

UNIVERSITY OF COLORADO DENVER
ANSCHUTZ MEDICAL CAMPUS

29TH ANNUAL STUDENT RESEARCH FORUM

AND

STUDENT RESEARCH AWARDS CONVOCATION

COLLEGE OF NURSING

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DECEMBER 16, 2014
ANSCHUTZ MEDICAL CAMPUS
EDUCATION 2 NORTH/SOUTH

29TH ANNUAL
UNIVERSITY OF COLORADO DENVER
ANSCHUTZ MEDICAL CAMPUS
STUDENT RESEARCH FORUM

Tuesday, December 16, 2014

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

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ABSTRACTS

**Aldeboran
Rodriguez**

Poster Title: PSYCHOMETRIC PROPERTIES OF A NOVEL PATIENT-CENTERED OBSTETRIC COMMUNICATION ASSESSMENT TOOL FOR UNDERGRADUATE MEDICAL EDUCATION

Category: Education

Poster Location: Education 2 South 1204

Poster Number: 1

Abstract: Introduction: Communication training is an essential component of undergraduate medical education, requiring critical evaluation of educational methods and materials. Validated assessment tools are needed to determine the efficacy of communication training programs and novel interventions. Objective: To characterize the psychometric properties of the Obstetric Communication Assessment Tool (OCAT) for a novel obstetric (OB) communication module. Methods: We developed and piloted four difficult OB Standardized Patient (SP) clinical scenarios: Religious Beliefs (RB), Angry Father (AF), Maternal Smoking (MS), and Intimate Partner Violence (IPV). An Objective Structured Clinical Examination (OSCE) trial run was performed with SPs and twenty-one third year OB/GYN clerkship students. Five trained Standardized Patient Reviewers (SPRs) independently scored twenty-four randomized video-recorded encounters using the OCAT. Scores were used to determine the psychometric rigor of the assessment tool. Internal consistency (IC) was estimated with Cronbach's alpha. Inter-rater reliability (IRR) was estimated using the Intraclass Correlation Coefficient-2 (ICC-2) test. Systematic variability in reviewer responses was assessed using the Stuart-Maxwell test. Results: IC was acceptable to excellent with Cronbach's alpha values (and 95% Confidence Intervals [CI]): RB 0.91 (0.86, 0.95), AF 0.76 (0.62, 0.87), MS 0.91 (0.86, 0.95), and IPV 0.94 (0.91, 0.97). IRR was unacceptable to poor with ICC-2 values: RB 0.46 (0.40, 0.53), AF 0.48 (0.41, 0.54), MS 0.52 (0.45, 0.58), and IPV 0.67 (0.61, 0.72). Stuart-Maxwell analysis indicated systematic variability in reviewer scoring. Conclusion: The OCAT demonstrates high IC but unacceptable IRR. Our findings suggest that the OCAT effectively discriminates learner performance but systematic differences in SPR rigor require a revised training regimen to improve reliability. Practice Implications: Training with challenging OB clinical encounters may better prepare students for high-risk clinical communication across medical specialties. Further, dedicated OB communication training is lacking, despite the wealth of uniquely sensitive and difficult clinical topics unaddressed by conventional communication curricula. We propose the optimization of the OCAT as an essential step toward development of an OB-focused communication module and discuss future directions of the project.

ABSTRACTS

Poster Title: The STING of inflammation

Category: Immunology and Autoimmune Diseases

Poster Location: Education 2 South 1307

Poster Number: 11

Abstract: Title: The STING of inflammation Authors: Packard TA, Mohning MP, Barthel L, Janssen WJ, Cambier JC University of Colorado School of Medicine, Department of Immunology and Microbiology & National Jewish Health, Department of Medicine Abstract: Stimulator of Interferon Genes (STING, a.k.a. MPYS, TMEM173) is a critical intracellular transducer of innate immune signals induced by cytosolic DNA. Activation of STING drives both apoptosis and production of type 1 interferons (IFN1). Thus STING is a vital defensive player in the front line of innate immunity to infectious agents. Recent studies have suggested that STING may also be activated by host-derived DNA, especially in the the context of reduced nuclease activity, and could play a role in autoimmune processes. We hypothesized that during inflammation in wild-type animals, STING can be activated by host-derived DNA in cellular debris as a damage-associated molecular pattern (DAMP). To begin to address this possible role for STING we utilized multiple models of in vivo sterile injury. Our studies demonstrate that STING-deficient animals have reduced inflammatory responses to sterile acute lung injury (ALI) and peritonitis, and reduced inflammation in response to cellular debris. We propose a model in which STING is activated by host-derived cellular debris containing DNA, driving production of type 1 interferon, and cell death--causing further release of debris. Together, this represents a vicious cycle serving to amplify and perpetuate inflammation.

Poster Title: Transmitted/founder hepatitis C viruses induce cell type- and genotype-specific differences within the liver

Category: Immunology and Autoimmune Diseases

Poster Location: Education 2 South 1307

Poster Number:13

Abstract: TRANSMITTED/FOUNDER HEPATITIS C VIRUSES INDUCE CELL TYPE- AND GENOTYPE-SPECIFIC DIFFERENCES WITHIN THE LIVER. Angela M Mitchell¹ (PhD, GS), Amy EL Stone¹, Linling Cheng¹, Kimberly Ballinger², Michael Edwards¹, Mark Stoddard³, Hui Li³, Lucy Golden-Mason¹, George Shaw³, Salman Khetani², Hugo R Rosen¹. ¹Department of Medicine, University of Colorado Denver; Aurora, CO. ²Department of Mechanical & Biomedical Engineering, Colorado State University; Fort Collins, CO. ³Departments of Medicine & Microbiology, University of Pennsylvania; Philadelphia, PA. The liver is comprised of many different cell types that, despite not sustaining productive viral replication, are able to sense HCV RNA and likely shape the outcome of infection. HCV transmitted/founder (T/F) viruses that result in productive infection possess sequences that favor efficient in vivo replication in humans, yet their biological effects on different cell types have not been characterized. Here, we tested the differential effects of genotype 1a, 1b, and 3a HCV T/F viral RNA (vRNA) on innate signaling within cells of the liver. HepG2 (but not Huh7.5.1) cells demonstrated robust transcriptional up-regulation of IFN-beta, IL-28A (IFNL2), IL-28B (IFNL3) and IL-29 (IFNL1) as compared to mock transfection. A human liver endothelial cell (LSEC) line showed even greater IFN upregulation than HepG2 cells, but supernatants from transfected LSECs and HepG2 both controlled HCV replication. Transfection of either a plasmacytoid or monocytic cell line with T/F genotype 3a vRNA induced relatively greater IFN levels than genotype 1a or 1b. Primary human hepatocytes were transfected for 8 hours, and RNA was subjected to an Affymetrix 2.0 microarray followed by confirmatory qRT-PCR. Although the vast majority (>98%) of transcripts were similar regardless of genotype, significantly higher levels of gene expression for CXCL10, CXCL11, EGR1 (early growth response protein 1), IFNLs, and IFIT3 were observed in genotype 3a. Novel full-length molecular clones of HCV induce broad IFN responses within hepatocytes and NPCs, highlighting that different signals imparted by the various cell types within the liver may lead to divergent outcomes of infection. The finding that genotype 3a induces higher production of IFNs from NPCs and enhanced chemokine production from primary hepatocytes may explain paradoxical epidemiological observations (higher recovery rate, but in persistence, higher rate of inflammation/fibrosis).

