and rural populations. Methods: The bibliographic databases of Pubmed and CINAHL were searched for studies examining the impact of the Care Transitions Intervention and the Transitional Care Model on patient/caregivers outcomes. Qualitative and quantitative studies were included. Data elements were extracted from ten studies to identify common themes and the impact on racial/ethnic minorities and rural populations. Results: The transitional care models were effective in reducing readmissions. Common themes identified between the models included, a single point of contact, the importance of communication, and the need for patients/caregivers engagement. The studies lacked a strong focus on racial/ethnic minorities or rural populations. Implications: The models were effective in lowering readmission rates, but the majority of participants were white, English-speaking, and urban dwelling. It is unknown if these care models are effective for racial/ethnic minorities and rural populations. More research is needed to determine if either transitional care model reduces readmission rates for minorities and rural populations, and what if any changes to the models are needed to contextualize them for underserved populations.

Dege, Carissa

Poster Title: METHYL CPG BINDING BY THE MI-2/NURD COMPLEX IS REQUIRED FOR TRANSCRIPTIONAL REPRESSION IN B CELLS.

Category: Immunology and Autoimmune Diseases

Abstract: METHYL CPG BINDING BY THE MI-2/NURD COMPLEX IS REQUIRED FOR TRANSCRIPTIONAL REPRESSION IN B CELLS. Dege C, (Ph.D., GS), Julita Ramirez and James Hagman. Integrated Dept. of Immunology, National Jewish Health, Denver, CO USA. We demonstrated previously that the mb-1 (Igα; Cd79a) promoter is demethylated progressively during its activation in early B cell development. Demethylation of promoter CpGs is initiated by the binding of Early B Cell Factor 1 (EBF1), which facilitates accessibility necessary for binding of mb-1 promoter DNA by Pax5 prior to transcription. This process is inhibited by Mi-2/Nucleosome remodeling and histone deacetylase (NuRD) chromatin remodeling complexes. The function of Mi-2/NuRD was evidenced by knockdown of its ATPase, Mi-2β (CHD4), which potentiated effects of EBF1 and Pax5. Recent work in the laboratory has focused on other components of the Mi-2/NuRD complex to assess its association with methylated DNA. Different Mi-2/NuRD complexes contain the Methyl Binding Domain proteins 2 or 3 (MBD2 or MBD3). MBD2 binds methylated cytosines, while MBD3 binds hydroxymethylated cytosines. Similar to depletion of Mi-2β, knockdown of MBD2 using shRNA potentiated mb-1 transcriptional activation in the presence of EBF1 and Pax5. This increased activation was similar to that obtained using 5-azacytidine, which reduces cytosine methylation by inhibiting DNA methyltransferases. In addition, cytosine methylation at mb-1 promoters is decreased in response to knockdown of MBD2. Knockdown of MBD2 also modestly increased chromatin accessibility at the mb-1 promoter in response to exogenous EBF1 and Pax5 expression (~2-fold compared to luciferase knockdown control). Due to its stability, we were unable to similarly tests for requirements for MBD3 in our system. Our data suggest that methyl-cytosine binding by Mi-2/NuRD complexes containing MBD2 is important for transcriptional attenuation of the mb-1 gene in B cells, when it recruits Mi-2/NuRD complexes to gene targets being repressed.

Derry, Molly

Poster Title: CHEMOPREVENTIVE POTENTIAL OF GRAPE SEED EXTRACT IN AZOXYMETHANE-INDUCED COLON TUMORIGENESIS IN THE A/J MOUSE MODEL: INTERLINKING miRNA EXPRESSION AND INFLAMMATORY AND CYTOKINE SIGNALING

Category: Pharmacology and Physiology

Abstract: CHEMOPREVENTIVE POTENTIAL OF GRAPE SEED EXTRACT IN AZOXYMETHANE-INDUCED COLON TUMORIGENESIS IN THE A/J MOUSE MODEL: INTERLINKING miRNA EXPRESSION AND INFLAMMATORY AND CYTOKINE

SIGNALING. M Derry (Ph.D., SOP), K Raina, V Balaiya, A Jain, S Shrotriya, R Agarwal and C Agarwal, Department of Pharmaceutical Sciences, University of Colorado, Aurora CO. Colorectal Cancer (CRC) is the second leading cause of cancer-related deaths worldwide and traditional therapies are associated with severe toxicity; therefore, natural products are appealing alternatives. Grape seed extract (GSE) is a complex polyphenolic mixture whose beneficial effects have been well documented. Most of CRC develops sporadically, and diet, lifestyle, and/or environmental factors contribute to CRC progression. Chemoprevention utilizes any agent to delay or stop cancer progression. Here in we investigate the chemoprevention potential of GSE against the Azoxymethane (AOM)-induced colon tumorigenesis. In our study A/J mice were divided into 5 groups: Group 1 received control diet (CD), Group 2 received 0.5% GSE in diet, and the other 3 groups received injections of AOM (5mg/kg) weekly, for six weeks. Two weeks post AOM, one group continued on CD and the other groups were supplemented with 0.25% and 0.5% GSE (w/w); animals were sacrificed at 32 and 42 weeks. GSE (0.25%-0.5%) in diet didn't exhibit toxic effects and resulted in a 55% decrease in colon tumor multiplicity. Tissue analysis revealed GSE' mechanisms of action: apoptotic death, and decreased proliferation and inflammation. Immunohistochemistry (IHC) analysis revealed that compared to controls, colon tissue from GSE-treated mice showed a 2-fold increase in apoptotic cells, 30% decrease in proliferative cells, and ~50% decrease in inflammatory mediator levels. Cytokine analysis of colon tissue revealed GSE treatment resulted in induction of GM-CSF, I-309, IL-1α, and BLC and reduction of IL-2, IL-1R, and IL-27 levels. miRNA analysis of colon tissue revealed upregulation of miR-19a, miR-20a, and let7a and down regulation of miR-196a, miR-21, miR-148a, and miR-103 with GSE treatment. In addition, GSE treatment resulted in decreased over-all expression of p21, β-catenin, c-myc, VEGF, and ERK 1/2. In conclusion, our results indicated that GSE is a non-toxic agent that exerts strong chemopreventive effect against sporadic colorectal cancer development, through modulation of apoptosis, proliferation, and inflammation pathways.

D'souza, Ryan

Poster Title:

Category: Hematology and Oncology

Abstract: A GENOME-WIDE RNA INTERFERENCE SCREEN TO IDENTIFY NOVEL REGULATORS OF CHROMOSOME SEGREGATION IN MITOSIS. RS D'souza (M.D., SOM), BG Mellone, E Larschan, Department of Molecular and Cell Biology, University of Connecticut, Storrs, CT. In the search for regulators of chromosome segregation, a variety of genome-wide approaches have been utilized. One such remarkable study, a mutagenesis screen in Schizosaccharomyces pombe, utilized the intensity of nuclei signal as a readout of successful chromosome segregation which identified novel regulators of chromosome segregation. Here we use a preliminary qualitative assessment of a genome-wide RNA interference (RNAi) screen of the Male-specific Lethal 1 protein (MSL1) in Drosophila S2 cells to identify novel regulators of

chromosome segregation. Knockdowns of these factors, by RNAi, led to multiple MSL1 foci per nucleus, in contrast to the wild-type phenotype of a single MSL1 focus per nucleus. We denoted this as the "fragmented MSL1 phenotype," reflecting an incorrect number of X chromosomes that have accumulated due to chromosome mis-segregation. Computational analysis of this RNAi screen yielded a total of 374 positive genes. Five identified novel genes, CG30020, NEK2, His4r, CG5880, and CG2865 were confirmed to display severe chromosome mis-segregation after RNAi knockdown. Thus, this computational approach of associating an easily discernible "fragmented MSL1 phenotype" with chromosome mis-segregation was successful in identifying novel regulators of chromosome segregation in Drosophila melanogaster. Additional cellular assays, such as investigating whether these novel factors co-localize and interact with known centromere proteins at the centromere locus, will shed light into their specific roles in the process of chromosome segregation.

Finn, Erin

Poster Title: THE EFFECTS OF BREASTMILK ON INFANT MICROBIOMES THROUGH PROMOTION VS INHIBITION OF BACTERIAL GROWTH

Category: Microbiology and Infectious Diseases

Abstract: THE EFFECTS OF BREASTMILK ON INFANT MICROBIOMES THROUGH PROMOTION VS INHIBITION OF BACTERIAL GROWTH. EE Finn, (M.D., MS), CE Gustafson, DN Frank, EN Janoff, University of Colorado School of Medicine, Aurora, CO. Purpose of Study: The development of an infant's intestinal microbiota has important health implications and has been linked to development of obesity, type 1 diabetes, and other immune conditions. Breastfed infants have different intestinal commensal bacteria compared with non-breast fed infants. We investigated the functional ability of breast milk to promote and/or inhibit growth of intestinal bacteria. Methods Used: We studied milk and stool from 17 healthy breastfed infants in Denver at birth, 1, 2, 6 and 12 months. Using a well-characterized strain of E. coli of intestinal origin, we assayed the ability of milks from women to modulate the growth of the bacteria over 2 hours. The bacteria growth assays were conducted in two environments, nutrient rich and nutrient poor. We used the nutrient rich environment (LB broth media) to examine the relative inhibition of bacterial growth and the nutrient poor environment (PBS) to examine the growth promoting effects of the various breast milks. Growth levels were measured using serial dilutions of milk/bacteria by the quantitative drop plate method. Summary of Results: Based on results of high-throughput ribosomal DNA sequencing to define the populations of colonizing bacteria over time, we found that Escherichia-Shigella genus (E. coli) was present in variable concentrations in different infants over time, some high (10-40% of bacteria) and other low (0-10%) at 1 month of age. In a nutrient poor environment, all breast milks enhanced growth of E. coli at various levels relative to the PBS control. In a nutrient rich environment some, but not all, milks inhibited growth of E. coli relative to a nutrient rich control. However, the ability of breast milk to inhibit or promote E. coli growth did not correlate with

Escherichia-Shigella concentrations found in the matched infant stool. Conclusions: Breast milk affects the growth of bacteria. The balance between promotion and inhibition of growth needs to be further investigated in order to deduce if the effects of one outweigh the other. These results may have implications for understanding and potentially modifying the intestinal microbiome during early infancy to limit the development of microbiome-related immune dysfunction later in life.

Francomano, Jesse

Poster Title:

Category: Health Care and Public Health

Abstract: UTILIZING SOCIAL NETWORKING SITES TO PROMOTE THE HEALTH OF ADOLESCENTS Jesse A. Francomano, BA (BS Nursing Student) & Scott B. Harpin, PhD, MPH, APRN-BC College of Nursing University of Colorado, Anschutz Medical Campus Aurora, CO INTRODUCTION: The aim of this study is to examine the strengths, weaknesses and best practices of utilizing social networking sites (SNS) in adolescent research. Also, to examine how SNS can facilitate ethically sound, high-quality health care to adolescents, particularly those at-risk for engaging in high-risk behaviors and vulnerable youth. SNS use has exploded in the last few years and is being adapted as an important tool for health care interventions. Specifically, Facebook's membership of over 800 million active users and ubiquitous presence on computers and smart phones, SNS have already provided a platform for adolescents to gain access to personal health information. As this platform continues to grow more conventional even among vulnerable youth, health providers and researchers need to be cognizant of SNS best practices for primary prevention, and how to better utilize these tools for health care delivery and health education. METHODS: A systematic literature review of health and social sciences literature from the past 5 years was organized according to the Matrix Method (Gerrard, 2006). Key words included: adolescents, social networking, health, Facebook and consent. 32 articles were reviewed for relevance and placed in a matrix for organization and summarization. Works were further grouped by shared content to understand themes of the current literature on SNS use in health care research with adolescents and young adults. Findings were validated by an outside expert to assure interrater reliability. RESULTS: Recurrent themes were apparent, including benefits of SNS use for health care education. Adolescents can utilize SNS for easy access to health information. SNS can be used effectively to remind patients about medications or health care appointments. SNS provide a platform for peer support and networking. SNS can provide a means for assessment of risk factors related to unhealthy lifestyles. Drawbacks include: ensuring safety for adolescents accessing information (mainly privacy and protection from potential 'sex predators'); technological barriers of both the user and the practitioner; and staying on top of the SNS technology as it often evolves frequently. DISCUSSION: Though themes are apparent, more research is needed in each area of SNS to better understand how such websites can be better utilized to provide access to adolescents

seeking health care and health information. SNS are an excellent means of reaching young people as they seek to privately and securely gain health information, and interact with heath systems. Given the broad reach of SNS, it is imperative that all health information be closely monitored for accurate and safe distribution. Finally, consent and privacy issues are omnipresent in SNS, which call for ethical standards of use.

Grabek, Katharine

Poster Title: DEFINING THE BROWN ADIPOSE TRANSCRIPTOME OF A CIRCANNUAL HIBERNATOR

Category: Metabolism and Endocrinology

Abstract: DEFINING THE BROWN ADIPOSE TRANSCRIPTOME OF A CIRCANNUAL HIBERNATOR. KR Grabek, (Ph.D., GS), and SL Martin, Human Medical Genetics and Genomics Program, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO. Obesity is a major health crisis in the United States. Currently nearly 70% of all U.S. adults are classified as overweight or obese. One novel, recently-recognized strategy in obesity treatment is the exploitation of brown adipose tissue (BAT). BAT uses free fatty acids as a fuel to produce heat via non-shivering thermogenesis (NST). Estimates suggest as little as 50g of metabolically active BAT can consume 20% of total daily energy expenditure in adults. However, for BAT to be successfully exploited as an obesity-treatment strategy, the mechanisms that underlie its growth and metabolic regulation must be characterized. Hibernating mammals make excellent natural models for studying this tissue. During the extended period of hibernation, they are dependent upon BAT for rewarming during repeated arousal episodes and to maintain a minimum body temperature in torpor. Moreover, the tissue undergoes an annual cycle of atrophy and hypertrophy. Our current study aims to characterize the transcriptomic changes that underlie the BAT phenotype in a circannual hibernator, the 13-lined ground squirrel, Ictidomys tridecemlineatus. Specifically, 27bp cDNA “tags” from BAT mRNA libraries representing 8 distinct physiological and seasonal states of the hibernator’s year were generated via the EcoP15I-tagged Digital Gene Expression (EDGE) methodology. These tags were next sequenced on an Illumina GAIIx and mapped to the 13-lined ground squirrel genome. After filtering, 27,440 unique tags were annotated to genes and are now being analyzed with statistical methods, including hierarchical clustering of individual samples, testing for differential gene expression among the states and clustering of gene expression patterns. Our preliminary results suggest that most gene expression changes are seasonal; transcripts involved in lipid metabolism dominate the period of hibernation, while those involved in apoptosis and RNA-processing dominate the period of homeothermy. After completion of all analyses, we expect to glean novel insights into the mechanisms that regulate BAT growth and metabolic activity throughout the dynamic phenotypic transitions of circannual hibernation, which may then be applied to devising novel strategies for treating human obesity.

Grudis, Jonathan

Poster Title: EXPRESSION OF CARDIOLIPIN BIOSYNTHESIS AND REMODELING ENZYMES IN ADULT HEART FAILURE

Category: Cardiovascular

Abstract: EXPRESSION OF CARDIOLIPIN BIOSYNTHESIS AND REMODELING ENZYMES IN ADULT HEART FAILURE. JE Grudis (M.D., SOM), KC Chatfield*, GC Sparagna#, J Hijmans^, RD Sobus^, CC Sucharov^, SD Miyamoto*, BL Stauffer^,#. *Department of Pediatric Cardiology, Children's Hospital Colorado, Aurora, CO; ^Division of Cardiology, University of Colorado Denver Anschutz Medical Campus, Aurora, CO; #Department of Integrative Physiology, University of Colorado, Boulder, CO. Background: Cardiolipin (CL) is a unique phospholipid that is an essential component of the inner-mitochondrial membrane (IMM) and is critical to normal energy metabolism. In the heart, CL exists predominantly in the tetralinoleic form, (18:2) 4CL, which has the greatest affinity for the IMM and protection against cellular apoptosis. Biosynthesis of CL occurs by means of a five-step enzymatic pathway. Tetralinoleic CL is formed by the remodeling of existing CL. Total CL content is lower in ventricular tissue from adult humans with idiopathic dilated cardiomyopathy (IDC). Purpose: The aim of this study was to determine which mitochondrial CL biosynthetic and linoleic remodeling enzyme levels are dysregulated in adult IDC. Methods: mRNA was isolated from failing adult left ventricle of patients with IDC obtained at the time of transplant (LV; n= 27; mean age = 51.7+14.5) and non-failing control LV from donor hearts not implanted for technical reasons (n= 15, mean age = 43.6+8.7). RT-PCR was employed to measure gene expression of CL biosynthesis and (18:2) 4CL remodeling enzymes. Results: In the biosynthesis pathway we found 37% lower CDP diacylglycerol synthase 2 and 35% lower phosphatidylglycerolphosphate synthase (both P

Gustafson, Claire

Poster Title: DIMINISHED ANTIBODY SUBCLASSES AND ALTERED CD40 SIGNALING IN HUMAN NEWBORN B CELLS WITH ANTIGEN-INDEPENDENT STIMULATION.