Poster Title: NATURAL KILLER CELLS DIRECTLY CONTRIBUTE TO ISCHEMIA REPERFUSION INJURY IN THE KIDNEY

Category: Immunology and Autoimmune Diseases

Poster Location: Education 2 South 1307

Poster Number:15

Abstract: NATURAL KILLER CELLS DIRECTLY CONTRIBUTE TO ISCHEMIA REPERFUSION INJURY IN THE KIDNEY. F Victorino (Ph.D, GS), K Brodsky, D Homann, HK Eltzschig, ET Clambey. Department of Immunology and Microbiology, Department of Anesthesiology, University of Colorado Anschutz Medical Campus. Acute Kidney Injury (AKI) is major concern in today's healthcare system and is caused by various conditions such as trauma, major surgery, and sepsis. Regardless of causation, fifty percent of AKI cases result from ischemia, resulting in necrosis and apoptosis of nephrons, the functional units of the kidney. Our lab uses a novel hanging weight system to induce AKI that recapitulates the pathogenesis and clinical manifestations of ischemia reperfusion injury (IRI). Due to limited research of natural killer (NK) cells in AKI, further studies are needed to understand their contribution to pathology. Here we explore the therapeutic benefits of NK1.1 depletion using our model of AKI. NK1.1 antibody treatment resulted in improved kidney function twenty-four hours after reperfusion compared to IgG controls. To determine when NK cells may contribute to IRI, numbers and kidney function was measured at 4, 8, and 24 hours after ischemia. Kidney dysfunction occurs at four hours yet, NK cell numbers were reduced and were comparable to sham surgery at all-time points. Despite precedence that NKT cells play a role in AKI by inducing interferon-gamma (IFN γ) production, here we show neither component contributes to IRI in our model. To determine how NK cells may be inducing damage, we characterized tissue resident NK (trNK) and classical NK (cNK) cells. Unexpectedly, there were no changes in composition of NK cell subsets or their activation status at 4 and 24 hours after IRI. In summary, our studies identified NK cells as the major NK1.1+ cell type responsible for kidney damage in IRI, and implicates trNK and cNK subsets as contributors to ischemic tissue injury.

Poster Title: NOVEL ROLE OF ALDH16A1 IN MODULATING EXTRACELLULAR URIC ACID

Category: Arthritis

Poster Location: Education 2 South 1304

Poster Number:17

Abstract: NOVEL ROLE OF ALDH16A1 IN MODULATING EXTRACELLULAR URIC ACID M Sandoval (Ph.D., Toxicology), Y Chen, M Lanasp-Garcia, R Johnson, V Vasiliou, J Brown. Department of Pharmaceutical Sciences, University of Colorado, Aurora, CO. Gout, a common form of inflammatory arthritis, is strongly associated with elevated uric acid concentrations in the blood (hyperuricemia). A recent study identified a rare single nucleotide polymorphism in the aldehyde dehydrogenase 16A1 (ALDH16A1) gene, ALDH16A1*2, shows a strong association with hyperuricemia and gout (Nature Genetics, Stefansson, 2011). ALDH16A1 is a novel and unique member of the ALDH superfamily in relation to its protein structure. Due to the absence of a conserved cysteine (Cys-302) residue in the active site, human ALDH16A1 is predicted to be a 'dead enzyme'. The purpose of this study is to characterize the novel ALDH16A1 isoform and determine if it plays a functional role in hyperuricemia and gout by modulating extracellular uric acid levels. **Methods:** Molecular modeling was performed to determine the homologous structure and enzymatic properties of human ALDH16A1. Tissue and sub cellular expression of ALDH16A1 was preformed on wild-type mouse tissue to assess the organ distribution and cellular location. Uric acid (UA) levels were measured in human kidney epithelial cells overexpressing ALDH16A1 and Aldh16a1(-/-) mice to assess the possible role of ALDH16A1 in uric acid transport or excretion. **Results:** Molecular modeling and enzyme activity assays determine that human ALDH16A1 protein lacks catalytic activity due to the absence of the catalytically important cysteine residue (Cys-302). Subcellular fractioning of wild-type tissue shows ALDH16A1 expression in both the subcellular and membrane fraction in many tissues including the liver and proximal tubules of the kidney. ALDH16A1 overexpressing cell lines had a decrease in intracellular UA levels and an increase in extracellular UA levels. On the contrary, Aldh16a1(-/-) mice had an increase in intracellular UA and a decrease in circulation serum UA levels. **Conclusion:** These results lead to the intriguing possibility that ALDH16A1 may play a functional role in uric acid metabolism.

Poster Title: A GENOME-WIDE RNA INTERFERENCE SCREEN TO IDENTIFY NOVEL REGULATORS OF CHROMOSOME SEGREGATION IN MITOSIS

Category: Basic Processes

Poster Location: Education 2 South 1209

Poster Number:19

Abstract: 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.

Poster Title: WHOLE EXOME NEXT-GENERATION SEQUENCING IDENTIFIES NOVEL DISEASE GENES IN PRIMARY VASCULAR ANEURYSMS

Category: Cardiovascular

Poster Location: Education 2 South 1203

Poster Number:20

Abstract: Background: Non-atherosclerotic arterial aneurysm is a highly morbid condition and its biological basis remains unclear outside the spectrum of an identifiable heritable connective tissue condition (e.g. Marfan or Ehlers-Danlos Syndromes). We identified a cohort of unrelated patients lacking a heritable connective tissue diagnosis in spite of manifesting multiple aneurysms and/or pseudoaneurysms in medium-sized arteries. We termed the condition multiple aneurysmal-pseudoaneurysmal syndrome (MAPS) and hypothesized that MAPS may be due to a novel disease gene. We utilized exome sequencing and bioinformatics analysis to identify potential disease genes which contribute to risk for MAPS. **Methods:** Next-generation exome sequencing was performed for 15 MAPS patients and one family with multi-generational arterial aneurysms. Bioinformatics filtering of identified putative 'mutations' followed by Ingenuity Pathway Analysis of suspicious genes was performed. **Results:** The familial MAPS phenotype was first targeted by exome sequencing to identify candidate MAPS genes. For sporadic MAPS cases, Ingenuity Pathway Analysis (IPA) software was used to search literature describing biochemical pathways between known vascular disease genes and bioinformatics-filtered candidate genes. Analysis of familial MAPS yielded 15 candidate genes, of which the PCDH12 gene was the most promising candidate due to its respective mutation being located in an extremely conserved gene region with a high bioinformatics score for predictive phenotypic damage. Analysis of sporadic MAPS using IPA software identified 6 candidate genes including BAG6, PRKCD, CTNNA1, JAG1, FN1, and MMP13. **Conclusion:** Exome sequencing with bioinformatics filtering in the novel aneurysm phenotype, MAPS, identified several promising aneurysm candidate genes. Knock-out/knock-in animal models are being developed to further explore the relationship between candidate genes and phenotypic expression.