Category: Immunology and Autoimmune Diseases

Abstract: DIMINISHED ANTIBODY SUBCLASSES AND ALTERED CD40 SIGNALING IN HUMAN NEWBORN B CELLS WITH ANTIGEN-INDEPENDENT STIMULATION. CE Gustafson (Ph.D., GS), DN Frank, TL Phang and EN Janoff. MAVRC, University of Colorado, Aurora, CO and Denver Veterans Affairs Medical Center, Denver, CO. Following initial IgM responses to infection or vaccine, antibody class switching (CS) to IgG or IgA isotypes is critical for effective protection. However, compared with adults, antibody CS is impaired in young infants. Thus, we modeled human antibody responses in newborns and adults in vitro to determine whether these differences are due to impaired T cell help to B cells and/or intrinsic

signaling defects in newborn B cells. We assessed the quantity and isotype of antibodies produced by circulating naïve B cells from newborns and adults by ELISA pre- and post-stimulation with bacterial toll-like receptor 9 agonist (CpG) and soluble (IL-21, IL-4) and cognate (anti-CD40) T cell factors. We also characterized the expression of mRNA from genes regulating CS by high-throughput global mRNA sequencing (Illumina Hi-Seq). We found that antibody production by adults after stimulation exceeded that by newborns, although the relative distribution of antibody isotypes was similar (IgM>>IgG>IgA). However, the proportions of transcripts for CS antibody subclasses IgG1, IgA1, and IgA2 in newborn B cells were reduced compared with adults. Both newborn and adult B cells showed similar upregulation of CS regulatory genes AID, RPA1 and EXO1. However, the expression of the surface signaling receptor CD40 was reduced on newborn B cells compared with adults. Moreover, downstream CD40 signaling differed between newborn and adult B cells. Thus, altered CD40 expression and differential downstream signaling in newborns B cells may underlie their reduction in antibody production and skewing of isotype subclasses. Modulation of CD40 expression by direct toll-like receptor stimulation on newborn B cells may overcome the limitations in newborn antibody responses and provide a mechanism to improve vaccine efficiency and efficacy in early infancy.

Habermehl, Gabriel

Poster Title: DETERMINANTS OF ROTAVIRUS-SPECIFIC ANTIBODY RESPONSES TO ORAL VACCINE IN SERUM IN INFANTS

Category: Microbiology and Infectious Diseases

Abstract: DETERMINANTS OF ROTAVIRUS-SPECIFIC ANTIBODY RESPONSES TO ORAL VACCINE IN SERUM IN INFANTS. GK Habermehl, (M.D., SoM), JT Rahkola, DN Frank, and EN Janoff, Department of Infectious Disease, University of Colorado, Denver, CO. Purpose of Study: Rotavirus (RV) is the leading cause of infant death from diarrhea worldwide. Protection against RV by the live oral vaccine varies by country. The determinants of immunogenicity (as a proxy for protection) by RV vaccine are largely unknown. The purpose of these studies was to correlate RV-specific IgG and IgA responses to live-attenuated oral vaccine in infant sera, with RV-Specific (RV-S) IgA in breastmilk, and gut microbiome diversity during the first year of life in both vaccinated and unvaccinated groups. Methods Used: 11 infants received RV vaccine at 2, 4, and 6 months. 2 infants were unvaccinated. We measured RV-S IgA and IgG in infant serum at 0, 1, 2, 6 and 12 months and in maternal breast milk at 2 months by ELISA. We coated microtiter plates (MaxiSorp; Nunc) with 2.9µg/ml virus, added dilutions of serum (1:4000-1:8000). We detected RV-S antibody with Biotin–labeled affinity-purified goat anti–human IgG or IgA (Jackson Immuno), and Strepavadin-HRP (Invitrogen)/TMB (BD) developer. Values were derived from standard curves. We compared values within groups over time by paired t test and between groups by unpaired t-test. Summary of Results: RV-S IgG and IgA were detected in infant sera by 12 months in all vaccinated infants and 1/2 unvaccinated infants albeit at lower levels. Maternal RV-S IgG reaches a nadir in infant sera at 6 months.

RV-S IgA was detected in most vaccinated infants by 6 months whereas RV-S IgG was not detected until 12 months, when levels of RV-S IgG exceeded those of IgA. The avidity of IgA was higher than that of IgG at 12 months. All mothers had similar levels of RV-S IgA in breast milk at 2 months. These levels did not correlate with the magnitude of infant vaccine responses. Preliminary data suggests the gut microbiome diversity at 2 months correlates with RV-S serum IgG response to vaccine at 12 months. Conclusions: As maternal RV-S IgG declines over time, RV-S IgA precedes RV-S IgG in infant sera, each requiring ≥2 doses. RV-S IgA likely offers protection at the site of infection in the gut compared with IgG. Further investigation is needed regarding the relationship of microbiome diversity and vaccine response and the underlying mechanisms.

Hoover, Whitney

Poster Title: PREDICTORS OF NEONATAL NEUROLOGIC BIRTH DEPRESSION AND INTRAVENTRICULAR HEMORRHAGE IN PRETERM PREMATURE RUPTURE OF MEMBRANES

Category: Child-Maternal Health and Reproductive Sciences

Abstract: Preterm birth is a major cause of adverse perinatal outcomes, including birth depression and intraventricular hemorrhage (IVH). Both birth depression and IVH contribute to lasting neurological disability, however the role of maternal characteristics in contributing to these outcomes have not been well defined. We sought to determine predictors of these adverse outcomes in pregnancies complicated by early preterm premature rupture of membranes (PPROM). We performed a retrospective cohort study of all singleton pregnancies with early PPROM 22 weeks GA at University of Colorado Hospital (UCH) from 1/1/ 2007-12/31/2011. Cases (n=229) were identified, confirmed, and abstracted from the UCH Perinatal Database. Adverse perinatal outcomes were defined as Apgar of

Hua, Jeremy

Poster Title: STRUCTURAL BRAIN MRI CHANGES FOLLOWING TESTOSTERONE SUPPLEMENTATION IN HEALTHY OLDER MEN

Category: Neuroscience and Brain and Behavior – Adult

Abstract: STRUCTURAL BRAIN MRI CHANGES FOLLOWING TESTOSTERONE SUPPLEMENTATION IN HEALTHY OLDER MEN. JT Hua (MD, SOM), DC Rojas, CM Filley, RS Schwartz, VS Pelak, Department of Neurology, University of Colorado School of Medicine, Aurora, CO. Men with low levels of endogenous testosterone have been shown to have mild impairments in memory, executive function, visuospatial abilities, and verbal fluency. Recent work has suggested that exogenous testosterone may improve cognitive performance in a curvilinear distribution. The aim of this study is to evaluate neuroanatomical transformations

after testosterone supplementation via Voxel-Based Morphometry (VBM), an imaging technique used to measure regional cortical changes in MRI scans following global brain shape normalization. We hypothesize that cortical thickness in the hippocampus, prefrontal cortex (Brodmann area 10), and the temporal-occipital-parietal junction of healthy older men is increased following low-dose supplementation compared to placebo and usual-dose groups. 32 healthy older men (mean: 64.0 yrs, range: 60-82 yrs) with low-normal testosterone levels (200-350 ng/dl) were randomized into one of three intervention groups: 1) no testosterone supplementation, 2) low-dose (25 mg/day), and 3) usual-dose (50 mg/day). T1-weighted brain MRI was acquired prior to and before the end of the one-year supplementation period. VBM was performed using an automated algorithm consisting of: mapping participants to a template MRI scan, extraction of gray matter for analysis of cortical thickness, modulation to account for brain size, and smoothing with a Gaussian kernel. Statistical analyses were performed with a mixed-design ANOVA. Preliminary analysis showed no group differences in the change in cortical thickness between the pre- versus post-supplementation scans when using an uncorrected significance threshold of p

Inturi, Swetha

Poster Title: ACTIVATION OF DNA DAMAGE REPAIR PATHWAYS IN RESPONSE TO NITROGEN MUSTARD-INDUCED DNA DAMAGE AND TOXICITY IN SKIN KERATINOCYTES

Category: Other:

Abstract: ACTIVATION OF DNA DAMAGE REPAIR PATHWAYS IN RESPONSE TO NITROGEN MUSTARD-INDUCED DNA DAMAGE AND TOXICITY IN SKIN KERATINOCYTES Swetha Inturi1; Neera Tewari-Singh1; Chapla Agarwal1; Carl W. White2 and Rajesh Agarwal1 Departments of Pharmaceutical Sciences1 and Pediatrics2, University of Colorado Denver, Aurora, CO Alkylating agent nitrogen mustard (NM), a structural analog of chemical warfare agent sulfur mustard (SM), upon exposure to tissues, forms adducts and crosslinks with DNA, RNA and proteins. The major mechanism of NM-induced toxicity involves DNA interstrand crosslinks (ICL) formation resulting in either induction of cell cycle arrest to facilitate DNA damage repair or cell death, in the case of inadequate repair. Consistently, NM (0.75 μM) exposure in mouse epidermal JB6 cells decreased cell growth and caused S-phase arrest by 16 h after exposure. Cells were then released to G2-M phase by 24 h and resumed normal cell cycle progression by 48 h after exposure. Repair of NM-induced DNA ICLs involves formation of DNA double strand breaks (DSB). Our studies showed an increase in comet tail extent moment starting between 4 and 8 h after onset of NM exposure, as well as an increase in levels of DNA DSB repair molecules (phospho H2A.X and p53, rad50 and XRCC1). The repair of DNA double strand breaks occurs via homologous recombination repair (HRR) or through the non homologous end joining pathway (NHEJ). The activation of the HRR pathway was evidenced by formation of Rad51 foci at 4 h after NM exposure, and activation of NHEJ

pathway was indicated by increases in phospho and total DNA-PK levels. To confirm this, NHEJ and HRR pathways were inhibited by using DNA-PK inhibitor NU7026 and Rad51 SiRNA, respectively. Inhibition of NHEJ did not result in a significant decrease in total cell number after 48 h of NM exposure and also did not affect the NM-induced S-phase arrest at 16 h. However, inhibition of the HRR pathway caused a 28% decrease in cell number, and a lack of NM-induced S-phase arrest, probably leading to an increase in the observed cell death. These studies indicate that HRR may be a key pathway involved in repair of NM-induced DNA DSBs. These findings may be useful in developing new therapeutic strategies against NM-induced skin toxicity.

Jackson, Brian

Poster Title: EARLY VERTEBRATE ORIGIN OF ALDH1B1 FROM ALDH2 GENE AND INACTIVATION OF ALDH1B1 BY HETEROMERIZATION WITH ALDH2*2

Category: Pharmacology and Physiology

Abstract: EARLY VERTEBRATE ORIGIN OF ALDH1B1 FROM ALDH2 GENE AND INACTIVATION OF ALDH1B1 BY HETEROMERIZATION WITH ALDH2*2. BC Jackson, (Ph.D., TXCL), RS Holmes, DS Backos, P Reigan, DC Thompson, and V Vasiliou, Department of Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO Vertebrate ALDH2 genes encode mitochondrial enzymes capable of metabolizing acetaldehyde and other biological aldehydes in the body. Mammalian ALDH1B1, another mitochondrial enzyme sharing 72% identity with ALDH2, is also capable of metabolizing acetaldehyde but has a tissue distribution and pattern of activity distinct from that of ALDH2. Bioinformatic analyses of several vertebrate genomes were undertaken using known ALDH2 and ALDH1B1 amino acid sequences. Phylogenetic analysis of many representative vertebrate species (including fish, amphibians, birds and mammals) indicated the presence of ALDH1B1 in many mammalian species and in frogs (Xenopus tropicalis); no evidence was found for ALDH1B1 in the genomes of birds, reptiles or fish. Predicted vertebrate ALDH2 and ALDH1B1 subunit sequences and structures were highly conserved, including residues previously shown to be involved in catalysis and coenzyme binding for human ALDH2. Studies of ALDH1B1 sequences supported the hypothesis that the ALDH1B1 gene originated in early vertebrates from a retrotransposition of the vertebrate ALDH2 gene. Given the high degree of similarity between ALDH2 and ALDH1B1, it is surprising that individuals with an inactivating mutation in ALDH2 (ALDH2*2) do not exhibit a compensatory increase in ALDH1B1 activity. We hypothesized that the similarity between the two ALDHs would allow for dominant negative heterotetramerization between the inactive ALDH2 mutants and ALDH1B1. Computational-based molecular modeling studies examining predicted protein-protein interactions indicated that heterotetramerization between ALDH2 and ALDH1B1 subunits was highly probable and may partially explain a lack of compensation by ALDH1B1 in ALDH2*2 individuals.

Kennel, Christopher

Poster Title: LOOKING FOR A PARKINSON'S DISEASE IMAGING BIOMARKER

Category: Neuroscience and Brain and Behavior – Adult

Abstract: LOOKING FOR A PARKINSON'S DISEASE IMAGING BIOMARKER. C Kennel (MD, SOM), A Shelton, B Berman MD, Dept. of Neurology, University of Colorado, Aurora, CO. Advances in functional connectivity magnetic resonance imaging (fcMRI) have led to new techniques that allow whole-brain visualization in vivo. These imaging studies, typically performed on resting subjects, are providing valuable insights into large-scale neuronal communication and whole-brain functional organization. While fcMRI holds promise for studying basal ganglia (BG) dysfunction associated with Parkinson's disease (PD), the majority of PD patients have tremors at rest, potentially complicating resting state fcMRI studies. Investigating BG functional connectivity during task performance could lead to a greater understanding of how striatal circuitry is altered in PD and avoid the potential confound of resting tremor. Parkinson's disease is a clinical diagnosis, and there is a pressing need for reliable PD imaging biomarkers. Task-based fcMRI studies of PD patients could help define such biomarkers, improve earlier diagnosis, and inform new drug or device development. We studied PD subjects aged 50-80 and age-matched, healthy volunteers. Subjects received physical, neurological, and cognitive assessments, then were scanned at the University of Colorado School of Medicine's Brain Imaging Center. FcMRI involved five-finger serial tapping sequences paced with audible cues and monitored via observation and electromyography. Image data was analyzed with SPM8, DPARSF and a MATLAB toolbox for functional connectivity that focused on six BG seeds per hemisphere plus the subject-specific motor region of interest determined by isolating the cortical area of maximum activation during the right and left hand tapping scans. Automatic anatomic labeling mapped functional connectivity of each seed with 116 brain regions. Ongoing work includes analyzing differences between the two groups and correlating PD disease severity with changes observed in functional connectivity. Analysis is ongoing and we expect that: 1) We will detect differences between the motor networks of healthy controls and PD patients; 2) The detectable level of motor network disturbance of PD patients will correspond to their motor symptom severity as measured by the Movement Disorders Society's Uniform Parkinson's Disease Rating Scale; and 3) Imaging will show additional disturbances in the basal ganglia's limbic and cognitive circuits in PD patients.

Kohler, Stephanie

Poster Title: GERMINAL CENTER T-FOLLICULAR HELPER CELLS (GC TFH) FROM NAÏVE HOSTS ARE HIGHLY PERMISSIVE TO HIV-1 EX VIVO

Category: Microbiology and Infectious Diseases

Abstract: GERMINAL CENTER T-FOLLICULAR HELPER CELLS FROM NAÏVE HOSTS ARE HIGHLY PERMISSIVE TO HIV-1 EX VIVO. Stephanie Kohler, MD Candidate for the School of Medicine, Joy Folkvord, MS, Elizabeth Connick, MD Purpose: TFH are 30-40 times more likely to be productively infected by R5 HIV in vivo. GC TFH, a TFH subset found in lymphoid germinal centers, express CXCR5 and PD-1. Whether GC TFH are more permissive to HIV than other TFH has not been established. Whether GC TFH are more susceptible to HIV that uses the CCR5 receptor (R5 HIV) versus HIV that uses the CXCR4 coreceptor (X4 HIV) disease has not been determined. Methods: Tonsils from 9 children were disaggregated; 5 million cells were infected by spinoculation with R5- or X4-tropic HIV-1 GFP reporter viruses or mock-infected and cultured in RPMI + 10% FBS. After 2 days, cells were stained for flow cytometry with antibodies to CD3, CD4, CD8, CXCR5, PD-1 and viability dye. Data were analyzed for phenotype and percentages of infected (GFP+) cells, gating on CD3+CD8- cells due to downregulation of CD4 by HIV infection. Statistical analysis was performed via non-parametric T-tests. Results: In mock-infected wells, CXCR5+ cells constituted a median of 50% (range, 38 to 76), GC TFH (CXCR5hiPD-1hi) a median of 19% (range, 12 to 26), and non-GC TFH (CXCR5medPD-1med) a median of 26% (range, 21 to 42) of CD3+CD8- cells. In R5 infected wells, the percent of CXCR5+ and non-GC TFH were similar (median 50 and 25 respectively) but the percentage of GC TFH tended to decrease (median 15, p=0.08). In X4 infected wells, the proportions were significantly lower (%CXCR5+: 43, p=0.01, %GC TFH: 9, p=0.0005, %non-GC TFH: 22, p=0.05). Percentages of GFP+ cells were higher in X4-infected wells (median, 1.2%) compared to R5-infected wells (median, 0.4%; p=0.04). In X4-infected wells, CXCR5+ cells were a median of 13 (range, 5 to 20. p=004) times more likely to be GFP+ compared to CXCR5- cells, and GC TFH were a median of 3 (range, 3 to 6; p=0.004) times more likely to be GFP+ than non-GC TFH. Similarly, in R5-infected wells, CXCR5+ cells were a median of 8 times (range 3 to 17; p=0.004) more likely to be GFP+ than CXCR5- cells, and GC TFH cells were 3 times (range, 2 to 6; p=0.004) more likely to be GFP+ than non-GC TFH. Conclusions: TFH, especially GC TFH, are highly permissive to both X4 and R5 HIV-1. This cannot fully account for levels of infected follicular cells in vivo nor for preferential replication of R5 virus in vivo.

Lamborn, Nathan

Poster Title: DOES THE AVAILABILITY OF ANESTHESIA MEDICATION COST AFFECT PROVIDER BEHAVIOR IN AN ACADEMIC ANESTHESIOLOGY GROUP?

Category: Surgery

Abstract: DOES THE AVAILABILITY OF ANESTHESIA MEDICATION COST AFFECT PROVIDER BEHAVIOR IN AN ACADEMIC ANESTHESIOLOGY GROUP? Nathan Lamborn (MD, SOM; MBA, UCD), Jose Melendez MD MBA, Clark Lyda Pharm D, Brain Davidson MD MBA, Department of Anesthesiology, University of Colorado, Denver, CO. Purpose of Study Medication and equipment expense is an area for potential cost reduction in the operating room environment. Providers often have no real or relative knowledge or education related to individual medication cost or reimbursement methods. A large portion of a hospital anesthesia department budget includes an impressive array of medications. Many factors help a clinician decide which medication to use for a particular patient and in any given case. Training, institutional culture, provider habit, availability and cost all play a role. National conversation about the cost of health care has departments looking for ways to reduce costs without reducing quality. Although pharmacy costs, and more specifically anesthetic pharmacy costs, only make up single-digit percentage points of a tertiary care center's budget, anesthetic drugs continue to stand out as a source of potential short term and long term savings. Our question is: Will anesthesia providers change clinical behavior if given information regarding medication costs as evidenced by a reduction of relative medication expenditure costs after an passive educational intervention? We seek to understand what extent provider knowledge of medication costs can influence the average cost of medication used in a the operating room. This problem has been identified, documented and discussed thoroughly in the past but it is unclear to what extend the cost saving measures identified in the past have been integrated into today's ORs. We wish to revisit this topic and look for areas to establish increased and continued cost savings. We aim to clearly establish some of the sources of OR anesthesia drug wastage so we can develop and establish long-term, sustainable cost saving solutions. The extent of drug wastage in the OR has been described multiple times in the literature. In a study in 2000, Gillerman et al quantified the wastage amount of five study drugs and found an average 26% un-administered rate totally $165,667 in a large tertiary hospital over one year accounting for at least 2% of the total annual pharmaceutical expenditure . Chaudhary et al (2012) showed a wastage rate of various anesthesia drugs ranging from 7.41% to 100% in some cases . The source of wastage was attributed to factors such as too large vial sizes or drug expiration. OR anesthesia drug expenses can also be increased by such practices as non-billing or selecting higher priced alternatives for certain cases. In response to the increasing focus of operating room costs several researchers in the past have sought out ways to potentially reduce them. Lubarsky et al (1997) showed that through the use of physician developed practice guidelines they reduced their anesthesia pharmaceutical cost by 50% in a tertiary setting without adversely affecting clinical outcomes . A study by Johnstone (1994) showed that a drug education series had the result of lowering drug costs for several

months before the results wore off once the lecture serious ended . Not all interventions were successful at saving costs, however. The study conducted by Horrow and Rosenburg (1994) placed cost labeled stickers on selected neuromuscular blocking and rapidly acting hypnotic agents . Their study did not show that labeling drug costs provided cost savings. One criticism of previous study designs is that they did not track clinician's knowledge of drug costs to verify the providers learned anything. Our study is different in that we provide a before and after survey to track general clinician knowledge regarding cost of common anesthesia medications. Our study also includes a wide variety of medications so marginal changes can be tracked and recorded. Today there is also a relative flat fee reimbursement (DRG-based) method versus the fee for service model more prevalent in 1994 when that study was done. Methods Used: This study will (need wording change!) conducted by first surveying anesthesia staff, then providing passive drug cost information, waiting three months, and again surveying the staff. The survey of clinical faculty, residents and CRNAs was conducted using online Survey Monkey. The survey contained ten multiple choice questions to test the knowledge of particular medication costs, and to gauge attitudes about medication cost and usage. After the intervention period a similar survey will be used to track improvement in knowledge and/or changes in attitude. The costs of the anesthesia medications are to be collected from pharmacy receipts for the anesthesia department during a control period and an intervention period. The control period for OR anesthesia drug costs is the six month period leading up to when we labeled the medications in the OR trays. After placing unit cost labels for each medication on all the drug trays in all the OR carts, cost data will be collected for another three months. The cost data from those three months will then be compared to the prior six months to look for any changes. The data will be normalized based on cost per case in order to account for variable changes in OR volume. To label the medication trays we first verified the unit cost of each vial/bottle of medication used in the OR. The data was then printed on a sticker and placed next to each medication name in each anesthesia medication tray. Stickers were printed on clear mail label sheets and then placed in all the trays contained within all the anesthesia carts in a single day. Inhaled anesthetics were also labeled on the anesthesia machines (vaporizers) themselves with printed labels. Anesthesia personnel, with the exception of the senior medical director and department chair, were not informed of the purpose of sticker placement with cost information. If the price changes during the duration of the study then that particular sticker will be updated. No instructions or other interventions were implemented during the study period. Summary of Results: This trial is currently in the intervention phase and data will be collected for the next three months. The first survey has been administered and the results gathered and the anesthesia trays have been labeled. Once the complete three months of intervention time has elapsed we will then be able to administer the follow up survey to track learning, and then collect the cost data to look for any changes. Survey results charts can be seen in Appendix 1. The results from the first survey can be preliminarily analyzed to gauge the extent of provider's medication knowledge and attitudes towards price. The response rate for the first survey was 70% for physicians, 61% for anesthesiology residents and 44% for CRNA/AAs. Years of experience was well distributed with

8% having less than one year, 22% 1-3 years, 36% 3-10 years, 4% 11-15 years and 12% more than 15 years. The majority, 64%, of responders reported they only had minimal medication cost knowledge, a few meds. 20% more reported they had adequate knowledge, half of meds. Two questions asked specifically which medication listed was the most expensive. Only 4% got the first one correct with 52% picking a wrong answer and 26% got the second question correct with 52% picking another wrong answer. Three questions then asked test takers to name the actual price of a medication. Not so surprisingly there was roughly equal distribution among all the answers signaling the test takers did not know the cost of the three medications. The next question asked how the hospital gets paid for medications used in the OR. 45% correctly answered that "An anesthesia equipment/medication payment is made to the hospital based on the case type (diagnosis related group), regardless of medication administered." 30% responded that "Each medication is charged to the patient and insurer pats for each based on use." This question sought to explore how well providers know how the hospital gets paid. The 45% who answered correctly might be more sensitive to medication costs since they know the pay is the same regardless of use. The 30% who believe the hospital gets paid by medications used might be less sensitive to cost thinking that it doesn't affect the hospital's costs. Further questioning and interviewing would be needed to understand the ramifications of these two beliefs. The final question asked "Does knowledge of individual medication cost influence your choice during an anesthetic case?" 7% responded "No influence." 20% responded "Very little influence." 29% responded "Little influence." 38% responded "Moderate influence" and 6% responded "Significant influence." Conclusions Reached: Once the full three months of intervention period has passed and the cost data and follow up data has been analyzed we will be able to draw final conclusion. Taken all together, the initial survey responses seem to demonstrate that providers are aware that the medication they choose impacts costs, and that they are influenced by this fact. However, they are also lacking the medication cost knowledge that could help them better select lower cost alternatives when possible. If our hypothesis is correct then when equipped with passive medication costs in the OR, providers will response and overall costs will decrease in the next three months. References: Hawkes C, Miller D, Martineau R, Hull K, Hopkins H, Tierney M. Evaluation of cost minimization strategies of anaesthetic drugs in a tertiary care hospital. Can J Anaesth. 1994 Oct;41(10):894-901. PubMed PMID: 8001207. Smith I. Cost considerations in the use of anaesthetic drugs. Pharmacoeconomics. 2001;19(5 Pt 1):469-81. Review. PubMed PMID: 11465307. http://www.ncbi.nlm.nih.gov/pubmed/11465307 Becker KE, Carrithers J: Practical methods of cost containment in anesthesia and surgery. J Clin Anesth 1994;6:388-99. http://www.ncbi.nlm.nih.gov/pubmed/7986511 Gillerman RG, Browning RA. Drug use inefficiency: a hidden source of wasted health care dollars. Anesth Analg. 2000 Oct;91(4):921-4. PubMed PMID: 11004049. Chaudhary K, Garg R, Bhalotra AR, Anand R, Girdhar K. Anesthetic drug wastage in the operation room: A cause for concern. J Anaesthesiol Clin Pharmacol. 2012 Jan;28(1):56-61. PubMed PMID: 22345947; PubMed Central PMCID: PMC3275973. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275973/ Lubarsky, David A. MD; Glass, Peter S. A. The Successful Implementation of Pharmaceutical

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Larson, Eric

Poster Title:

Category: Cardiovascular

Abstract: AGE-RELATED DECREASES IN HEART RATE ARE CORRELATED WITH DECREASED EXCITABILITY OF INDIVIDUAL SINOATRIAL MYOCYTES. ED Larson (Ph.D., GS), WA Sumner, RA Bannister, and C Proenza, Department of Physiology and Biophysics, University of Colorado, Aurora, CO. Cardiovascular disease is one of the largest killers in the United States and its prevalence has been well documented to increase with age. While gross changes in cardiac anatomy and function have been well examined in aged subjects, much less is known about what occurs at a cellular level. Each heart beat is trigged by the generation of spontaneous action potentials by myocytes in the sinoatrial node. These rhythmically generated action potentials are produced by a concert of ion channels including hyperpolarization-activated cyclic nucleotide-sensitive (HCN) channels and voltage-gated calcium channels. In nearly all mammalian species, the maximum heart rate elicited by stress or age declines with age. Furthermore, the intrinsic heart rate (i.e., in the absence of autonomic input) declines with age as well, and is likely the result of a sinoatrial node defect. Myocytes from the sinoatrial node have been shown to fire slower in aged animals, but little work has been done to look at the intrinsic excitability of the myocytes. In this study, we sought to examine functional, age-dependent electrical remodeling of individual sinoatrial myocytes from young (2-3 m/o) vs old (>32 m/o) mice. Electrocardiogram (ECG) measurements in vivo showed that the intrinsic and maximal heart rates were reduced with age. We next showed this to be result of sinoatrial node dysfunction, as current clamp recordings from isolated sinoatrial node myocytes fired action potentials slower in aged mice, mirroring the age-related changes in heart rate. Stimulation with 1 μM isoproterenol yielded a slower average maximum firing rate in aged sinoatrial myocytes. In attempt to explore the mechanistic cause of these age-related deficits in action potential generation, we recorded L-type calcium (ICaL) and hyperpolarization-activated currents (If) in isolated myocytes from young and old mice. We found significant reductions in L-type calcium current density. Additionally If density as significantly reduced along with a hyperpolarizing shift in voltage dependence in elderly mice. These studies may provide

mechanistic understanding about fundamental processes that limit the physical capacity of the elderly.

law, luke

Poster Title:

Category: Hematology and Oncology

Abstract: COMPARING THE EFFICACY OF GAS6/MER PETHWAY INHIBITORS IMER AND UNC MER TKI WITH AND WITHOUT AN ADP INHIBITOR (P2Y1 AND P2Y12) IN VITRO AND IN VIVO Growth Arrest Specific gene 6 (Gas6) is a ligand that signals through the platelet surface Mer receptors, resulting in platelet activation and thrombus formation through the intermediate molecules P13k and AKT, culminating in β3 integrin phosphorylation. ADP activates this same pathway through P13k, and it is our hypothesis that inhibiting the receptors for ADP should lead to greater inhibition of platelet activation, and further thrombus destabilization. This study investigates the novel anti-platelet agents iMer and UNC MER TKI in the presence of ADP inhibitors in order to further elucidate this pathway involved in platelet activation, and to asses if a combination of these agents lead to superior results. We used en vitro and en vivo assays of human and murine platelets to measured the effect on platelet inhibiton of iMer and UNC Mer TKI with GDP inhibitors. In vitro studies included standard aggregometry and aggregate formation on collagen surfaces in a microfluidic flow chamber and flow cytometry. In vivo studies included a FeCl3-induced model of carotid artery injury and a collagen/epinephrine-induced pulmonary embolism (PE) model to compare thrombosis protection between littermate C57BL/6 mice treated with inhibitors or vehicle control. A paired t-test was used to compare samples in aggregation, microfluidic flow surface area coverage, as well as elapsed time to initial and stable occlusions in the FeCl3model and survival time in the PE model.

Li, Dongying

Poster Title:

Category: Basic Prrocesses

Abstract: ENDOCYTIC TRANSPORT DURING EPITHELIAL LUMEN MORPHOGENESIS. D Li, (Ph.D., GS), C Willenborg, B Appel, and R Prekeris, Department of Cell and Developmental Biology, School of Medicine, University of Colorado, Denver, CO Proper sorting and targeting of endocytosed proteins is necessary for the maintenance of epithelial cell polarity and apical lumen formation. A leading model of epithelial lumen morphogenesis suggests that to form the apical lumen, apical proteins must be transcytosed via Rab11-containing recycling endosomes and fuse at the lumen formation site, also known as apical membrane initiation site (AMIS). While the importance of Rab11-endosomes in the development

of the apical lumen is now well established, we know little about the machinery that regulates formation, transport and targeting of these Rab11-endosomes during lumen formation. FIP5, a Rab11 effector protein, is known to be involved in apical-directed transport in polarized cells and is thought to act as a scaffolding protein that recruits and binds effectors of endocytosis. It was recently demonstrated that FIP5 is required for the formation and targeting of Rab11-endosomes to AMIS. Additionally, it has been shown that FIP5 functions by binding to Sorting Nexin 18 (SNX18) and kinesin-2 to mediate formation/scission and transport of apical endocytic carriers. In this study, utilizing various molecular and biochemical techniques along with 3D tissue culture assays and fluorescence microscopy, we demonstrate that during apical lumen formation FIP5 is phosphorylated by GSK3β, and that this phosphorylation regulates FIP5 binding to SNX18 and kinesin-2 and is required for apical protein transport to AMIS in vitro. Furthermore, to test whether FIP5-dependent endocytic transport also mediates lumen formation in vivo, we used zebrafish intestine as our model system. Via in situ hybridization and confocal microscopy combined with morpholino knockdown strategy, we show that depletion of FIP5 inhibits the proper formation of zebrafish intestinal lumen and also leads to ectopic formation of microvilli-containing apical membranes. In summary, this study finds that FIP5 mediates the formation of the epithelial lumen via sequential interaction with SNX18 and kinesin-2, and the function of FIP5 during lumen initiation and expansion is regulated by GSK3β phosphorylation.