Poster Title: Cellular and population analyses of signal filtering at olfactory bulb glomeruli

Category: Neuroscience and Brain and Behavior – Adult

Poster Location: Education 2 South 2305

Poster Number:22

Abstract: GABAergic periglomerular (PG) cells in the olfactory bulb receive direct input from olfactory sensory neurons (OSNs) while also targeting glutamatergic external tufted (ET) cells that mediate feed-forward excitation of output mitral cells (MCs). It has been postulated that intraglomerular inhibition mediated by PG cells provides an alternate mechanism to lateral inhibition to decorrelate similar odors. PG cells, which have a high input resistance, should be preferentially activated when a glomerulus receives weak OSN input (e.g., due to an “off-target” odor), resulting in inhibition of the glomerulus. Stronger inputs, in contrast, should excite excitatory elements at the glomerulus sufficient to overcome inhibition. In this study, we used patch-clamp and imaging approaches in rat olfactory bulb slices to assess this hypothesis. We first tested the assumption that PG cells are more responsive than ET cells to current input. Following electrical stimulation of OSNs, PG cells indeed required much smaller monosynaptic excitatory post-synaptic currents to generate action potentials than ET cells. At the same time, however, the relatively large dendritic arbor of ET cells resulted in them having much larger EPSCs, which would favor ET cell excitation. During simultaneous pair-cell recordings ($n = 4$), the EPSCs in ET and PG cells, respectively, were 241 ± 134 pA and 45 ± 21 pA at a given stimulus intensity (4.5-10 μ A). To test directly whether activation of PG cells or ET cells is favored at low levels of OSN activity, we used a population analysis of fura-2, AM associated calcium signals in VGAT-Venus transgenic rats, which selectively labels GABAergic cells. Weak OSN stimuli (5-20 μ A) resulted in ~ 10 times more active presumed PG cells versus ET cells, although the relative number of active ET cells increased 3-fold ($p = 0.0002$) with stronger stimuli (10-50 μ A) to a value (ET to PG cell ratio = 0.35 ± 0.05) that matched the total cell count ratio (ET to PG cell ratio = 0.37). Thus, the high input resistance of PG cells offsets their disadvantage of having a small number of OSN contacts, such that PG cells are mainly excited when a glomerulus receives weak input, but ET cell excitation catches up to PG cells with stronger input. These results support the hypothesis that the PG/ET cell microcircuit underlies a glomerular signal-filtering mechanism that could drive olfactory contrast enhancement.

Poster Title: A NOVEL HSP90 INHIBITOR ACTIVATES COMPENSATORY HEAT SHOCK PROTEIN RESPONSES AND AUTOPHAGY AND PROTECTS AGAINST MUTANT A53T ALPHA-SYNUCLEIN TOXICITY.

Category: Neuroscience and Brain and Behavior – Adult

Poster Location: Education 2 South 2305

Poster Number:24

Abstract: A NOVEL HSP90 INHIBITOR ACTIVATES COMPENSATORY HEAT SHOCK PROTEIN RESPONSES AND AUTOPHAGY AND PROTECTS AGAINST MUTANT A53T ALPHA-SYNUCLEIN TOXICITY. R Xiong¹, (Ph.D., Toxicology). D Siegel¹, WB Zhou², RR Kitson³, CJ Moody³ and D Ross¹, ¹School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Anschutz Medical Campus, Aurora, CO, United States, ²School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, ³School of Chemistry, University of Nottingham, Nottingham, United Kingdom. A potential cause of neurodegenerative diseases including Parkinson's disease (PD) is the accumulation of misfolded protein aggregates that in turn leads to neurotoxicity. Targeting Hsp90 is an attractive strategy to halt neurodegenerative diseases, and treatment of benzoquinone ansamycin (BQA) Hsp90 inhibitors such as geldanamycin (GA) and 17-AAG have been found to be beneficial in A53T α -synuclein PD disease models. However, current BQA inhibitors result in off-target toxicities via mechanisms involving redox cycling and arylation of nucleophiles at the C19 position of the benzoquinone ring. We have developed novel 19-substituted BQAs (19BQAs) as a means to prevent arylation. Our results show that 19BQAs were redox stable and exhibited little toxicity in SH-SY5Y cells relative to their parent quinones (GA, 17-AAG and 17-DMAG) as examined by oxygen consumption, trypan blue, MTT and Annexin/PI apoptosis assays, while they retained the ability to induce potentially protective heat shock proteins (HSPs) and autophagy as determined by increased protein levels of Hsp70, Hsp27 and LC3 II respectively. We demonstrated that 19-phenyl-GA, a potent inducer of HSPs and autophagy, significantly reduced the oligomer formation and neurotoxicity induced by mutant A53T α -synuclein in SH-SY5Y cells. In addition, we have found that mTOR/p70S6K signaling was involved in mutant A53T α -synuclein toxicity in SH-SY5Y cells and treatment with 19-phenyl-GA could significantly block the activation of p-mTOR and p-p70S6K. These results indicate that 19BQAs may provide a means to modulate protein-handling systems including HSPs and autophagy thereby reducing the aggregation and toxicity of proteins such as mutant A53T α -synuclein (supported by CA51210, ES018943 and Parkinsons UK).

Poster Title: PROLONGED NEUROINFLAMMATION FOLLOWING A SINGLE CLOSED HEAD INJURY (CHI) IN MICE

Category: Neuroscience and Brain and Behavior – Adult

Poster Location: Education 2 South 2305

Poster Number:26

Abstract: CHRONIC NEUROINFLAMMATION IN A MOUSE MODEL OF CONCUSSION
Alyssa G. Blood, Chelsea E. Corser-Jensen, and Kim A. Heidenreich Department of Pharmacology and Neuroscience Program, School of Medicine University of Colorado Denver, Anschutz Medical Campus, Aurora, CO 80045 Approximately 20% of individuals with concussion (mild traumatic brain injury), including those with sports-related concussions, remain symptomatic months after injury. The neuropathological mechanisms responsible for delayed recovery are not well understood. To investigate the role of neuroinflammation as an underlying mechanism of post-concussive syndrome, we established an experimental model of closed head Injury (CHI) that mimics mild traumatic brain injury in humans. Male C57 Bl6/J mice (10-12 weeks) were subjected to CHI using the ImpactOne, an electromagnetically-controlled piston device (angle 20°, probe size 5mm, velocity 5m/sec, dwell time 100 msec, depth 3 mm). Sham-operated mice underwent the same procedures but did not receive an impact. At various times after injury (2 hours to 30 days), the mice were anesthetized, transcardially perfused with 4% paraformaldehyde, and fixed brains were sectioned for histology (H&E) and immunohistochemistry using antibodies to Iba-1 (a marker of microglial activation) and GFAP (a marker of activated astrocytes). No overt brain lesions were detected by H&E in sham or CHI mice at any time point. At 7 days post-injury, there were significant elevations in Iba-1 (detectable as early as 2 hours post-injury) and in GFAP staining in the ipsilateral dentate gyrus, cerebral cortex, and external capsule in CHI mice as compared to sham mice. Deficits in long-term potentiation, a measure of synaptic plasticity, were also detected at this time point. GFAP staining of animals 30 days post injury remained elevated in the cortex; Iba-1 remained elevated at 30 days post injury in the external capsule. These data indicate that the onset of neuroinflammation is very rapid and remains elevated beyond the acute phase of injury. These findings have profound implications for the treatment of mTBI. Studies are ongoing to explore the feasibility of using anti-inflammatory treatments to attenuate the prolonged neuroinflammation associated with mTBI.