Makhija, Manisha

Poster Title: INTER-PARTICLE AND PARTICLE/MATRIX INTERACTIONS INVOLVING REACTIVE NANOGEL ADDITIVES

Category: Materials and Methods

Abstract: INTER-PARTICLE AND PARTICLE/MATRIX INTERACTIONS INVOLVING REACTIVE NANOGEL ADDITIVES M Makhija (DDS/ISP, SODM), SH Lewis, JW Stansbury Nanogel-modified dental resin and composite materials have shown reduced levels of polymerization shrinkage and stress. However, nanogel dispersions in reactive resins complicate interpretation of specific contributions of nanogels to overall polymer structure. Objective: The goal of this study is to gain a better understanding of interactions between the nanoparticles and interactions between nanogels and the dispersive matrices before and after polymerization. To achieve this, inert solvents and solvent mixtures were employed as the matrices that both disperse and infiltrate the reactive nanogels. Methods: A reactive nanogel was prepared from isobornyl methacrylate and UDMA (80:20 mole ratio) and then dispersed into either xylene (XYL), methyl ethyl ketone (MEK) or a 1:1 XYL/MEK mixture. Viscosity and refractive index of 5 to ≥50 wt% dispersions of nanogel in the various solvents were determined with a viscometer and refractometer. By inclusion of an initiator in the inert solvents, photopolymerizations involving the nanogel dispersions were conducted at varied nanogel loading levels. Reaction kinetics/conversion were followed by near-IR spectroscopy. Results: At a consistent 50 wt% nanogel loading, relative viscosities of the XYL, MEK and 1:1

XYL/MEK dispersions were 2334(±95), 227(±34) and 123(±4) mPa*s, respectively. The refractive index of each dispersion varied linearly with nanogel loading with the plots converging to 1.507±0.006 when extrapolated to 100%. Using increments of 5 wt% nanogel loading in the various solvents, the minimum nanogel content necessary to produce a macroscopic network upon polymerization (percolation threshold) was 20, 30 and 35 wt% for the nanogel dispersed in XYL, 1:1 XYL/MEK and MEK, respectively, and the photopolymerization rates, regardless of nanogel loading level, decreased in this same order. Conclusions: The appreciable difference in solvent solubility parameter shows that with this nanogel, inter-particle interactions are enhanced in XYL and that co-solvent mixtures, which can represent resin comonomers, remain non-partitioned with respect to nanogel infusion.

Marker, Ryan

Poster Title: SHORT-INTERVAL INTRACORTICAL INHIBITION INCREASES DURING EXPOSURE TO PSYCHOSOCIAL STRESS IN HEALTHY ADULTS

Category: Neuroscience and Brain and Behavior – Adult

Abstract: SHORT-INTERVAL INTRACORTICAL INHIBITION INCREASES DURING EXPOSURE TO PSYCHOSOCIAL STRESS IN HEALTHY ADULTS. RJ Marker (Ph.D., GS), JL Stephenson, KS Maluf, Department of Physical Medicine and Rehabilitation, University of Colorado Anschutz Medical Campus, Aurora, CO. Previous studies have documented altered activation of inhibitory networks within the motor cortex among a variety of patient populations with impaired muscle relaxation. These impairments are often exacerbated by psychosocial stress, yet the effects of stress on intracortical inhibition are currently unknown. The purpose of this study was to investigate changes in intracortical inhibition during exposure to an acute psychosocial stressor in healthy adults. Transcranial magnetic stimulation was used to assess short-interval intracortical inhibition (SICI), previously shown to be mediated by GABAA neurotransmission involving inhibitory interneurons within the primary motor cortex. Participants were instructed to relax their neck and shoulder muscles as background muscle activity and motor evoked potentials were recorded with surface electrodes on the upper trapezius muscle at baseline and during periods of low and high psychosocial stress. The low stress condition comprised easy mental math with no accuracy demand, performed in the presence of a familiar investigator providing positive feedback. The high stress condition comprised difficult mental math performed with time and accuracy constraints in the presence of an authoritative investigator providing no positive feedback. Perceived anxiety and cardiovascular responses increased significantly between the low and high stress conditions, demonstrating the efficacy of the stress protocol. Intracortical inhibition increased in the high stress compared to the low stress condition ($p = 0.034$). Motor threshold performed with no visual feedback of muscle activity decreased from low to high stress conditions ($p = 0.049$). Resting and active motor thresholds, performed with visual feedback of muscle activity, remained unchanged across conditions, as did background muscle activity. These findings

suggest that healthy adults increase the activation of intracortical inhibitory pathways to help maintain a relaxed muscle during exposure to acute psychosocial stressors. Future research is necessary to determine whether impairments of intracortical inhibition contribute to the inability of some patient populations to relax their muscles under stress.

Martin, kimberly

Poster Title: ENERGY BASED LIGATION IN AN ATHEROSCLEROTIC SWINE MODEL: A MUTIVARIATE ANALYSIS

Category: Surgery

Abstract: ENERGY BASED LIGATION IN AN ATHEROSCLEROTIC SWINE MODEL: A MUTIVARIATE ANALYSIS. K. Martin (Ph.D.,GS), P. Montero Department of Surgery University of Colorado, Denver, Co. Energy ligation of vessels is common and although rare, failures occur. Atherosclerotic disease state may contribute to seal failures via: 1 collagen to elastin ratio has been shown to contribute to burst pressure 2 vasculature collagen content is altered with atherosclerotic disease. Purpose: determine if seals created using a common bipolar sealing instrument are compromised in atherosclerotic vasculature. Methods: Experimental group: Yucatan swine (n=7) with an identified genetic locus predisposing them to atherosclerosis. A Yorkshire pig was used as a normal control. The control animal was fed a standard pig chow diet. The femoral and iliac arteries were denuded with a Fogarty catheter. Animals were fed the high fat diet for 28 weeks. Baseline and monthly cholesterol testing was performed. At 28 weeks artery diameters were measured, and sealed and divided in vivo with the LigaSure Atlas. Sealed artery sections were excised with the side of the seal proximal to the aorta subjected to burst pressure testing. Half of the seal distal to the aorta was kept intact for histology, and collagen/elastin quantification and burst testing were performed. A mixed linear model was used to assess variables contributing to burst pressure. Covariates included were: vessel size, degree of atherosclerosis, collagen and elastin content. Results: One animal died of congestive heart failure due to extensive coronary artery blockage. Atherosclerosis was observed in 90% of sites in induced animals with severe atherosclerosis observed in 62%. Mean luminal occlusion was 30% (+ 0.025). Control animals were normal. Cholesterol levels were elevated in experimental animals (n=7) mean=617 mg/dl relative to the control mean =128 mg/dl (p

McCullough, James

Poster Title: ACUTE KIDNEY INJURY: B-CELLS AND THE ROLE OF IL-10

Category: Immunology and Autoimmune Diseases

Abstract: ACUTE KIDNEY INJURY: B-CELLS AND THE ROLE OF IL-10. JW McCullough, (MD, SOM), J Thurman. Department of Medicine, University of Colorado, Aurora, CO. Ischemia/reperfusion injury (IRI) to the kidneys results in a robust inflammatory response. The role of B-cells in this response is very complex and experimental data suggests that distinct B cell subsets can cause both aggravation and mitigation of injury. Evidence for a protective role of B-cells has been linked to the expression of the anti-inflammatory cytokine IL-10. It is the goal of this research to monitor changes of IL-10 expression following ischemia and identify the role of IL-10 in limiting renal IRI. Kidney ischemia was induced in mice by bilateral clamping of the renal pedicles for 24 minutes followed by reperfusion for 24 to 96 hours. Serum, kidneys, and spleen were collected at various timepoints after reperfusion, and analysis of IL-10 expression was performed and compared with sham-treated mice. IL-10 protein in the serum was measured by ELISA. Tissue expression of IL-10 RNA in kidneys and spleen were examined with quantitative PCR. Serum analysis of IL-10 protein showed a 2-fold increase at 24 hours of reperfusion relative to sham-treated mice. Serum levels returned to sham levels at 48 hours and increased again at 72 hours. IL-10 expression in the spleen increased approximately 2-fold compared to that of sham-treated animals after 24 hours of renal reperfusion, and maintained increased levels of expression at 48 and 72 hours. IL-10 expression in the kidney increased 5-fold relative to sham-treated animals at 24 hours of reperfusion. Expression had declined at 48 and 72 hours but remained elevated relative to sham-treated animals. In response to kidney ischemia, RNA expression of IL-10 in the kidney and spleen increases by 5-fold and 2-fold, respectively, when compared to sham treated animals. Additionally, expression of the IL-10 protein also increases based on increased levels of IL-10 in serum of experimental mice compared to sham-treated mice. This increased expression of IL-10 may be part of a protective response by B-cells against damage to the kidney caused by ischemia and subsequent inflammation. Future experiments will be focused on further characterization of IL-10 expressing B-cell populations, and modulating IL-10 expression in mouse models in order to observe the effects on renal IRI.

Miller, Matthew

Poster Title: IDENTIFYING FACTORS ASSOCIATED WITH MEDICAL-LEGAL NEED IN HOSPITAL-BASED CLINICS

Category: Health Care and Public Health

Abstract: IDENTIFYING FACTORS ASSOCIATED WITH MEDICAL-LEGAL NEED IN HOSPITAL-BASED CLINICS MW Miller (MD, SOM), S Hallenberger, S Wong, M Federico, L Schultz, D Fox Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO. Medical-Legal Partnerships (MLP) provide a path to addressing sociolegal issues that affect patient health. To date, MLP studies have focused on program descriptions, and have not sought to characterize the families that have sociolegal needs, nor on a maximally informative screening strategy. Here we sought to characterize families who present with sociolegal need, examine demographic associations with expressed medical legal need, and assess the information gained through screening over time. During the study period 10/27/09 and 05/01/12, we conducted a parent-completed five-question screening for housing, benefits, and safety. Questionnaire data and demographic information were collected at well-child visits and at asthma clinic visits. Chi-square analysis for each variable were used to determine what demographic factors positively correlated with positive screening for MLP need, with odds ratios (OR) and 95% confidence intervals (CI) reported. Over the study period, 8803 screenings were obtained from 5008 unique patients. 26% of families screened positive at least once over the study period, and 38% of families were screened more than one time. Patients were 50% under 1 year old, 46% female, and 47% Hispanic. Race was 27% Black, 27% White, and 44% reporting other races. Insurance status was 76% Medicaid, 18% private insurance, and 4% uninsured. Age of child was associated with increased positive screening, with those 5-12 and >12 years having higher rates of positive screening compared to those

Nacht, Jacob

Poster Title: TRANSFERS FROM US EMERGENCY DEPARTMENTS, 2002-2009: IMPLICATIONS FOR REGIONALIZATION AND PATIENT SAFETY

Category: Health Care and Public Health

Abstract: TRANSFERS FROM US EMERGENCY DEPARTMENTS, 2002-2009: IMPLICATIONS FOR REGIONALIZATION AND PATIENT SAFETY. M Macht (MD,MPH), J Nacht (BS), AA GINDE (MD,MPH), Department of Emergency Medicine, University of Colorado School of Medicine, Denver, CO. Background: Increased interest in regionalization and patient safety has focused attention on the practice of interfacility transfer from the ED. While ED transfer has been described in geographically limited studies of select conditions (e.g., myocardial infarction, stroke, trauma), the practice has not been previously described nationally for the breadth of presentations of transferred patients. Objectives: We sought to describe the

demographic and clinical characteristics of patients transferred from US EDs and the reasons for their transfer. Methods: We performed a retrospective, cross-sectional analysis of the 2002-2009 National Hospital Ambulatory Medical Care Survey. We compared characteristics of patient visits that had the ED disposition of transfer or hospital admission . Additionally, we analyzed reason for transfer for available years (2005-2008). Weighted analyses produced nationally representative estimates, and chi-square test was used to make bivariate comparisons. Results: From 2002-2009, 1.7% (95%CI, 1.5-1.8) of ED visits were transferred to another facility. Transferred patients were more likely to be

Oberndorfer, Tyson

Poster Title: ALTERED INSULA RESPONSE TO SWEET TASTE PROCESSING AFTER RECOVERY FROM ANOREXIA AND BULIMIA NERVOSA

Category: Neuroscience and Brain and Behavior – Adult

Abstract: ALTERED INSULA RESPONSE TO SWEET TASTE PROCESSING AFTER RECOVERY FROM ANOREXIA AND BULIMIA NERVOSA. TA Oberndorfer (M.D., SOM), GK Frank, AN Simmons, A Wagner, D McCurdy, JL Fudge, TT Yang, MP Paulus, and WH Kaye. University of California at San Diego, Department of Psychiatry, San Diego, CA; University of Colorado at Denver and Health Sciences Center, Department of Psychiatry, Denver, CO Purpose: Recent studies suggest that altered function of higher-order appetitive neural circuitry may contribute to restricted eating in anorexia nervosa and overeating in bulimia nervosa. This study used sweet tastes to interrogate gustatory neurocircuitry involving the anterior insula and related regions that modulate sensory-interoceptive-reward signals in response to palatable foods. Methods: Recovered anorexic and recovered bulimic subjects were studied to avoid confounding effects of altered nutritional state. Functional magnetic resonance imaging measured higher-order brain response to repeated tastes of sucrose and sucralose (Splenda®) in order to disentangle neural processing of caloric and non-caloric sweet tastes. A whole-brain functional analysis was constrained to the anatomical regions of interest. Results: Compared to matched control women (n=14), recovered anorexics (n=14) had diminished ($F[1,27]=7.79$, $p=0.01$) and recovered bulimics (n=14) had exaggerated ($F[1,27]=6.12$, $p=0.02$) right hemodynamic anterior insula response to tastes of sucrose. Furthermore, the anterior insula and caudate findings for the recovered subjects were more exaggerated in response to sucrose (lower in recovered anorexics and higher in recovered bulimics) in contrast to sucralose. Conclusions: The anterior insula and related regions integrate sensory/reward aspects of taste and interoceptive awareness in the service of homeostasis. These data support the possibility that restricted eating and weight loss occurs in anorexia nervosa because feeding elicits diminished insula homeostatic response to hunger, whereas overeating in bulimia nervosa is related to exaggerated hunger signal. This response may reflect the integration of signals related to sweet taste as well as the caloric content of food.

Osgood, Ross

Poster Title: POLYCYCLIC AROMATIC HYDROCARBONS EXHIBIT DIFFERENTIAL TUMOR PROMOTING PROPERTIES IN CULTURED MURINE LUNG CELLS

Category: Materials and Methods

Abstract: POLYCYCLIC AROMATIC HYDROCARBONS EXHIBIT DIFFERENTIAL TUMOR PROMOTING PROPERTIES IN CULTURED MURINE LUNG CELLS RS Osgood1 (Ph.D., GS), BL Upham3, T Hill2, KL Helms3, P Babica3, and AK Bauer2 1Departments of Pharmaceutical Sciences and 2Environmental and Occupational Health, University of Colorado Anschutz Medical Campus, Aurora, CO; 3Department of Pediatrics and Human Development, Michigan State University, East Lansing, MI Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants as well as major components of tobacco smoke. Exposure to PAHs represents a significant health concern due to their association with a variety of cancer endpoints. PAH research has primarily focused on the genotoxicity of high molecular weight PAHs, but recent evidence suggests that the low molecular weight PAHs may act through distinct mechanisms to promote, rather than initiate, neoplasia. We evaluated two sidestream smoke PAHs, 1-methylanthracene (1-MeA) and 2-methlyanthracene (2-MeA), for their ability to inhibit gap junction intercellular communication (GJIC) with a concomitant effect on the major pulmonary gap junction protein connexin 43 (Cxn43) as well as to activate mitogen activated protein kinases (MAPK) in murine lung cells. These pathways represent potential mechanistic targets for PAH perturbation. Murine C10 cells (a non-tumorigenic type II alveolar pneumocyte, and progenitor cell type of lung adenocarcinoma) were used to assess the effects of 1-MeA and 2-MeA on GJIC and MAPKs over a time course of 15 minutes to 4 hours. Detection of MAPKs and Cxn43 protein was determined by immunoblot, and GJIC was assessed by a scrap-load dye transfer assay. 1-MeA inhibited GJIC in a dose and time dependent manner while its isomer, 2-MeA, did not. Treatment with 1-MeA also inhibited Cxn43 protein expression, supporting gap junction closure. In addition, activation of ERK1/2 and p38 MAPK was observed in response to 1-MeA. The ability of 1-MeA to both inhibit GJIC as well as activate MAPKs supports a role for low molecular weight tobacco-smoke PAHs to act as tumor promoters in lung cells, and is consistent with previous studies that suggest these compounds may act as tumor promoters in liver cells. The differences observed between 1-MeA and 2-MeA suggests that the ability of low molecular weight PAHs to inhibit GJIC and activate MAPKs is highly dependent on chemical structure. Such structure-activity relationships are often indicative of discrete toxicological mechanisms. Future work will address whether other low molecular weight PAHs exhibit tumor promoting properties and the underlying mechanisms.

Parker, Jonathon

Poster Title: GEFITINIB SELECTIVELY REDUCES TUMOR CELL MIGRATION IN EGFR-AMPLIFIED HUMAN GLIOBLASTOMA.

Category: Hematology and Oncology

Abstract: GEFITINIB SELECTIVELY REDUCES TUMOR CELL MIGRATION IN EGFR-AMPLIFIED HUMAN GLIOBLASTOMA. JJ Parker (MD/PhD, MSTP), KR Dionne, R Massarwa, M Klaassen, L Niswander, P Canoll, BK DeMasters, A Waziri. Purpose: Tissue invasion is a hallmark of most human cancers and remains a major source of treatment failure in patients with glioblastoma (GBM). Although EGFR-amplification has been previously associated with more invasive tumor behavior, existing experimental models have not supported quantitative evaluation of inter-patient differences in tumor cell migration or testing of patient-specific responses to therapies targeting invasion. To explore these questions, we optimized an ex vivo organotypic slice culture system allowing for labeling and tracking of tumor cells within human GBM slice cultures. Experimental Design: Using time-lapse confocal microscopy of retrovirally-labeled tumor cells within slices, baseline differences in migration speed and efficiency were determined and correlated with EGFR-amplification in a cohort of patients with GBM. Slices were treated with gefitinib to evaluate anti-invasive effects associated with targeting EGFR. Results: Migration analysis identified significant patient-to-patient variation at baseline. EGFR-amplification was correlated with increased migration speed and efficiency when compared to non-amplified tumors. Critically, gefitinib resulted in a selective and significant reduction of tumor cell migration within EGFR-amplified tumors. Conclusions: These data provide the first identification of patient-to-patient variation in tumor cell migration within living human tumor tissue. We found that EGFR-amplified GBM are inherently more efficient in their migration and can be effectively targeted by gefitinib treatment. These data suggest that stratified clinical trails are needed to evaluate gefitinib as an anti-invasive adjuvant for EGFR-amplified GBM patients. In addition, these results provide proof-of-principle that primary slice cultures may be useful for patient-specific screening of agents designed to inhibit tumor invasion.

Powell, Davalyn

Poster Title: Prdm1a directly regulates neural crest specification in zebrafish

Category: Developmental Neuroscience and Brian Behavior - Child

Abstract: PRDM1A DIRECTLY REGULATES NEURAL CREST SPECIFICATION IN ZEBRAFISH. DR Powell, (Ph.D., GS), L Hernandez-Lagunas, and KB Artinger, Department of Craniofacial Biology, School of Dental Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO. Neural crest cells are multipotent precursor cells that are induced at the neural plate border by a series of complex signaling and genetic interactions. Several

transcription factors, termed neural plate border and neural crest specifiers, are necessary for early neural crest development. However, the nature of their interactions and regulation is not well understood. Here, we have established the genetic interactions between prdm1a, tfap2a, and foxd3, all key regulators of neural plate border and neural crest specification in zebrafish embryos. Through rescue experiments and chromatin-immunoprecipitation (ChIP), we have determined that Prdm1a directly binds to and transcriptionally regulates putative enhancers for the neural crest specifiers foxd3 and tfap2a and that they are each a functional direct target of Prdm1a regulation. Based on these and previous data, we predict that Prdm1a is a transcriptional activator of foxd3 and tfap2a at the neural plate border. Additional data using dominant-activator and dominant-repressor Prdm1a constructs suggest that Prdm1a functions both as a transcriptional activator and transcriptional repressor during development. By comparing RNA-seq and ChIP-seq data, we will elucidate the nature of Prdm1a regulation of neural crest specification genes at the transcriptional level. Through this work, we have demonstrated that Prdm1a is a key regulator in the gene network that is required for proper neural crest formation.

Powers, Matthew

Poster Title: Postoperative management in laryngotracheal reconstruction; report of sedation related outcomes

Category: Surgery

Abstract: Objective: To report sedation related outcomes in varied postoperative approach after single-stage laryngotracheal reconstruction (ssLTR) in children at a single center tertiary care pediatric hospital. Methods: Retrospective review of 34 children who underwent ssLTR, excluding anterior cricoid split, tracheal resection, and cricotracheal resection. Primary outcome measures included length of stay, pulmonary complications, nursing concerns, withdrawal syndromes, failures and need for further post operative treatment. Results: 19 patients were sedated and 15 patients were non-sedated. The two groups were similar in age, male/female ratio, race distribution, and weight. Prematurity was the primary risk factor for subglottic stenosis. Median hospital day doubled in patients who were sedated and paralyzed (24 days) versus those who were non-sedated (12 days). Overall 79% of patients who were sedated had symptoms of withdrawal versus 6% of patients managed without sedation. Nursing concerns were higher when attempting to achieve adequate sedation versus in maintaining a patient awake. The impact of withdrawal alone in prolonged hospital stay was significantly associated with level of sedation ($p=0.00716$) and the probability of delayed discharge secondary to withdrawal increases significantly with increased days of sedation. Four short term failures occurred and there is no correlation to the postoperative sedation management. Discussion: Patients may be safely managed with varied methods of postoperative sedation management. Sedated patients have a high likelihood of withdrawal. Number of days sedated is a significant predictor of probability of extended stay due to withdrawal alone. Therefore, avoidance of sedation is recommended to decrease morbidity in patients undergoing ssLTR

Powers, Matthew

Poster Title: Outcomes of Tube Thoracostomy in South African Penetrating Trauma Patients

Category: Surgery

Abstract: Objectives: Tube thoracostomy is one of the most common procedures performed in South African emergency settings, particularly in underserved areas such as townships. We sought to examine outcomes, primarily length of stay and presence of complications, based on presenting factors in these patients. Methods: We conducted a 1-year chart review of patients presenting to a South African emergency department with penetrating chest trauma and consequent pneumothorax to document initial presenting features, as well as length of stay and presence of complications throughout stay. We then ran statistical analysis on these data to determine if certain presenting factors (bilateral pneumothorax, presence of hemothorax, age, time of presentation etc.) had an impact on the presence of complications or length of stay. Results: Presence of bilateral pneumothorax and the presence of diminished breath sounds on initial clinical exam were associated with an increased risk of complications through stay. In terms of length of stay, presence of bilateral pneumothorax, type of diagnosis (pneumothorax vs hemothorax), appearance of pneumothorax on CXR, and diminished breath sounds were all associated with prolonged length of stay in the ICU. Discussion: These data may be useful to emergency staff in resource limited settings, as they can provide clinicians with valuable tools to predict the incidence of complications and/or the possibility of a prolonged length of stay in penetrating chest trauma patients.

Qamoh, Yazen

Poster Title: IMPACT OF REVISED PIPERACILLIN/TAZOBACTAM BREAKPOINTS ON PSEUDOMONAS AURUGINOSA SUSCEPTIBILITIES AND DEVELOPMENT OF A SITE SPECIFIC DUAL ANTIBIOGRAM

Category: Pharmacology and Physiology

Abstract: IMPACT OF REVISED PIPERACILLIN/TAZOBACTAM BREAKPOINTS ON PSEUDOMONAS AERUGINOSA SUSCEPTIBILITIES AND DEVELOPMENT OF A SITE SPECIFIC DUAL ANTIBIOGRAM. Y Qamoh (B.S., Pharm D Candidate), SW Mueller, and D N Fish, School of Pharmacy, University of Colorado, Denver, CO. Early administration of active antibiotics in patients infected with Pseudomonas aeruginosa (PSA) is associated with improved outcomes. PSA isolates at the University of Colorado Hospital (UCH) have been most frequently susceptible to piperacillin/tazobactam (P/T) compared to other beta lactam antibiotics. Revised P/T breakpoints for PSA will result in more isolates considered resistant to P/T. The purpose of this study is to determine: 1) the impact of lower breakpoints on PSA susceptibility to P/T at UCH and 2) which empiric combinations of antibiotics provide the highest likelihood of containing an active agent against PSA in pre-defined patient populations (dual antibiogram).

All PSA isolates from the 2011 calendar year at UCH were identified. Isolates from cystic fibrosis (CF) patients with mucoid and non-mucoid PSA were separated from intensive care unit (ICU) and floor patients. All four groups were analyzed separately. For each unique isolate, susceptibility to antibiotics (P/T, cefepime (CEF), ceftazidime (CTZ), doripenem (DOR), ciprofloxacin (CIP), amikacin (AMK), tobramycin (TOB), gentamicin (GNT) and colistin) was collected. A breakpoint of ≤64mcg/mL was compared to ≤16mcg/mL for P/T to assess the expected impact on our antibiogram. Empiric regimens of extended spectrum β-lactam antibiotics as monotherapy or in combination with either CIP or an aminoglycoside were compared for PSA susceptibility to at least one drug in the regimen. Three-hundred and forty-two PSA isolates were identified. Floor, ICU, CF non-mucoid and mucoid groups had 196, 50, 54 and 42 isolates, respectively. Overall, the breakpoint change decreased PSA susceptibility to P/T from 90.6 to 85.9 percent.The greatest impact was in non-mucoid CF isolates, followed by floor, ICU, and mucoid isolates. P/T susceptibility varied by up to 18 percent between floor, ICU and CF non-mucoid populations. More floor and ICU isolates were susceptible to CTZ than P/T after accounting for changes in breakpoints. Combinations of AMK with any beta lactam were active against greater than 98 percentof floor and ICU isolates. Combinations of CIP with P/T, CTZ or CEF were active against 91.8 to 97.4 percent of floor and 90 to 94 percent of ICU isolates. Among CF non-mucoid isolates, P/T was the most active and the addition of TOB increased the probability of coverage more than any other agent. Every other two-drug combination covered less than 83.3 percent of isolates. Mucoid CF isolates did not show significant changesdue to the high susceptibility of P/T and CTZ monotherapy. DOR monotherapy and in all frequently used combinations had a lower probability of activity against PSA compared to other agents. Changes in P/T breakpoints impacted PSA susceptibility by 2 to 5.6 percent depending on the patient population. Differences in susceptibility patterns were found between our pre-specified populations. CTZ has the greatest chance to cover PSA as monotherapy but the addition of AMK to any beta lactam covered nearly all floor and ICU isolates. The addition of CIP increases the probability of coverage by 4 to 14 percent. For non-mucoid CF isolates TOB should be added to the regimen. Floor, ICU and CF isolates have different susceptibility patterns and a population specific dual antibiogram can provide useful information on appropriate regimens.

Ramirez, Jacob

Poster Title: POLYMERIC NANOPARTICLE DESIGN TO CONTROL PERFORMANCE OF RESIN-DISPERSED NANOGEL ADDITIVES

Category: Materials and Methods

Abstract: POLYMERIC NANOPARTICLE DESIGN TO CONTROL PERFORMANCE OF RESIN-DISPERSED NANOGEL ADDITIVES JJ Ramirez (DDS, SODM), MD Barros, SH Lewis, JW Stansbury Objective: This study details the effects of nanogel size and molecular weight on properties, such as inter-particle spacing, viscosity, conversion and shrinkage stress,

when reactive nanogel additives are dispersed in dental monomers and polymers. Methods: Nanogels were prepared from an 80/20 mole ratio of isobornyl methacrylate and ethoxylated bisphenol-A dimethacrylate with nanogel size and weight (as determined by triple-detector GPC) controlled by changes in chain transfer agent concentration, initiator addition methods and conversion. Samples of 0 (control), 20, 30 and 40 wt% nanogel homogeneously dispersed in BisGMA/TEGDMA (70/30 mass ratio) containing initiator were prepared and analyzed for initial viscosity (viscometer) and stress development during photopolymerization (tensometer coupled with near-IR for conversion measurement). The reactive nanogels were also dispersed in toluene containing initiator and polymerized in order to determine the minimum loading level necessary to produce a macroscopic polymeric network (percolation threshold). Results: Based on synthetic conditions used, nanogels of identical composition but average molecular weights (Mw) that varied from 32 to 355 kDa were obtained. Percolation threshold was found to be greater for the smaller nanogel particle sizes. As an example, the following data pertains to the 40 wt% loading of selected sized nanogels in the BisGMA/TEGDMA resin: Nanogel Mw, kDa Hydrodynamic radius, nm Viscosity, Pa*s Conversion, % Stress, MPa 110 6.2 1159(35) 68.5(0.7) 1.01(0.09) 59 4.9 668(119) 76.0(1.7) 1.26(0.09) 39 4.0 212(26) 67.0(1.4) 1.04(0.09) no nanogel (resin control) 1.3(0.06) 71.7(0.6) 2.69(0.06) Conclusions: Greater nanogel size dramatically increased viscosity of the nanogel-filled resin. The nanogel-based stress reduction potential was essentially independent of nanogel size; therefore, smaller particle sizes that minimize viscosity effects are preferable. The viscosity results and the inverse relationship between nanogel size and percolation threshold indicate that larger particles take up more of the dispersing monomer/solvent, which effectively increases the volume fraction of the swollen nanogel particles.

Reddi, Anand

Poster Title: MICRORNA-9 TARGETS THE ADHERENCE JUNCTION PROTEIN α-CATENIN IN SKIN SQUAMOUS CELL CARCINOMA METASTASIS

Category: Hematology and Oncology

Abstract: MICRORNA-9 TARGETS THE ADHERENCE JUNCTION PROTEIN α-CATENIN IN SKIN SQUAMOUS CELL CARCINOMA METASTASIS A Reddi (MD, MS), R White, J Neiman, G Han and XJ Wang Department of Pathology, University of Colorado School of Medicine, Denver, CO 80045 Introduction: Squamous cell carcinoma (SCC) is the second most common form of skin cancer. MicroRNAs (miRs), small noncoding RNAs that suppress gene expression, have emerged as molecular regulators of tumor initiation and metastasis. We show that targeting mouse K15+ epidermal stem cells with KrasG12D and Smad4 mutations, two frequent mutations in human SCC, resulted in metastatic SCC. In our model, SCC metastasis involved expansion of side-population (SP+) cancer stem cells by miR-9. In the present study we investigated miR-9 tumor suppressor targets in SCC. Methods: To determine miR-9 target genes, clinically associated with human SCC disease, we searched the bioinformatics database

TargetScan. To validate targets, we performed gene and protein expression analyses in mouse and human SCC cell lines overexpressing miR-9 as well as in cell lines with knockdown expression of miR-9. Additionally, we validated miR-9 targets in K15.KrasG12D.Smad4-/- mouse tumors. We determined intracellular signaling by a transcriptional luciferase assay, small inhibitory RNA (siRNA) screen and immunoblotting. Finally, we validated miR-9 expression in human SCC tissue samples. Results: We found that miR-9 targeted the adherence junction protein α-catenin in vitro and in vivo, leading to β-catenin nuclear translocation as well as β-catenin-mediated expression of ATP binding cassette (ABC) transporters (a molecular determinant of the SP+ phenotype). Transplanting mouse and human SCC cells overexpressing miR-9 in vivo resulted in SCC lung metastases in mice. Conversely, knockdown of miR-9 inhibited metastasis in vivo. Mouse and human cells overexpressing miR-9 had increased expression of ABC transporter family isoforms, a chemoresistance gene family, and were resistant to Docetaxel induced cell death. Inhibition of β-catenin by siRNA abrogated ABC transporter expression. In human metastatic SCC lesions, miR-9 is a biomarker for metastasis and its expression correlates with loss of membrane α-catenin. Conclusions: MicroRNA regulation of the adherence junction is an unrecognized signaling axis involved in SCC oncogenesis and miR-9 is a biomarker of SCC metastasis.