Poster Title: AEOL 10150 IMPROVES MORBIDITY AND MORTALITY AFTER LETHAL LUNG- SULFUR MUSTARD EXPOSURES

Category: Pulmonary and Critical Care

Poster Location: Education 2 South 2304

Poster Number:28

Abstract: AEOL 10150 IMPROVES MORBIDITY AND MORTALITY AFTER LETHAL LUNG- SULFUR MUSTARD EXPOSURES. McElroy, C, (Ph.D., GS)1, 2; Min, E2; Huang, J2; Loader, J1; Hendry-Hofer, T1; Garlick, R1; Rioux, J1; Veress, L1; Smith, R1; Osborne, C1; Anderson, D3; Holmes, W3; Paradiso, D3; White, C1; Day, BJ2, 1 1. University of Colorado, Aurora, CO, United States. 2. National Jewish Health, Denver, CO, United States. 3. USAMRICD, Aberdeen, MD, United States. Sulfur mustard (bis 2-chloroethyl ethyl sulfide, SM) is a powerful bi-functional vesicating and potent alkylating chemical warfare agent. SM causes blistering of exposed epithelial surfaces, leading to inflammation and necrosis. The respiratory tract is highly susceptible to SM-mediated injury. Although the exact mechanism of SM toxicity has not been elucidated, it is believed that it causes tissue injury through excessive production of reactive oxygen species resulting in DNA damage, and depletion of glutathione. The manganese porphyrin, AEOL10150, is a catalytic antioxidant with a broad spectrum of activities including superoxide and hydrogen peroxide dismutation, and is also capable of scavenging peroxynitrite and lipid peroxides. To evaluate the effectiveness of AEOL10150 in suppressing oxidative stress leading to toxicity in vivo, we delivered 1.4mg/kg sulfur mustard (approximate LD50 at 48 hours) from a water jacketed vapor generator directly into anesthetized rats via intratracheal intubation, followed 1 hour later by administration of either AEOL10150 (5 mg/kg, sc) or saline (sc) and comparing several AEOL10150 dosing regimens. Our results show that AEOL10150, when used as a rescue agent, was able to effectively improve survival from sulfur mustard inhalation from 33% (controls) to 89% (AEOL 10150, Q4H). We have demonstrated an improvement in clinical markers with AEOL10150 administration (Q4H), including pulse oximetry (23% increase), heart rate (21% increase), and clinical scoring (decrease of 4.3 on a scale of 0-10, where 0 is no outward distress) at euthanasia, when compared to saline controls. There was also a 56.3% reduction in the lung occlusive casts that result from sulfur mustard exposures in the major airways of animals that received AEOL10150 (Q4H).

Poster Title: Reefer Madness: Marijuana and Medical Education

Category: Education

Poster Location: Education 2 South 1210

Poster Number:3

Abstract: REEFER MADNESS: MARIJUANA AND MEDICAL EDUCATION. MH Chan, (MD, SOM), ML Cole, J McKinnon, DW Bowles, DD Matlock, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO. Little is known about the public and personal health effects of widespread marijuana use, and little consensus exists amongst physicians regarding appropriate uses. However, the majority of Americans now favor the legalization of marijuana, and two states have legalized recreational marijuana. We surveyed medical students in one of these two states to assess their opinions and experiences with marijuana in medicine, and to assess their thoughts on medical education. We distributed a voluntary, anonymous, online survey to all medical students at the University of Colorado School of Medicine. Items included personal and professional opinions, as well as experiences with, and attitudes toward medical and recreational marijuana use. Questions related to clinical experiences were included in third and fourth year students' surveys. This protocol was reviewed and granted institutional review board exemption. Our overall response rate was 37.8%, with 236 students participating. Students indicated support for legalization of marijuana (64%), and believed that physicians should be able to recommend marijuana to a patient without penalization (93.6%), though only a minority (29%) would recommend marijuana to a patient under current law. Four out of every five students believed that medical school curriculum did not adequately address the risks and/or benefits of marijuana use in either the preclinical or clinical setting. Less than half of responding third and fourth year students believed that their clinical preceptors possessed adequate knowledge about marijuana (39.6%), and nearly 20% indicated that they had seen a physician act unprofessionally towards a patient on the basis of marijuana use. Students across all years indicated a desire to see further marijuana research (96.6%), and believed that marijuana could play a role in the treatment of a variety of medical conditions, though they expressed concern for potential physical and mental harm (68.4% and 77.0%, respectively). Our data suggests that medical students are not confident in medical education as it pertains to marijuana, despite training in a state with a high prevalence of use. Furthermore, they report misgivings about instructors' knowledge base on this topic, and have identified it as a potential area of concern in terms of professionalism. Lastly, this survey offers possible insight into the attitudes of the next generation of physicians, with strong support for marijuana legalization and nearly unanimous support for further marijuana research, despite personal misgivings about recommending marijuana.

Poster Title: Retrospective Cohort Analysis to Evaluate the Impact of Institutional Guidelines for VTE Prophylaxis in Hospitalized Medically-Ill Patients

Category: Cardiovascular

Poster Location: Education 2 South 2302

Poster Number:31

Abstract: RETROSPECTIVE COHORT ANALYSIS TO EVALUATE THE IMPACT OF INSTITUTIONAL GUIDELINES FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS IN HOSPITALIZED MEDICALLY ILL PATIENTS. SK Shawar, (PharmD Candidate 2015) and T Trujillo (PharmD, FCCP, FAHA, BCPS -AQ Cardiology). Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Denver CO. **Background:** hospitalization for acute medical illnesses increases the risk for venous thromboembolism (VTE) yet prophylactic measures are under and inappropriately used. **Purpose:** The University of Colorado Hospital (UCH) has implemented institutional guidelines for VTE prevention subsequent to the release of the 2012 Chest guidelines. Implementation included guideline dissemination, provider education, provision of decision support tools, and optimization of order entry options. This study aims to assess the appropriateness of VTE prophylaxis prescribing at UCH for medically ill patients before and after hospital guideline implementation, and assesses the utility of PADUA risk score to predict clinical VTE events. **Methods:** This retrospective comparative cohort study included medically ill patients admitted to UCH 9 months before and 9 months after implementation of institutional VTE prevention guidelines in September 2012. Patients included had a minimal hospital stay of 48 hrs. Patients admitted with VTE, bleeding or currently on therapeutic anticoagulation were excluded. The primary endpoint is the rate of appropriate VTE prophylaxis prescribing in the pre and post patient cohorts. Secondary endpoints included the incidence of VTE by clinical presentation and major bleeding in both groups. Major bleeding is defined as clinically overt bleeding, a fall in hemoglobin of ≥ 2 g/dL within 24 hrs, or a transfusion of ≥ 2 units of packed red blood cells. A sample size of 300 patients in each group is needed to detect an absolute difference of 10% in the primary endpoint with 80% power and a significance level of 0.05. **Results:** appropriate VTE prophylaxis rate increased from 66.89% to 86.41% (p

Poster Title: PHARMACOLOGIC VENOUS THROMBOEMBOLISM PROPHYLAXIS IN
HOSPITALIZED PATIENTS WITH CHRONIC LIVER DISEASE

Category: Cardiovascular

Poster Location:

Poster Number:33

Abstract: PHARMACOLOGIC VENOUS THROMBOEMBOLISM PROPHYLAXIS IN HOSPITALIZED PATIENTS WITH CHRONIC LIVER DISEASE: KJ Moorehead (PharmD Candidate), SW Mueller University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences **Purpose:** Chronic liver disease (CLD) is a common co-morbidity in hospitalized patients. Coagulopathy resulting from CLD does not protect from venous thromboembolism (VTE), contributing to uncertainty regarding the appropriateness of VTE prophylaxis (ppx) in this population. We aim to describe patient characteristics associated with pharmacologic VTE ppx and determine the clinical impact of VTE ppx in patients with CLD. **Methods:** This retrospective cohort study evaluated patients with CLD, by ICD-9 code, with an international normalized ratio (INR) of at least 1.3, hospitalized for 72 hours or greater between November 2012 and October 2013. Baseline severity of liver disease, coagulopathy, risk factors for VTE and bleed were compared between patients given VTE ppx and not given ppx. Primary outcomes included the incidence of VTE and major bleeding events, defined as a fall in hemoglobin of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red blood cells within 24 hours. **Results:** Of the 300 CLD patients included, 157 (52%) received pharmacologic VTE ppx. Characteristics associated with administration of ppx were lower baseline activated partial thromboplastin time, INR, total bilirubin, model for end-stage liver disease (MELD), and higher Padua score, hemoglobin, platelets, and antiplatelet agent use. In the ppx group, VTE and portal vein thrombosis (PVT) occurred in 12 (7.6%) and 8 (5.1%) patients versus 4 (2.8%) and 12 (8.4%) of the non-ppx, respectively ($P=0.07$ and 0.2 , respectively). In the ppx group, major bleeding occurred in 47 (30%) versus 49 (34.3%) non-ppx ($P=0.46$). VTE ppx was not associated with VTE, VTE plus PVT, or bleed outcomes by multivariate regression. **Conclusions:** Use of pharmacologic VTE ppx in CLD patients was not associated with a lower risk of VTE during hospitalization nor did it increase the risk of bleeding. Further studies examining the risks and benefits of VTE ppx in this population are necessary.

Poster Title: PERIOPERATIVE INTRAVENOUS TRANEXAMIC ACID IN TOTAL KNEE AND HIP ARTHROPLASTY: EFFECTS ON SURGICAL BLOOD LOSS, TRANSFUSION REQUIREMENTS, AND THROMBOEMBOLIC COMPLICATIONS

Category: Surgery

Poster Location: Education 2 South 2206

Poster Number:35

Abstract: PERIOPERATIVE INTRAVENOUS TRANEXAMIC ACID IN TOTAL KNEE AND HIP ARTHROPLASTY: EFFECTS ON SURGICAL BLOOD LOSS, TRANSFUSION REQUIREMENTS, AND THROMBOEMBOLIC COMPLICATIONS S Phong (PharmD Candidate in School of Pharmacy), LK Golightly (PharmD, BCPS), G Barber (RPh, MPH, FASHP), C Lyda (PharmD), C Hogan (MD), MR Dayton (MD), Department of Inpatient Pharmacy, University of Colorado Hospital, Aurora, CO. Purpose: Total knee and hip arthroplasty is commonly associated with substantial surgical blood loss. Considerable clinical evidence has shown benefits of tranexemic acid (TXA) use to reduce blood loss in joint replacement surgeries. However, clinical guidelines are equivocal, and utilization of TXA is based on individual provider's preference. Safety with thrombotic events remains a concern with the use of TXA. The purpose of this study was to evaluate the safety and efficacy of TXA use in primary, revision, and bilateral total knee arthroplasty (TKA) and total hip arthroplasty (THA) by subspecialty surgeons in an academic medical center. Methods: The institutional review board approved this retrospective cohort study. Study subjects included adult inpatients undergoing either total knee or hip arthroplasty within a 12 month period from November 2012 to October 2013. The treatment group included patients of a surgeon who used intravenous TXA 10mg/kg x2 in all patients without contraindications. The control group included patients of a surgeon who did not use TXA. Both surgeons practiced with similar post operative management methods. The primary outcome of interest was objective measures of blood loss including hemoglobin, hematocrit values and requirements of blood transfusion. Secondary outcomes comprised of evidence of postoperative thromboembolism, other complications and cost. Results: The relative risk of the control versus treatment group was 0.23% (95% CI 0.07-0.73) and the number needed to treat with TXA to avoid one blood transfusion was calculated to be seven. (Please also see attached word document for graphs). Conclusion: In patients undergoing joint replacement surgery, perioperative administration of IV TXA was associated with diminished postoperative anemia and lesser transfusion requirements. Cost consequences from decreased need for blood transfusion were favorable. No serious treatment-related adverse effects were identified.

**Poster Title: UTILITY OF INTRAOPERATIVE NEUROLOGIC MONITORING DURING
VERTICAL EXPANDABLE PROSTHETIC TITANIUM RIB EXPANSION SURGERY**

Category: Surgery

Poster Location: Education 2 South 2206

Poster Number:37

**Abstract: UTILITY OF INTRAOPERATIVE NEUROLOGIC MONITORING DURING
VERTICAL EXPANDABLE PROSTHETIC TITANIUM RIB EXPANSION SURGERY** Jaren
LaGreca, BA (MD, GS)*; Tara Flynn, BA; Patrick J. Cahill, MD; Amer Samdani, MD; Michael
G. Vitale, MD, MPH; Ron El-Hawary, MD, MSc, FRCS(C); John T. Smith, MD; Jonathan H.
Phillips, MD; John M. Flynn, MD; Michael Glotzbecker, MD; Sumeet Garg, MD* University of
Colorado Dept. of Orthopedics and Children's Hospital Colorado* Purpose: The vertical
expandable prosthetic titanium rib (VEPTR) device is implemented for the treatment of thoracic
insufficiency syndrome and early-onset scoliosis in children. Implantation of the device within
the thorax, and subsequent expansion procedures, facilitates correction of the deformity.
Intraoperative neurologic monitoring (IONM) is a tool to warn against potential neurologic
injury. This study investigated whether IONM identified new neurologic injuries during
expansion procedures, if IONM signal changes had not been present at VEPTR implantation.
Methods: A retrospective study reviewed IONM records at 17 institutions. Results: There were a
total of 540 consecutive VEPTR procedures (218 patients): 160 implant, 90 revision, 258
expansion, and 32 removal procedures. IONM detected neurologic changes in 18/540 procedures
(3.3 %): 5 implant, 5 revision, 3 expansion, and 5 removal. Neurologic injury occurred in 3/218
patients (1.4%), or 3/540 procedures (0.6%). All 3 of the neurologic injuries were associated
with implant procedures. The rate of neurologic injury for implant procedures was 1.9%. All 3 of
the patients experienced upper extremity motor deficits, and one patient also had an upper
extremity sensory deficit. All neurologic injuries had full postoperative recovery, on average
after 57 days (range: 17- 124 days). Conclusion: There is a higher incidence of neurologic injury
during VEPTR implant procedures, as compared to no instances of neurologic injury among all
other VEPTR procedure types. IONM did detect a neurologic signal change during one routine
expansion procedure in a patient without history of neurologic injury or signal loss, however this
resolved after an increase in blood pressure. IONM did not identify new neurologic injuries in
patients undergoing VEPTR expansion who did not previously have a history of IONM signal
change or neurologic injury. IONM may not be necessary in patients undergoing VEPTR
expansion procedures who have not previously had neurologic injury or signal loss.