Reidy, Rosemary

Poster Title: THEORY OF MIND DEVELOPMENT IS IMPAIRED IN 4-YEAR-OLD CHILDREN WITH PRENATAL EXPOSURE TO MATERNAL TOBACCO SMOKING

Category: Developmental Neuroscience and Brain and Behavior – Child

Abstract: THEORY OF MIND DEVELOPMENT IS IMPAIRED IN 4-YEAR-OLD CHILDREN WITH PRENATAL EXPOSURE TO MATERNAL TOBACCO SMOKING RE Reidy (B.A., SOM), RG Ross (M.D., Dept Psychiatry), SK Hunter (Ph.D., Dept Psychiatry) Purpose: Theory of Mind (ToM) is the capacity to appropriately judge and attribute mental states of the self and others and is a component of social cognition which has garnered great attention in recent years. ToM deficits are found in various neurodevelopmental disorders and social and environmental factors have been found to influence ToM development. However, there has been little work focused on how exposure to toxins may influence development of social cognition. This report is a first step to address that gap in the literature by examining the impact of tobacco, the most common prenatal toxin exposure. Methods: One hundred and one children underwent ToM testing; 18 had prenatal exposure to tobacco. Children underwent testing at 40 and 48 months of age with two sets of false belief tasks. The first was a locations false belief task which required children to predict where a protagonist would search for an object based on a false belief about the object location. The second task was a contents false belief task which required children to attribute knowledge about the contents of a mislabeled box to the self and others. Results: At 40 months of age, children were rarely able to correctly answer either form of ToM false belief test questions and there were no significant differences according to prenatal tobacco

exposure. At 48 months of age, there was no significant difference in performance on locations false belief test questions but children with prenatal tobacco exposure showed impaired performance on contents false belief test questions. Conclusions: ToM, as tested by this paradigm, is rarely developed at 40 years of age and is partially developed at 48 months of age. Maternal smoking during pregnancy results in impaired performance on Theory of Mind tasks; however, this impairment is not identifiable until 48 months of age. It is unknown whether the deficits identified here are transient and reflect developmental delay or are more long-lasting. Additional evaluation at 60 months of age, when nearly all children should be able to complete the task, would assist in resolution of this issue.

Rice, Jessica

Poster Title: Genome-Wide Analysis of Somatic Chromosomal Alterations in Premalignant Airway Lesions Using a Novel Analytical Algorithm

Category: Pulmonary and Critical Care

Abstract: GENOME-WIDE ANALYSIS OF SOMATIC CHROMOSOMAL ALTERATIONS IN PREMALIGNANT AIRWAY LESIONS USING A NOVEL ANALYTICAL ALGORITHM. JL Rice (M.D., SOM), I Nakachi, YE Miller, MW Geraci, SPORE in Lung Cancer, Department of Medicine, University of Colorado, Denver, CO. Chromosomal instability is central to the process of carcinogenesis. In lung squamous cell carcinogenesis, the histopathologic changes in bronchial epithelia that precede cancer development in heavy smokers have been well documented, and several studies have supported the concept that somatic chromosomal alterations (SCAs) may be better prognostic biomarkers than premalignant histology alone. However, the detection of SCAs in small premalignant lesions using high-resolution microarrays remains challenging since clinical sample heterogeneity dilutes the aberrant cell information. To overcome this hurdle, we first described and validated an algorithm for sensitive SCA detection, termed delta-theta (θ). This concise algorithm is derived from the difference in allelic balance between paired tumor and normal samples determined from single nucleotide polymorphism microarrays (SNP arrays), controlling for natural copy number variations by directly reflecting somatic events. In a simulated titration series of cancer and normal cell mixtures, delta-θ allows for the detection of SCAs even with a large proportion of normal cells (up to 90%) and possesses significant sensitivity for LOH, including copy-neutral events. We then applied this analytic strategy to heterogeneous clinical specimens including whole biopsies and brushings compared to the patient's blood. Somatic chromosomal alterations were successfully detected across the whole genome in all invasive cancer cases (6/6) and half of cases with dysplasia or carcinoma in situ (5/10). Fluorescence in situ hybridization (FISH) and copy number qPCR assays were performed on selected specimens to validate SCAs identified using SNP microarray and delta-θ. In the lesions studied, we observed not only previously well-described SCAs (e.g., 3p del, 3q amp, and 9p del), but also unique abnormalities. To our knowledge, this is the first study to use a SNP array-based approach to successfully identify

SCAs in preinvasive bronchial lesions across the entire genome using whole bronchial biopsies and brushings. We believe this is an important novel method that expands our ability to assess genomic instability in the airway epithelia as a biomarker of lung cancer risk.

Rosen, Sheri

Poster Title:

Category: Hematology and Oncology

Abstract: EFFECTS OF FIBROBLAST AND MACROPHAGE CO-CULTURE ON FIBROBLAST ACTIVATION AND COLLAGEN DEPOSITION Sheri Rosen1, Qiuchen Guo1, Clarissa Durand-Rougely1, Pepper Schedin1 1. Medicine, University of Colorado School of Medicine, Aurora, CO, United States. Women have an increased risk of breast cancer after a complete pregnancy and, if diagnosed within five years postpartum, have a worse prognosis than nulliparous or pregnant women. The increased risk and poor diagnosis of breast cancer are thought to be associated with postpartum breast involution, which is a coordinated program of epithelial cell death and stromal remodeling resulting in gland architecture resembling the pre-pregnant state. In rodents, the involuting mammary gland microenvironment has wound healing-like characteristics, such as influx of M2-like macrophages and abundance of fibrillar collagen, which are potential driving forces of tumorigenesis. Activated fibroblasts are a major source of fibrillar collagen, indicating that fibroblasts may be activated to contribute to collagen deposition. Further, macrophages can interact with fibroblasts in vivo and influence their function. My work is to use an in vitro model to study if the interaction between macrophages and fibroblasts can increase collagen deposition. Here we describe a 3D co-culture model that incorporates interaction between fibroblasts and macrophages. The co-cultures were observed by light microscope and photographed. Activation of fibroblasts was detected by staining for α-smooth muscle actin, a marker for myofibroblasts and, with collagen I, was examined by immunofluorescence. Our model demonstrates that in 3D culture there is a physical interaction between fibroblasts and macrophages resulting in increased survival of both populations. Further, the presence of M1 macrophages with fibroblasts increases collagen deposition in this system as determined by the increased intensity of signaling by immunofluorescence. These data support a model by which M1 macrophages, an immune cell population in the involuting mammary gland, contribute to collagen deposition. M1 macrophages are known to be the primary responders to wound environments and may contribute to a microenvironment favorable for tumorigenesis. Further research will investigate the interactions between endogenous mammary macrophages and fibroblasts to determine whether we can use drugs to target this interaction and block subsequent collagen production as a possible prophylactic treatment during postpartum involution.

Salazar, Monica

Poster Title: snAPP: Students Novel Approach to Practice Problems

Category: Education

Abstract: snAPP: STUDENTS' NOVEL APPROACH TO PRACTICE PROBLEMS. M Salazar, (MD, SOM), EK Sandsmark (MD, SOM), J Schwan (MD, SOM), L Ayres (MD, SOM), L Mehner (MD, SOM), R Gilmer (MD, SOM), J Odom, G Guiton, PhD, M Taylor, MD Department of Medicine, University of Colorado, Denver, CO. Effective learning methods are hotly debated and frequently researched. Previous dogma held that optimal retention occurs by repeated exposure, and that test retrieval was nothing more than a quantitative measure of learning. It has become increasingly clear, however, that the test-taking process itself is a highly effective learning method, independent of study time. Increasingly, educators deliberately use Test Retrieval Learning Practices (TRLP) to promote learning. Simultaneous with advances in our understanding of TRLP methods have come technical strides in electronic delivery of curriculum. Because of their swift deployment and convenience of use, digital learning environments and mobile applications are also gaining popularity among students. In a study comparing web-based learning tools to traditional materials, 71% of students preferred the web-based module. Combining TRLP with novel device technology is a logical next step in medical education, but remains unfamiliar to many educators currently. A collaboration of medical students and faculty at the University of Colorado School of Medicine created snAPP: Students' Novel Approach to Practice Problems, a mobile application based on the principles of TRLP. As a study tool, medical students wrote practice questions inspired by learning objectives for each course. Faculty reviewed and edited student-written questions to ensure their relevance and accuracy. Finalized questions from each lecture and explanations to correct answers were compiled into weekly quizzes accessible from iPod, iPad and iPod Touch. All content was also made available online. Medical students receive TRLP automatically, complete at their own pace, and receive feedback on correct answer choices. Data collection for current MS1 students began with the Molecules 2 Medicine (M2M) Block in October of 2012. Central data collection permits analysis of usage and performance markers with in-class examinations and the USMLE. Currently, data is pending on utilization and M2M examination performance.

Sandoval, Monica

Poster Title: ROLE OF ALDH16A1 IN GOUT VIA PROTEIN-PROTEIN INTERACTIONS WITH HPRT1

Category: Immunology and Autoimmune Diseases

Abstract: ROLE OF ALDH16A1 IN GOUT VIA PROTEIN-PROTEIN INTERACTIONS WITH HPRT1 M Sandoval (Ph.D., Molecular Toxicology), Donald Backos, Brian Jackson, Ying Chen, Phillip Reigan, David C. Thompson and Vasilis Vasiliou. University of Colorado Skaggs School of Pharmaceutical Sciences, Aurora, CO. Purpose: Gout, a common form of inflammatory arthritis, is strongly associated with elevated uric acid concentrations in the blood (hyperuricemia). A recent study identified a SNP in the ALDH16A1 gene, ALDH16A1*2, showing a strong association with gout and serum uric acid levels. ALDH16A1 is a novel and rather unique member of the ALDH superfamily in relation to its gene and protein structures. It has been identified as a protein interacting with maspardin (mast syndrome) as well as other cytosolic and transporter proteins. Hypoxanthine-guanine phosphoribosyltransferase (HPRT1) is a potentially important binding target for ALDH16A1 in the context of gout pathophysiology, given that HPRT1 has a key role in the purine salvage pathway and absence or reduced function are known to cause hyperuricemia and gout. Methods: Molecular modeling was performed to determine if ALDH16A1 is catalytically inactive and the binding ability of ALDH16A1 to HPRT1. Reverse transcription and semi-quantitative PCR was performed to assess the expression of ALDH16A1 transcript variants in human kidney and liver cell lines. Western blotting and immunohistochemical (IHC) analysis were performed to examine ALDH16A1 expression in mouse tissues. Results: Molecular modeling predicts that both the short and long forms of human ALDH16A1 protein would lack catalytic activity due to the absence of the catalytically important cysteine residue (Cys-302) in mammalian but may interact with the HPRT1 protein. Interestingly, such protein-protein interactions with HPRT1 are predicted to be impaired for the long or short forms of ALDH16A1*2. ALDH16A1 spliced variants are expressed in HepG-2, HK-2 and HK-293 human cell lines. Immunohistochemistry and Western blot analysis revealed ALDH16A1 expression in several mouse tissues including kidney, where uric acid homeostasis occurs. In addition, we found that ALDH16A1 is a cytosolic and membrane protein. Conclusion: These results lead to the possibility that association between ALDH16A1 and HPRT1 may be required for optimal HPRT activity; disruption of this interaction may contribute to the hyperuricemia seen in ALDH16A1*2 carriers.

Sandsmark, Emilee

Poster Title: snAPP: Students Novel Approach to Practice Problems

Category: Education

Abstract: snAPP: STUDENTS' NOVEL APPROACH TO PRACTICE PROBLEMS. M Salazar, (MD, SOM), EK Sandsmark (MD, SOM), J Schwan (MD, SOM), L Ayres (MD, SOM), L Mehner (MD, SOM), R Gilmer (MD, SOM), J Odom, G Guiton, PhD, M Taylor, MD Department of Medicine, University of Colorado, Denver, CO. Effective learning methods are hotly debated and frequently researched. Previous dogma held that optimal retention occurs by repeated exposure, and that test retrieval was nothing more than a quantitative measure of learning. It has become increasingly clear, however, that the test-taking process itself is a highly effective learning method, independent of study time. Increasingly, educators deliberately use Test Retrieval Learning Practices (TRLP) to promote learning. Simultaneous with advances in our understanding of TRLP methods have come technical strides in electronic delivery of curriculum. Because of their swift deployment and convenience of use, digital learning environments and mobile applications are also gaining popularity among students. In a study comparing web-based learning tools to traditional materials, 71% of students preferred the web-based module. Combining TRLP with novel device technology is a logical next step in medical education, but remains unfamiliar to many educators currently. A collaboration of medical students and faculty at the University of Colorado School of Medicine created snAPP: Students' Novel Approach to Practice Problems, a mobile application based on the principles of TRLP. As a study tool, medical students wrote practice questions inspired by learning objectives for each course. Faculty reviewed and edited student-written questions to ensure their relevance and accuracy. Finalized questions from each lecture and explanations to correct answers were compiled into weekly quizzes accessible from iPod, iPad and iPod Touch. All content was also made available online. Medical students receive TRLP automatically, complete at their own pace, and receive feedback on correct answer choices. Data collection for current MS1 students began with the Molecules 2 Medicine (M2M) Block in October of 2012. Central data collection permits analysis of usage and performance markers with in-class examinations and the USMLE. Currently, data is pending on utilization and M2M examination performance.

Sawyer, Brandon

Poster Title: Scope of Practice and Autonomy of Physician Assistants in Rural vs. Urban Emergency Departments

Category: Health Care and Public Health

Abstract: SCOPE OF PRACTICE AND AUTONOMY OF PHYSCIAN ASSISTANCE IN RURAL VERSUS URBAN EMERGENCY DEPARTMENTS. B. S. Sawyer, (M.D., Medical School), AA Ginde Objectives: Physician assistants (PAs) are being utilized in greater numbers in both rural and urban EDs (Emergency Departments) to mitigate the EM workforce shortages, improve efficiency of emergency physicians, and reduce the cost of emergency care. We sought to compare the scope of practice and autonomy of PAs (Physician Assistants) in rural vs. urban EDs, and hypothesized rural PAs would have a broader scope of practice and higher reported autonomy, while receiving less direct supervision. Methods: Using the American Academy of Physician Assistants Masterfile, we surveyed a random sample of 400 PAs who self-identified EM as their specialty. We classified location as rural or urban by zip code-based Rural-Urban Commuting Area codes, and over-sampled 200 rural PAs to ensure adequate rural representation. PAs were asked about conditions managed, procedures performed, and physician supervision. Groups were compared groups using chi-square test. Results: To date, 241 (60.2% response rate adjusted for exclusions) of 400 PAs in 44 states responded, of which 201 were valid responses (105 rural, 96 urban) from PAs currently practice in EDs. In the past year, rural PAs more frequently managed: cardiac arrest (67 vs 44%); stroke (86 vs. 72%); multi-system trauma (83 vs. 70%); active labor (44% vs. 23%); critically ill child (82 vs. 65%; all p

Schlegel, Jennifer

Poster Title: MER RECEPTOR TYROSINE KINASE IS A NOVEL THERAPEUTIC TARGET IN METASTATIC MELANOMA.

Category: Other:

Abstract: MER RECEPTOR TYROSINE KINASE IS A NOVEL THERAPEUTIC TARGET IN METASTATIC MELANOMA. J. Schlegel (PhD, GS), M. Sambade, S. Sather, A.C. Tan, A. Winges, S.J. Moschos, J.J. Tentler, S.G. Eckhardt, D. DeRyckere, X. Wang, S.V. Frye, H.S. Earp, J. Shields, and D.K. Graham. Department of Pediatrics University of Colorado, Aurora, CO, USA. Metastatic melanoma is one of the most aggressive forms of cutaneous cancers. While recent therapeutic advances have increased patient survival, prognosis remains dismal. Mer is a receptor tyrosine kinase with oncogenic properties that is often overexpressed or activated in various malignancies. Melanoma patient samples and cell lines were utilized to evaluate the frequency of Mer overexpression in melanoma. Cell lines harboring wildtype and mutant BRAF were selected for further studies including characterizing the effects of shRNA mediated inhibition of Mer in signaling, colony formation and tumorigenesis. Additionally a

small molecule inhibitor of Mer, UNC1062 was utilized for in vitro studies to demonstrate the applicability of targeting Mer pharmacologically. Our analyses indicate that Mer transcript expression increases with melanoma disease progression and that Mer is overexpressed in more than 40% of melanoma cell lines compared to normal tissues. Increased Mer overexpression however did not correlate with mutations in BRAF or RAS. Activation of melanoma cells with the Mer ligand Gas6 revealed a role for Mer in melanoma as a regulator of anti-apoptotic and pro-survival signaling pathways. Inhibition of Mer expression via shRNA resulted in decreased ERK, Akt, and Stat6 signaling downstream of Gas6 activated Mer. In addition, the inhibition of Mer expression reduced colony forming potential and reduced tumor volume by 60% in a murine xenograft melanoma model. Treatment of melanoma cells with UNC1062 a novel Mer-selective small molecule tyrosine kinase inhibitor, blocked the activation of Mer-mediated downstream signaling pathways, reduced colony formation in soft agar and inhibited invasion of melanoma cells. Mer expression increased with melanoma disease progression and is frequently overexpressed in melanoma cell lines. Inhibition with either shRNA or a small molecule inhibitor reduced the oncogenic capacity of melanoma cell lines. This work establishes Mer as a therapeutic target in metastatic melanoma and provides rationale for the further development of a Mer-targeted pharmacologic therapeutic.

Schwan, Josianna

Poster Title: A GAMMA SECRETASE INHIBITOR SYNERGISTICALLY KILLS MELANOMA CELLS WITH ABT-737/ABT-263 THROUGH A NOXA DEPENDENT MANNER.

Category: Hematology and Oncology

Abstract: A GAMMA SECRETASE INHIBITOR SYNERGISTICALLY KILLS MELANOMA CELLS WITH ABT-737/ABT-263 THROUGH A NOXA DEPENDENT MANNER. J Schwan, (MD, SOM), KA Partyka, A Almeida, YG Shellman, and DA Norris, Department of Dermatology, University of Colorado Denver, Aurora, CO. Despite the recent promising development of therapies targeting BRAF/MEK signaling in melanoma, many patients relapse or don’t respond to these treatments due to lack of the specific mutations targeted by these therapies. Thus, developing other treatment options is still urgent for melanoma. Targeting Bcl-2 anti-apoptotic proteins, such as the small molecule ABT-737, has been actively investigated for melanoma treatments. However, ABT-737 alone is not very effective in killing melanoma cells: many tumors also rely on other Bcl-2 proteins, such as Mcl-1, whose over-expression can contribute to cell resistance to ABT-737 therapy. The induction of Noxa, which selectively inhibits Mcl-1, is able to overcome this resistance. Gamma Secretase Inhibitors (GSIs) have been shown to induce apoptosis in malignant melanoma cells through induction of Noxa. Thus, in the present study, we tested the effects of the combination of ABT-737 and Gamma Secretase Inhibitors (GSI) on malignant melanoma cells. We used MTS and Immunoblot assays to assess for cell viability and apoptosis. We also examined whether Mcl-1 or Noxa plays a role in the

induced killing by knocking down each protein with shRNAs and determining the effects on the treatment response of multiple melanoma cell lines. We found that the combination of ABT-737 and GSI strongly induced apoptosis, more than either drug alone, in multiple melanoma cell lines, but not normal melanocytes. Additionally, the combination dramatically induced Noxa/Mcl-1 ratio. Knocking down Mcl-1 sensitized cells to ABT-737, and knocking down Noxa protected cells from the combination treatment. Furthermore, the combination of GSI and ABT-263 induced Noxa-dependent killing of melanoma cells, very similarly to the combination of ABT-737 and GSI. Overall, our data suggests the combination of ABT-737/ABT263 with GSI is a promising treatment strategy, worthy of further investigation.

Shah, Monil

Poster Title: CHECKPOINT KINASE 1 INHIBITION SUPPRESSES CELL GROWTH AND ENHANCES RADIATION SENSITIVITY IN MEDULLOBASTOMA CELLS

Category: Hematology and Oncology

Abstract: CHECKPOINT KINASE 1 INHIBITION SUPPRESSES CELL GROWTH AND ENHANCES RADIATION SENSITIVITY IN MEDULLOBASTOMA CELLS. MR Shah, (MD, SOM), S. Venkataraman, P. Harris, I. Alimova, S. Hobernicht, V. Amani, A. Griesinger, D. Birks, SA Schittone, A. Donson, N. Foreman, R. Vibhakar, Department of Pediatrics, University of Colorado, Denver, CO. Medulloblastoma is the most common malignant brain tumor in children and remains a therapeutic challenge due to its significant therapy-related morbidity. Checkpoint kinase 1 (CHK1) is highly expressed in many cancers and regulates critical steps in mitotic progression and DNA-damage response. Activation of CHK1 pathway promotes radiation resistance in tumor cells. Recent studies suggest that targeting CHK1 with a small molecule inhibitor, to sensitize tumors to a variety of DNA-damaging agents, is a promising approach to tumor therapy. The expression of CHK1 mRNA in medulloblastoma tumor samples was examined using microarray analysis. Western blot analysis was conducted on all tumor samples to analyze expression level of CHK1 protein. The impact of CHK1 on cell proliferation was evaluated by inhibiting its function using a small molecular inhibitor AZD7762. Colony formation studies were conducted to examine the long-term impact of AZD7762 on medulloblastoma cell growth. Flow cytometry was used to measure apoptosis. Analysis of gene expression and western blot analysis revealed that CHK1 mRNA and protein levels are overexpressed in all medulloblastoma patient samples when compared to normal cerebellum. Inhibition of CHK1 by a low nanomolar concentration of AZD7762, a small molecule inhibitor of CHK1, potently inhibited cell growth, suppressed the colony-formation ability, and increased cellular apoptosis of medulloblastoma cells. Our data suggest that targeting CHK1 with a small molecule inhibitor is an attractive strategy in treatment of medulloblastoma. Future experiments will be focused on treating medulloblastoma cells with CHK1 inhibitor prior to ionizing radiation exposure to examine its effect on radiation sensitivity.

Shrotriya, Sangeeta

Poster Title: The chemopreventive effect of grape seed extract in 4-nitorquinoline 1-oxide-induced oral carcinogenesis

Category: Hematology and Oncology

Abstract: According to National Cancer Institute, head and neck squamous cell carcinoma (HNSCC) accounts for 6 percent of all malignancies in the United States with approximately 49,260 new cases and 11,480 deaths expected in 2010 alone. In HNSCC, radiation and chemotherapy are the conventional treatment options available but unfortunately, recurrence of disease after chemo/radiation therapy along with therapy associated toxicity and development of resistance against conventional treatments, together decrease their efficiency. In this regard, several animal studies in past decade have shown that consumption of fruits and vegetables and/or the supplements derived from them are associated with reduced risk of cancer development including HNSCC. In the present study, we investigated the chemopreventive efficacy of grape seed extract (GSE) during the post-initiation phases of oral carcinogenesis initiated with 4-nitroquinoline 1-oxide (4-NQO) in C57B1/6 mice for 16 weeks time period. Initially, animals were divided into untreated control, 4NQO treated and GSE treated groups. The animals in 4-NQO treated group and animals in GSE- treated group received 100 µg/mL of 4NQO in drinking water for 16 weeks to induce tongue carcinoma and animals in untreated group received tap water. 8 weeks after 4NQO exposure, animals in GSE –treated group were fed with diets containing GSE (0.2% w/w in AIN-76A diet) for another 8 weeks and animals in both untreated group and 4NQO group received basal AIN-76A diet throughout the study period of 16 weeks. The H& E staining showed that GSE treatment decreased the overall incidences of tongue lesions (hyperplastic, dysplastic and papilloma) by approximately 65%. Moreover, the treatment of GSE delayed the progression of carcinogenesis as indicated by decreased number of hyperplastic lesions and absence of dysplatic lesions and papilloma formation. The cell proliferation and apoptosis was estimated by 5-bromodeoxyuridine (BrdU)-labeling index and TUNEL were compared among the groups. We observed that GSE treatment decreased cell proliferation as indicated by decrease BrdU positive cells and increased TUNEL positive cells. There was no significant change in body weight and diet consumption among the groups. Together, results from the current study suggest that GSE is a promising chemopreventive agent in human oral cancer.

Sinatra, Elizabeth

Poster Title: Promoting Prenatal Behavioral Change Counseling Among Health Care Providers

Category: Child-Maternal Health and Reproductive Sciences

Abstract: PROMOTING PRENATAL BEHAVIORAL CHANGE COUNSELING AMONG HEALTH CARE PROVIDERS, EM Sinatra (B.S.), AR Chandler (B.A.), JA Leiferman (Ph.D,

M.S.). Colorado School of Public Health, University of Colorado, Denver, CO. The primary aim of the project was to conduct focus groups with pregnant women to examine their perceptions on patient and health care provider (HCP) communication during prenatal visits pertaining to health behavioral change. In particular, to determine what types of communication facilitate or prevent patient engagement and adherence to certain health behaviors related to smoking cessation, engagement in physical activity, healthy eating and healthy weight gain, and stress management. Participants were recruited from the Baby Blanket Program database at the University of Colorado Hospital clinics. Twenty-four pregnant, English-speaking women between the ages of 18 and 46 years old, the majority of which had full health insurance coverage, participated in a focus group and completed a brief survey that assessed sociodemographic factors and health behaviors. The transcripts were coded for themes and patterns. Results identified numerous current practices of HCPs, facilitators and barriers in care, and patient recommendations related to effective patient-provider communication. Notable results include: Physical activity; patients feel common and consistent sources of information is a facilitating factor. Healthy eating and healthy weight gain; patients desire aid with self-monitoring and charting of weight gain throughout pregnancy. Stress management; patients feel there is a lack of comprehensive screening questions, minimal follow-up, and are more apt to manage stress if they learn how it affects baby. Smoking cessation; patients are screened only at initial exam and desire information about second-hand smoke hazards. Other unique results will be discussed. Findings will provide the necessary data to inform the development of an educational module aimed at enhancing patient-provider communication on health behavior change. Information learned from this study will help better understand what facilitates and prevents women from engaging in healthy behaviors during their pregnancy, in addition to improving patient and provider communication. This research was funded by the March of Dimes.

Singh, Surendra

Poster Title: THE ROLE OF ALDEHYDE DEHYDROGENAGE 1B1 IN ALCOHOL METABOLISM AND COLON CANCER

Category: Hematology and Oncology

Abstract: THE ROLE OF ALDEHYDE DEHYDROGENAGE 1B1 IN ALCOHOL METABOLISM AND COLON CANCER Singh S.1 (Ph.D., GS), Chen Y.1, Matsumoto A.1, Peters J.2, Vasiliou V.1 1Department of Pharmaceutical Sciences University of Colorado Anschutz Medical Campus, Aurora, CO 80045 2Department of Veterinary and Biomedical Sciences Pennsylvania State University, University Park, PA 16802 Aldehyde dehydrogenases (ALDHs) are a group of NAD(P)+-dependent enzymes involved in the metabolism of a wide spectrum of aliphatic and aromatic aldehydes. ALDH1B1 is a mitochondrial homotetrameric enzyme, which is 65% and 72% identical to ALDH1A1 and ALDH2 proteins, respectively. Our in vitro studies have shown that human ALDH1B1

metabolizes acetaldehyde with an apparent Km of 55 μM, indicating an important role of this protein in alcohol metabolism. We have recently shown that ALDH1B1 expression in normal colon is sparse and confined to the crypt base where stem cells reside; whereas ALDH1B1 is extensively expressed in cancer cells of human colonic adenocarcinomas. Similar upregulation of ALDH1B1 was also observed in colon tumors from the multiple intestinal neoplasia (MIN) mice. These findings suggest a potential role of ALDH1B1 in colon carcinogenesis. To assess the in vivo role of ALDH1B1, we have generated transgenic Aldh1b1(-/-) null mice, these mice are fertile and have a normal growth pattern. ALDH1B1 messenger and protein were undetectable in examined tissues. We also examined expression of ALDH2 and ALDH1A1 in these organs and did not find compensatory upregulation of these isozymes. Ethanol pharmacokinetics following a single injection of ethanol (i.p. 5g/kg) revealed higher acetaldehyde levels at 3 and 24 hours in female and at 24 hours in male Aldh1b1(-/-) mice. Further studies using the Aldh1b1(-/-) knockout mice that include comprehensive ethanol pharmacokinetics, alcohol drinking preference, and experimental colon carcinogenesis are currently underway in order to determine the role of ALDH1B1 in alcohol metabolism and colon cancer.

Sippel, Trisha

Poster Title: Arginase induced immunosuppression in glioblastoma and stroke

Category: Immunology and Autoimmune Diseases

Abstract: ARGINASE INDUCED IMMUNOSUPPRESSION IN GLIOBLASTOMA AND STROKE. TR Sippel (PhD, GS), T Shimizu, PS Herson, and A Waziri, Departments of Neurosurgery and Anesthesiology, University of Colorado Anschutz Medical Campus, Aurora, CO. Purpose: We have described a mechanism of immunosuppression in glioblastoma (GBM) patients where circulating activated neutrophils release Arginase I (ArgI) and suppress T cell function via depletion of arginine. This can be reversed in vitro by inhibiting ArgI or supplementing arginine. The event responsible for neutrophil activation in GBM patients remains indeterminate, however we hypothesize that profound necrosis associated with GBM may be central to this process. Interestingly, stroke patients (in whom infarcted tissue undergoes necrosis) exhibit clinical immunosuppression that negatively influences morbidity and overall recovery. Given the parallels between these two neurological disorders, we hypothesize that the neutrophil-ArgI axis may also induce immunosuppression in ischemic stroke patients. Material and Methods: Ischemic stroke was induced in mice through middle cerebral artery occlusion (MCAO). Proportions of lymphoid and myeloid lineage cells, along with T cell CD3ζ expression levels, were evaluated in blood and spleen samples. T cell functional capacity, including proliferation and IFN-γ production, was evaluated in vitro. Results: Animals with ischemic stroke demonstrated immunosuppression by decreased splenic weight, decreased T cell proliferation, and limited IFN-γ production when compared to sham controls. Suppression of T cell function correlated with increased ArgI in functional cultures and increased presence of activated granulocytes within the spleen. Direct ex vivo T cells from stroked mice also expressed

lower levels of CD3ζ, consistent with decreased levels of arginine. Critically, stroke animals T cell function could be rescued in vitro by arginine supplementation. Conclusions: This data suggests that ischemic stroke may be associated with downstream arginine depletion and peripheral T cell dysfunction. Although confirmatory data from patients will be required, these results suggest that parallel aspects of brain inflammation between GBM and ischemic stroke may induce a final common pathway of ArgI-mediated immunosuppression. We propose that in vivo targeting of ArgI activity may provide clinical benefit for improving immune function and overall clinical outcomes for patients with ischemic stroke.