Poster Title: ESTROGEN AND COGNITION IN WOMEN: POTENTIAL VASCULAR MECHANISMS

Category: Neuroscience and Brain and Behavior – Adult

Poster Location: Education 2 South 2306

Poster Number:39

Abstract: ESTROGEN AND COGNITION IN WOMEN: POTENTIAL VASCULAR MECHANISMS. E. Royer, (MD, SOM), K. L. Hildreth MD, K.. L. Moreau PhD, W. M. Kohrt PhD, Department of Medicine, University of Colorado, Denver, CO. Traditional cardiovascular risk factors increase the risk of Alzheimer's disease (AD). The loss of estrogen (E2) with menopause appears to augment the age-associated increase in these risk factors, which may help explain the additional increased risk of AD in aging women. E2 helps maintain neuronal integrity, particularly in the prefrontal cortex (PFC) which supports executive function and working memory, and is vulnerable in AD. E2 is also vasoprotective. E2-deficient postmenopausal women show arterial stiffening and impaired endothelial function compared to age-matched premenopausal women; these impairments are attenuated with E2-based hormonal therapy. Arterial stiffening and endothelial dysfunction have been linked to small-vessel cerebrovascular disease and cognitive impairment. Mechanisms for the effects of E2 on cognition are not known, but acute changes in both vascular function and brain activation occur with ovarian suppression. This study investigates whether vascular dysfunction mediates the negative effects of E2 on brain activation. **Methods:** 34 healthy, premenopausal women (40-60y) randomized to 6-months of gonadotropin releasing hormone agonist (GnRHa) or placebo will be enrolled. Measures of 1) vascular function ([carotid artery compliance] and endothelial function [artery flow mediated dilation]); and 2) PFC activation (fMRI during a working memory task) are obtained at baseline and 6-months. To isolate the effects of E2, participants randomized to GnRHa (n=17) receive 3 additional months of GnRHa with E2 add-back, with outcomes assessed at 9-months. **Expected Results:** GnRHa treatment will be associated with reduced arterial compliance and endothelial function, and these changes will be correlated with decreased PFC activation. Changes observed with GnRHa will be reversed with E2 add-back. **Conclusion:** This study is a novel investigation of vascular dysfunction as a possible mechanism underlying the negative effects of E2-deficiency on cognition. Use of a controlled model of ovarian suppression and incorporation of an E2 add-back condition help distinguish effects of E2 from those of aging or other ovarian hormones. Results will inform future studies investigating sex-specific therapeutic interventions to prevent cognitive decline in aging women.

Poster Title: ADOLESCENT FEMALES WITH SEVERE SUBSTANCE AND CONDUCT PROBLEMS SHOW HYPOACTIVITY OF THE RETROSPLLENIAL CORTICAL REGION OF THE DEFAULT MODE NETWORK

Category: Developmental Neuroscience and Brain and Behavior – Child

Poster Location: Education 2 South 2306

Poster Number:40

Abstract: ADOLESCENT FEMALES WITH SEVERE SUBSTANCE AND CONDUCT PROBLEMS SHOW HYPOACTIVITY OF THE RETROSPLLENIAL CORTICAL REGION OF THE DEFAULT MODE NETWORK. SY Chumachenko (MD, SoM), MS Dalwani, and JT Sakai, School of Medicine, University of Colorado, Denver, CO. Purpose of Study: Conduct and substance use disorders (CD and SUD) are highly comorbid, and both are characterized by problems of inhibitory control. To date very limited research has linked CD and SUD in adolescents to differences in the brain's default mode network (DMN). Because CD and SUD present differently between genders, we wanted to examine this relationship between CD and SUD in an all-female sample. Methods used: 21 adolescent females with severe substance and conduct problems and 20 healthy controls, aged 14-18 years (mean 16.5) played a risk-taking decision task with interspersed periods of rest within a functional magnetic imager. Independent component analysis was utilized to extract the DMN component, and the component signal's intensity was analyzed for group differences. Summary of Results: Patients showed significantly decreased DMN activity bilaterally in the retrosplenial cortex (Brodmann areas 29 and 30), and this effect remained even after accounting for several potential confounds, including age, IQ, measures of attention-deficit/hyperactivity disorder and major depressive disorder, current medication use, or handedness. These findings replicate our previous results in the retrosplenial cortices of the DMN component utilizing an all-male adolescent sample. Conclusions Reached: Our findings suggest an across-gender replicable functional neurological connection between severe adolescent substance and conduct problems and a brain region involved in episodic memory recall and internal mentation. Such patient-control differences in DMN activity especially in the retrosplenial cortex merit further investigation.

Poster Title: Toxicologic Assessment of Surgical Outpatients

Category: Surgery

Poster Location: Education 2 South 2201

Poster Number:42

Abstract: TOXICOLOGIC ASSESSMENT OF SURGICAL OUTPATIENTS. SJ Lofgreen, (MD, SOM), K Plath, B Davari, J Melendez, B Whitaker, J Galinkin. Little is known about the drugs that patients have in their bodies at the actual time of undergoing surgery. We attempted to better characterize this unknown by obtaining the urine of 500 patients in the pre-operative suite. To objectively measure this data, we screened the urine samples with a high-performance liquid chromatography mass spectrometer (HPLC-MS) in search of 112 drugs and metabolites. We found detectable levels of ethanol in 25.6%, opiates in 18.0% and illicit substances in 5.6% of samples. We believe that these unexpected results may change an anesthesiologist's approach to peri-operative management.

Poster Title: CLINICAL OUTCOMES AND BIOMECHANICAL ASSESSMENT OF PES PLANUS IN CHILDREN WITH CEREBRAL PALSY

Category: Surgery

Poster Location: Education 2 South 2201

Poster Number:44

Abstract: Many children with cerebral palsy exhibit an overly flexible lever-arm associated with pes planus, commonly described as a flexible flat foot. Since efficient locomotion depends on the body's innate mechanical levers, any abnormality along the lever-arm greatly impacts ambulation. Treatment may consist of orthotics or surgery depending on severity, but no standard clinical measurement objectively quantifies the severity of the flexible flat foot. The objective of this study is to formulate a reliable method for quantitatively classifying the degree of flexibility within a flat foot based on x-ray measurements that strongly correlate to qualitative clinical evaluations. All pediatric subjects, previously diagnosed with ambulatory cerebral palsy, underwent a complete gait analysis and weight-bearing x-rays at the Children's Hospital Colorado prior to any bony surgical procedure of the foot. Both feet of each subject are categorized as a control, with no diagnosis of pes planus, or as mild, moderate or severe, with a diagnosis of pes planus. X-rays are measured in terms of: forefoot abduction, collapse of longitudinal arch, and hindfoot valgus. A one-way ANOVA compared the qualitative clinical ratings of severity, including controls, and the x-ray measurements. The lateral calcaneal pitch angle significantly differed between all categories. The AP talonavicular coverage angle and Meary's lateral 1st metatarsal talar angle significantly differed between all categories except mild severity. The AP talocalcaneal angle significantly differed between the controls and all categories of severity but did not significantly differ within each category of severity. The lateral talocalcaneal angle showed no statistically significant differences. Since pes planus exists along a spectrum, subjects exhibit a range of severities that can be quantified by x-ray measurements. The results suggest that collapse of the longitudinal arch and forefoot abduction most strongly distinguish levels of severity, while AP measurements of hindfoot valgus may be more useful for determining no diagnosis from a diagnosis. Further analysis of the x-ray measurements may present specific thresholds for a definitive quantitative classification of severity. Identifying the pathological mechanisms underlying gait abnormality will hopefully aid in treating a flexible flat foot.