Snow, Anson

Poster Title: Synthetic β-Glucogallin Reduces Sorbitol Levels in Transgenic Mice Overexpressing Aldose Reductase In The Lens

Category: Vision

Abstract: Synthetic β-Glucogallin Reduces Sorbitol Levels in Transgenic Mice Overexpressing Aldose Reductase In The Lens Diabetes mellitus is the leading cause of new blindness in the United States. Thus, advancing research in medical treatments that delays or inhibits the progression of diabetic eye diseases is important. There are currently several theories on the pathogenesis of diabetic eye disease, but the activation of the polyol pathway and its enzyme aldose reductase (ALR2) is of particular interest. We hypothesize that inhibition of ALR2 using ALR2 inhibitors (ARI) may be a good strategy to prevent diabetic eye disease. However, recent clinical trials of ARIs have failed due to toxicity or inadequate penetration of ARI in target tissues. In India, the Amla or Indian gooseberry (Emblica officinalis) is commonly used in traditional medicine for its preventive properties against diabetes. Specifically, it has been found that Amla contains 1-O-galloyl-β-D-glucose (β-glucogallin), which is a natural inhibitor of ALR2. In this study, we investigated the effects of synthetic β-glucogallin on ex vivo organ culture using lenses microdissected from a transgenic mouse strain engineered to over-express human ALR2. Our results demonstrate that synthetic β-glucogallin decreases sorbitol produced from ALR2 in lenses from this transgenic mouse model. Therefore, this study demonstrates that β-glucogallin is capable of penetrating into the intact lens tissue and effectively blocking ALR2 activity. Our studies indicate that β-glucogallin deserves further study as a clinically effective aldose reductase inhibitor for the delay or prevention of diabetic eye disease.

Stoermer, Kristina

Poster Title: MYELOID CELL ARGINASE 1 ENHANCES VIRAL LOADS IN A MOUSE MODEL OF ROSS RIVER VIRUS-INDUCED RHEUMATIC DISEASE

Category: Microbiology and Infectious Diseases

Abstract: MYELOID CELL ARGINASE 1 ENHANCES VIRAL LOADS IN A MOUSE MODEL OF ROSS RIVER VIRUS-INDUCED RHEUMATIC DISEASE. KA Stoermer (Ph.D., GS), A Burrack, L Oko, RG Gill, and TE Morrison, Department of Immunology, University of Colorado School of Medicine Mosquito-borne alphaviruses, such as chikungunya virus (CHIKV) and Ross River virus (RRV), cause a debilitating, and often chronic, musculoskeletal inflammatory disease in humans and mice. We hypothesized that the damage to musculoskeletal tissues in RRV or CHIKV-infected mice promotes a wound healing response characterized by M2 macrophages. Indeed, we found that musculoskeletal inflammatory lesions, and macrophages present in these lesions, had high expression of arginase 1 (Arg1) and Ym1/Chi3l3 in the absence of FIZZ1/Relmα that is consistent with a suppressive M2-like phenotype. Strikingly, mice deleted for Arg1 in macrophages and neutrophils (LysMCre;Arg1F/F) had dramatically reduced viral loads at late, but not early, times post-inoculation indicating that genetic deletion of Arg1 in myeloid cells resulted in enhanced RRV clearance. To define effectors of viral clearance in WT mice, CD8+ and/or CD4+ T cells were depleted using antibodies and viral loads were assessed at 14 dpi. Depletion of CD8+ T cells increased RRV loads, whereas depletion of CD4+ T cells had minimal impact on RRV loads. Additionally, CD8+ T cells isolated from inflamed musculoskeletal tissues expressed the effector cytokines interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) following re-stimulation ex vivo. Interestingly, CD4+ T cells isolated from inflamed musculoskeletal tissues expressed IFN-γ and TNF-α as well as the immunomodulatory cytokine interleukin-10, which may promote Arg1 expression and/or other immunosuppressive activities in myeloid cells. Similar T cell depletion studies in LysMCre;Arg1F/F mice suggest that (1) co-depletion of CD8+ and CD4+ T cells restores RRV loads to similar levels seen in Arg1-sufficient mice and (2) the contribution of CD4+ T cells to RRV clearance is enhanced in the absence of Arg1. Our findings suggest that Arg1 activity in macrophages at the sites of inflammation and infection inhibits RRV clearance by modulating T cell responses. These studies have provided new insights into the immunological mechanisms that regulate virus clearance and the role of myeloid cells in inflammation and immunity.

Stone, Amy

Poster Title: PLASMACYTOID DENDRITIC CELLS PRODUCE TYPE III INTERFERONS IN RESPONSE TO HEPATITIS C VIRUS RNA

Category: Immunology and Autoimmune Diseases

Abstract: PLASMACYTOID DENDRITIC CELLS PRODUCE TYPE III INTERFERONS IN RESPONSE TO HEPATITIS C VIRUS RNA. AEL Stone (Ph.D., GS), S Giugliano, G Schnell, L Cheng, KF Leahy, L Golden-Mason, M Gale, Jr and HR Rosen Department of Medicine, University of Colorado Denver, CO and University of Washington Seattle, WA.
Plasmacytoid dendritic cells (pDCs) represent less than 1% of circulating blood leukocytes and are key initiators of the immune response to viruses. pDCs are distinct from conventional DCs (cDCs) due to their ability to initiate interferon (IFN) production in response to viral antigens. Hepatitis C Virus (HCV) infects 200 million people and leads to a chronic infection in 80% of people infected. Single Nucleotide Polymorphisms (SNPs) in the Type III Interferon gene IL-28B have been associated with viral clearance. We currently do not understand why some patients clear the infection while the majority of infected patients develop chronicity or the mechanism of action for the IL-28B SNP. We hypothesized that pDCs are critical to the early response to HCV and that viral dysregulation of normal function impairs the antiviral response. Using a pDC line, we have characterized the in vitro response to viral antigens including RNA from the 3'UTR of HCV (pU/UC). Co-culture with viral Toll-like Receptor ligands rapidly produces Type I and III IFN mRNA. Transfection with pU/UC, leads to rapid induction of Type I and III IFN mRNA and proteins as well as Pattern Recognition Receptor genes and proteins, specifically members of the RIG-I family. Conditioned media from pDCs transfected with pU/UC RNA leads to a reduction in viral replication in the JFH-1/Huh7.5.1 in vitro HCV replication system that is partially mediated by Type III IFNs and JAK/STAT pathway activation. Freshly isolated human pDCs from healthy subjects respond to pU/UC with upregulation of IFN genes which varies by IL-28B genotype. This data suggests a mechanism of action for the IL-28B SNP that induces increased overall levels of IFNs. Together, this data suggests that pDCs may play a key role in recognition and early response to HCV infection and that pDC-derived proteins may lead to localized viral control in the livers of infected HCV patients.

Ung, Timothy

Poster Title: Supratotal Tumor Resection in Glioblastoma Patients Correlates With Increased Progression Free Survival

Category: Surgery

Abstract: Supratotal Tumor Resection in Glioblastoma Patients Correlates With Increased Progression Free Survival. T Ung (MD Candidate), R Kumar, H Winston, BK Demasters and A Waziri, Department of Neurosurgery, University of Colorado, Denver, CO. Background: Glioblastoma (GBM) is a malignant tumor of the central nervous system that continues to carry a dismal prognosis despite advancements in therapy. Recent data has associated the extent of surgical resection with a survival advantage. However, there has been no research into the potential benefits of "supratotal" (SuTR) versus gross total (GTR) and sub total (STR) resection. Here, we attempt to evaluate the benefit of SuTR of primary GBM by: 1) Assessing the incidence of transient/fixed post-operative deficit 2) Evaluating post-operative corticosteroid dependence and 3) Characterizing progression-free survival (PFS). Methods: Our retrospective case series evaluated 123 patients that had undergone surgical treatment of primary GBM at The University of Colorado Hospital from 2007-2011. Patients undergoing biopsy and those lost to follow-up were excluded leaving subtotal resection (STR) [n=24], gross total resection [n=24], and SuTR [n=11]. Results: New neurological deficit was seen at an increased rate in patients undergoing SuTR [11%] compared to GTR [4.0%]. However, long-term steroid dependence was decreased, SuTR [0.0%], GTR [40%] and PFS was significantly increased, SuTR [400 Days], GTR [308 Days] when comparing SuTR to GTR. Conclusion: SuTR of GBM resulted in longer PFS and decreased steroid dependence when compared to GTR and STR. Long-term follow up and larger studies may establish SuTR as a potential surgical management technique when achievable for initial tumor resection for GBM patients.

VanderWeide, Luke

Poster Title: Addition of dexmedetomidine to the standard of care for severe alcohol withdrawal

Category: Pulmonary and Critical Care

Abstract: ADDITION OF DEXMEDETOMIDINE TO THE STANDARD OF CARE FOR SEVERE ALCOHOL WITHDRAWAL. LA VanderWeide, (Pharm.D., SOP), CJ Foster, and S Mueller, University of Colorado Denver Skaggs School of Pharmacy and Pharmaceutical Sciences. The current standard of care for severe alcohol withdrawal is benzodiazepines administration based on a symptom driven alcohol withdrawal protocol. Large doses of benzodiazepines are related to complications such as prolonged ICU stay, increased incidence of delirium, and the possibility of respiratory depression requiring mechanical ventilation. Although data is limited, dexmedetomidine has been used as an adjunctive therapy for severe alcohol withdrawal and may be useful in this regard as it provides light sedation as well as a reduction in

heart rate and blood pressure, which are elevated in withdrawal. The objective of this study was to evaluate the use of dexmedetomidine as an adjunctive treatment for severe alcohol withdrawal. This retrospective study analyzed patients admitted to the ICU for severe alcohol withdrawal as evidenced by a Clinical Institute Withdrawal Assessment of Alcohol (CIWA) score > 8. Patients had to be over 18 years old and must have received dexmedetomidine for alcohol withdrawal. Clinical measures included patient vital signs, CIWA scores, benzodiazepine use, and dexmedetomidine dose and duration. These values were compared before and after dexmedetomidine initiation using paired t-tests with a significant p value of

Welsh, Seth

Poster Title: MOLECULAR MECHANISMS OF EBF1-MEDIATED GENE SILENCING IN B CELL DEVELOPMENT

Category: Immunology and Autoimmune Diseases

Abstract: MOLECULAR MECHANISMS OF EBF1-MEDIATED GENE SILENCING IN B CELL DEVELOPMENT. SJ Welsh, (Ph.D., GS)a, C Degeb, D Straignb, K Lukinb, H Leib, and J Hagmana,b. aMolecular Biology, University of Colorado School of Medicine. bIntegrated Department of Immunology, National Jewish Health. The transcription factor Early B Cell Factor 1 (EBF1) is required for normal B cell development. EBF1 is expressed throughout B cell lymphopoiesis, but not in terminally differentiated plasma cells. In regulating over 500 genes, EBF1 drives B cell identity by turning on genes necessary for B lineage specification but also by repressing genes from non-B cell lineages. EBF1 activates genes required for B cell signaling, metabolism, cellular adhesion, and migration. Gene repression by EBF1 is far less understood. One gene that is repressed by EBF1 is the Natural Killer (NK) cell-specific gene Cd244 which encodes for a NK cell surface receptor. Cd244 is not expressed in normal B cells. Loss of EBF1 results in the absence of B cell receptors, lack of immunoglobulin gene rearrangement, arrest at a B-biased progenitor stage, loss of B cell identity, and promiscuous expression of Cd244 on B-biased cells. Mechanistically, EBF1 acts as a pioneer factor regulating chromatin via CpG demethylation, histone modification, and by its interactions with chromatin remodeling complexes. The details of these interactions, especially concerning gene repression, remain unclear. In conjunction with its developmental role, EBF1 has also been identified as a tumor suppressor, as the loss of EBF1 contributes to drug resistance and cancer relapse in B-progenitor acute lymphoblastic leukemia (ALL) patients. Recently, an oncogenic fusion protein with EBF1 fused to an active tyrosine kinase of platelet derived growth factor receptor β (EBF1:PDGFRβ) has been discovered in a sub-population of ALL patients. How EBF1:PDGFRβ-mediated oncogenesis affects normal EBF1 function is entirely unknown. Our goal is to better understand EBF1 regulatory function. We propose to, (1) determine the molecular mechanisms of EBF1-mediated gene repression in B cell development by using shRNA technology, high-throughput screening, and TALEN-mediated mutagenesis, and (2) to utilize our plasmacytoma cell reporter

system to elucidate the functional consequences of the newly discovered oncogenic fusion protein EBF1:PDGFRβ on normal EBF1 and B cell development.

Winkler, Zach

Poster Title: Identification of a Novel Predictor of Anabolic/Catabolic Balance and Nutritional Status in Critical Illness: What Can Be Learned From Elite Athletes?

Category: Pulmonary and Critical Care

Abstract: Critically ill patients and patients undergoing major surgery present with a number of unique physiological responses which must be managed appropriately to achieve optimal outcomes. Current research addresses the metabolic and stress response in peri-operative and critically ill patients but, there is a consensus that these responses need to be better characterized. Currently, there is no useful biomarker that can be followed to predict nutrition status and adequacy of nutrition delivery. With a better understanding of patient nutritional and stress markers physicians could target nutritional and pharmacological therapies for their patients based on their catabolic/anabolic balance. This may also potentially decrease hospital length of stay, morbidity, and increase quality of life. To accomplish this goal my project will focus on the quantification of a number of stress markers that were collected from the serum of patients in a critically ill (WATTCH Trial, 203 patients with day 1 to day 28 samples available). Specifically, I will be examining the stress markers shown by previous work in patients and elite Tour de France athletes and other extreme professional athletes to relate to the severity of a patient's catabolic state. Markers to be analyzed will include: total serum cortisol, , albumium, total creatine kinase, LDH, ACH, GH, testosterone, troponin I, CBC, IL-6, creatinine, CRP and, EPO. Preliminary data analysis of testosterone, LDH, and creatine kinase does not show a statistically significant association between these serum marker levels over time and death or sepsis. After accounting for age and sex analysis of cortisol shows an association between the log of its mean serum levels and the odds ratio of death and the odds ratio of sepsis. The odds ratios were 2.674 and 2.685, respectively and the p-values were 0.031 and 0.026, respectively. In addition, for every ug/dL increase in the log of the mean cortisol level correlated with an increase of the log mean IL-10 value by 1.845 pg/mL. Cortisol levels correlated well with adverse patient events such as death and sepsis while the analysis of LDH, creatine kinase, and testosterone were found to be statistically insignificant.

Wong, Chelsea

Poster Title: SYNTHETIC LETHAL SCREENS FOR THE DISCOVERY OF NOVEL TARGETS IN ACUTE MYELOID LEUKEMIA WITH ISOCITRATE DEHYDROGENASE MUTATIONS.

Category: Hematology and Oncology

Abstract: SYNTHETIC LETHAL SCREEN FOR THE DISCOVERY OF NOVEL TARGETS IN AML WITH ISOCITRATE DEHYDROGENASE MUTATIONS. Chelsea Wong (BSc), Francesca Alvarez-Calderon, Dan Pollyea, James DeGregori. Department of Biochemistry and Molecular Genetics, University of Colorado, Denver, CO. Acute myeloid leukemia (AML) is a heterogeneous disease, characterized by recurrent genetic abnormalities. AML is the most common acute adult leukemia and second most common childhood acute leukemia. Recently, heterozygous isocitrate dehydrogenase (IDH) mutations, in both the cytosolic (IDH1) and mitochondrial (IDH2) homologues, have been identified in approximately 33% of AML patients. Mutations in IDH abrogate its ability to catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). The mutated protein has a dominant negative effect on wild-type IDH, leading to the production and marked accumulation of 2-hydroxyglutarate (2-HG), a metabolite undetectable in the IDH wild-type setting. Given the structural similarity between 2-HG and α-KG, elevations in 2-HG interfere with α-KG dependent dioxygenase enzymes, contributing to the development of AML. We hypothesize that abnormal metabolic profiles in AML with IDH mutations may specifically sensitize these AML cells to the targeting of particular signaling pathways. Current standard therapeutic approaches to treating AML involve combinations of nucleoside analogs and anthracyclines, which are highly toxic. Despite treatment, the majority of patients ultimately die of their disease. While IDH mutations are common in AML and confer an overall adverse prognosis, little is known about the metabolic perturbations they cause, or how these perturbations alter gene and signaling pathway dependencies. The aims of this project are three fold: to generate AML cell lines that express the mutant version of IDH1 or IDH2; to characterize the metabolic perturbations these mutations cause in leukemia cells; and to perform an unbiased kinome-wide screen to identify novel therapeutic approaches that will sensitize AML cells to kinase inhibition in the presence of IDH mutations. AML cell lines with IDH mutations do not currently exist. The overall goal of this project is to target the gene products and pathways to specifically eliminate AML with IDH mutations, with the ultimate goal of developing novel and targeted interventions that may lead to therapeutic strategies for this common and aggressive AML subtype.