Poster Title: SPECKLE TRACKING ECHOCARDIOGRAPHY TO SCREEN FOR
PULMONARY HYPERTENSION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Category: Cancer - Lung and Skin

Poster Location: Education 2 Bridge

Poster Number:46

Abstract: APPLICATION OF SNP MICROARRAYS TO THE GENOME-WIDE ANALYSIS OF CHROMOSOMAL INSTABILITY IN PREMALIGNANT AIRWAY LESIONS. JL Rice (M.D., SOM), I Nakachi, WA Franklin, YE Miller, MW Geraci, SPORE in Lung Cancer, Department of Medicine, University of Colorado, Denver, CO Chromosomal instability is central to carcinogenesis. In lung squamous cell carcinogenesis, the histopathologic changes in bronchial epithelia that precede cancer development have been well documented, and several studies have supported the concept that somatic chromosomal alterations (SCAs) are prognostic biomarkers than premalignant histology alone. However, the detection of SCAs in premalignant lesions using high-resolution microarrays remains challenging because 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%). We verified the sensitivity of delta- θ by analyzing heterogeneous tissue with known tumor content, then applied this analytic strategy to heterogeneous clinical specimens including whole biopsies and brushings compared to the patient's blood. SCAs were successfully detected across the whole genome in all invasive cancer cases (6/6) carcinoma in situ (3/3), and moderate to severe dysplasia (3/11). Fluorescence in situ hybridization (FISH) and CN-qPCR assays were performed to validate SCAs identified using SNP microarray and delta- θ . In the lesions studied, we observed not only previously well-described SCAs but also unique abnormalities, and widespread airway sampling demonstrated that field cancerization reflected by SCAs at multiple sites was detectable. 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.

Poster Title: Oncogenic Role of Nuclear MerTK in Leukemia

Category: Cancer - Other

Poster Location: Education 2 Bridge

Poster Number:48

Abstract: ONCOGENIC ROLE OF NUCLEAR MERTK IN LEUKEMIA GD Kirkpatrick (MD, PhD, MST Program), JMW Maller, CT Cummings, KD Davies, S Sather, D DeRyckere, DK Graham Department of Pediatrics, University of Colorado School of Medicine. **Background:**

Cancer is the leading cause of disease-related death in children under age 15, with acute lymphoblastic leukemia (ALL) the most common malignancy. Optimization of conventional chemotherapy regimens has greatly improved survival rates over the last 50 years, but many patients fail treatment and these cytotoxic strategies carry substantial risk of long-term side effects, including future malignancies. As such, there is a clear unmet need for more targeted, less toxic treatments. The Mer receptor tyrosine kinase (MerTK) is ectopically expressed in subsets of both B- and T-ALL, and has been established as a promising target for novel tyrosine kinase inhibitors developed by our group. However, the mechanisms underlying MerTK-driven oncogenesis in ALL have not been completely explained by MerTK kinase activity, and a better understanding of these mechanisms is necessary. Recently, our lab has discovered the presence of full-length MerTK in the nucleus, a novel finding that broadens the scope of MerTK function beyond that of a surface receptor. We hypothesize that nuclear MerTK contributes to the oncogenic phenotype associated with aberrant MerTK expression in leukemia by regulating transcriptional processes. If this hypothesis is correct, targeting MerTK nuclear activity in addition to kinase signaling may be more effective than inhibiting kinase activity alone.

Methods/Conclusions/Future Directions: MerTK was identified in the nucleus using fractionation and western blotting as well as immunofluorescent microscopy. Sequence analysis of MerTK revealed a nuclear localization sequence (NLS), and MerTK add-back cell lines containing an intact or mutated NLS have shown that nuclear MerTK expression contributes to increased colony forming capacity and decreased chemosensitivity in vitro. These experiments will be continued in multiple leukemia cell lines, while the mechanism by which MerTK is translocated to the nucleus will be elucidated using immunoprecipitation and fluorescence microscopy. Finally, ChIP-seq analysis will identify nuclear genomic regions regulated by MerTK.

Poster Title: West Nile virus requires mTORC1-directed activation of 4E-BP/eIF4E for viral genomic translation

Category: Microbiology and Infectious Diseases

Poster Location: Education 2 South 1303

Poster Number:5

Abstract: West Nile virus requires mTORC1-directed activation of 4E-BP/eIF4E for viral genomic translation Shives, Katherine D1; Beckham, J. David1,2 Since its introduction in New York City in 1999, West Nile virus (WNV) has spread across the continent to become the leading cause of epidemic encephalitis in North America. As member of the family Flaviviridae, WNV is part of a group of clinically-important human pathogens including Dengue virus and Japanese encephalitis virus. This family of (+) sense, 5' capped, single stranded RNA viruses have limited coding capacity and are therefore obligated to co-opt a significant amount of cellular factors in order to translate their genomes effectively. Our previous work has shown that WNV infection induces the activation of the host factor mTOR. MTOR is a highly evolutionarily conserved serine/threonine kinase that acts as a central cellular censor of nutrient status and exercises control of vital anabolic and catabolic cellular responses such as protein synthesis and autophagy, respectively. Following inducible genetic knock-out of the major mTOR complex (TORC1) co-factor Raptor we show that TORC1 supports flavivirus protein synthesis via cap-dependent protein synthesis pathways and supports subsequent WNV growth. MTOR governs cap-dependent translation initiation signals through the effector kinase S6K as well as the eIF4E binding protein (4E-PB), and therefore additional S6K1^{-/-};S6K2^{-/-} MEFs and rpS6p^{-/-} MEFs were utilized to further probe the role of mTOR/S6K/rpS6 activity during WNV infection without altering 4EBP1 function; correspondingly we utilized 4E-BP1;4E-BP2 ^{-/-} MEFs to determine the role of 4E-BP/eIF4E function with intact mTORC1/S6K/rpS6 signaling. We hypothesize that optimal WNV growth and translation depends upon the promotion of cap-dependent translation initiation steps that are controlled by the S6K and 4EBP proteins. We now show that WNV does indeed require the activation of mTORC1 effector 4E-BP for efficient viral growth, and that the S6K/rpS6 pathway does not contribute to translation of the viral genome.

Poster Title: MAPK Pathway Inhibition Overcomes Differential Mechanisms of Resistance to the Src inhibitor, Dasatinib, in BRAF- versus RAS-Mutant Thyroid Cancer

Category: Cancer - Breast and Thyroid

Poster Location: Education 2 Bridge

Poster Number:51

Abstract: MAPK PATHWAY INHIBITION OVERCOMES DIFFERENTIAL MECHANISMS OF RESISTANCE TO THE SRC INHIBITOR, DASATINIB, IN BRAF- VERSUS RAS-MUTANT THYROID CANCER. TC Beadnell (PhD GS), S Riffert, RE Schweppe Dept. of Med. University of Colorado There is currently a dearth of therapies for patients with anaplastic and advanced stages of papillary thyroid cancers. In addition to frequent MAPK pathway mutations, our lab has recently identified Src as an alternative, clinically relevant target in thyroid cancer. However, like many targeted therapies long term efficacy of targeting Src using a single-agent approach is naïve, due to the presence of multiple potential escape mechanisms. Thus in an effort to more effectively target Src we generated two BRAF- and two RAS-mutant thyroid cancer cell lines resistant to the Src inhibitor, dasatinib. Interestingly, all four dasatinib-resistant (DR) cell lines exhibit increased MAPK pathway activation, whereas only the RAS-mutant DR cell lines acquired the c-SRC gatekeeper mutation (T341M), which suggests a potential clonal evolution. Having observed MAPK pathway activation as a potentially conserved mechanism of resistance we first determined the efficacy of MAPK pathway inhibition and discovered that MEK inhibition with trametinib is able to overcome resistance to dasatinib. Similar to previous tyrosine kinase resistance models, culturing in the presence of dasatinib further enhances MEK inhibitor sensitivity which was determined by calculating trametinib IC50 values released from 2 μ M dasatinib (Average IC50 = 1.28 μ M) versus trametinib IC50 values maintained in 2 μ M dasatinib (Average IC50 = 0.081 μ M). Interestingly, increased MEK inhibitor sensitivity in the presence of dasatinib correlated with inhibition of Src signaling in the BRAF-mutant DR cell lines. Interestingly, we observed a paradoxical increase in Src signaling in the RAS-mutant DR cell lines, which appears to result from a loss of Src negative feedback phosphorylation (p-Src Y527) due to dasatinib off-target effects on the Src negative regulator, CSK. Consistent with increased MEK inhibitor sensitivity in the RAS-mutant DR cell lines, phosphorylation of both the Grb2 binding site on FAK (p-FAK Y925) and ERK1/2 was increased when the cells were maintained in dasatinib. Taken together our work provides important insight into Src inhibitor resistance mechanisms, and will aid in the advancement of therapeutic approaches to combat resistance to the Src inhibitor, dasatinib.

Poster Title: SIX2 MEDIATES EPIGENETIC REGULATION OF EPITHELIAL-TO-MESENCHYMAL MARKERS TO PROMOTE METASTASIS

Category: Cancer - Breast and Thyroid

Poster Location: Education 2 Bridge

Poster Number:53

Abstract: SIX2 MEDIATES EPIGENETIC REGULATION OF EPITHELIAL-TO-MESENCHYMAL MARKERS TO PROMOTE METASTASIS. MUJ Oliphant (Ph.D., BRS), HL Ford, CA Wang, AC Tan, and J Costello, Department of Pharmacology and Department of Medicine, University of Colorado, Denver, CO. While studying the role of the Six1 homeoprotein in metastasis we discovered a possible compensatory pathway: upregulation of Six2. Our previous studies demonstrate that Six1 knockdown (KD) in mammary carcinoma cells inhibits metastasis. However, in the few metastases that develop in the presence of Six1 knockdown, Six2 is upregulated. These data suggest that Six2 may compensate for loss of Six1. Indeed, we show that Six2, like Six1, enhances metastasis. Surprisingly, our data suggest that the mechanism by which Six2 mediates metastasis appears to be somewhat different from that by which Six1 mediates metastasis. We show that Six2 regulates E-cadherin levels, in contrast to Six1, which has not been show to downregulate E-cadherin expression, but rather to lead to its re-localization. We have further dissected the mechanism by which Six2 downregulates E-cadherin, and find that it upregulates Zeb2 (a known repressor of E-cad), but also leads to methylation of the E-cadherin (CDH1) promoter. When Six2 is overexpressed, DNA methyltransferases (DNMT1, 3a and 3b) are increased at the mRNA level, providing a possible mechanism by which Six2 leads to CDH1 promoter methylation and silencing (Fig 1). Our preliminary data suggest that Six2 may reprogram cells to a less differentiated/less epithelial state via altering the promoter methylation of not only E-cadherin, but also other genes involved in the Epithelial-to-Mesenchymal Transition (EMT) to promote metastasis.

Poster Title: NON-CELL AUTONOMOUS ROLES OF EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT)-INDUCING FACTORS IN MEDIATING INCREASED METASTASIS OF HETEROGENEOUS TUMORS

Category: Cancer - Breast and Thyroid

Poster Location: Education 2 Bridge

Poster Number:55

Abstract: NON-CELL AUTONOMOUS ROLES OF EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT)-INDUCING FACTORS IN MEDIATING INCREASED METASTASIS OF HETEROGENEOUS TUMORS. D Neelakantan (Ph.D., GS), R Iwanaga, DJ Drasin and HL Ford. Department of Pharmacology, University of Colorado Anschutz Medical Campus, CO. Breast cancer is the second leading cause of cancer related deaths in women and more than 90% of these deaths result from metastatic disease rather than from primary tumor (PT) burden. The PT itself is a heterogeneous mass of cells. Thus a better understanding of metastasis and cancer cell dynamics within the PT will aid in developing efficient strategies to increase patient survival. Twist1 and Snail are two EMT-inducing transcription factors (TFs) that cell-autonomously increase metastasis. Our data show that they can also non-cell autonomously increase in-vitro invasion and migration, and alter expression of numerous EMT-related genes, when conditioned medium taken from TF-expressing cells is placed on non-TF-expressing cells. We show that their non-cell autonomous effects are in part, due to their upregulation of another known EMT-related TF, Six1 and loss of Six1 downstream of these TFs mitigates these effects, indicating that Six1 is a key downstream player. Overexpression and knockdown of Six1 itself, in many mouse and human breast carcinoma models, non-cell autonomously influences various “metastatic” properties, and expression of EMT-related proteins in non-metastatic non-Six1 expressing cells in-vitro. We also show that Six1 expression in metastatic cells is sufficient to non-cell autonomously increase the metastasis of weakly metastatic, non Six1-expressing cells, when these cells are fluorescently tagged and co-injected into mice. Using biochemical methods we show that the factor(s) responsible for the metastatic phenotype is a heat stable protein. Using mass spectrometry analysis, we have identified factor(s) secreted by TF-expressing cells, and are assessing their role in mediating increased metastasis. Importantly, only a few cells within the PT undergo EMT and have the potential to metastasize and Twist1, Snail and Six1 have the ability to both induce EMT and increase metastasis. Since they are also associated with poor prognosis and increased metastasis in many cancers, it’s critical to understand how they mediate aggressive phenotypes both cell and non-cell autonomously, ultimately leading to increased metastasis of cells within the heterogeneous tumor.

Poster Title: A TDO2-AhR Signaling Axis Regulates Metastatic Phenotypes in Triple-Negative Breast Cancer

Category: Cancer - Breast and Thyroid

Poster Location: Education 2 Bridge

Poster Number:57

Abstract: A TDO2-AhR Signaling Axis Regulates Metastatic Phenotypes in Triple-Negative Breast Cancer. Thomas Rogers, Nicholas D'Amato, Travis Nemkov, Lisa Greene, Michael Gordon, Kirk Hansen, Jennifer Richer. Department of Pathology, University of Colorado-AMC, Department of Biochemistry and Molecular Genetics, University of Colorado-AMC Anoikis resistance is a critical trait of cancer cells progressing through the metastatic cascade. This is particularly important for the triple-negative breast cancer (TNBC) subtype, which has a peak risk of recurrence within the first three years post-diagnosis and an increased mortality rate in the first five years as compared to other breast cancer subtypes. We performed global profiling of TNBC cells in adherent versus forced suspension culture conditions (using poly-HEMA coated plates) for 24 hours. These data revealed that TNBC cells surviving in suspension upregulate multiple genes involved in tryptophan catabolism, also known as the kynurenine pathway (KP), including the rate limiting enzyme tryptophan 2,3,-dioxygenase (TDO2) and kynureninase (KYNU). A key metabolite of this pathway has been found to activate the aryl hydrocarbon receptor (AhR), which was also up-regulated in suspended cells. Results: KP activity is upregulated in TNBC cells grown in forced-suspension culture as measured by HPLC. Furthermore, the kynurenine pathway promotes the activation of the aryl hydrocarbon receptor in TNBC cells grown in forced-suspension culture. Targeting TDO2 and AhR with small molecule inhibitors or shRNAs decreases anoikis resistance, migration/invasion, and proliferation of TNBC cells. Additionally, increased NF- κ B activity in forced-suspension culture promotes the upregulation of TDO2, KYNU, and AhR. Lastly, TDO2 expression in human breast cancers was highly overexpressed in invasive ductal breast carcinoma as compared to normal breast and is also significantly higher in ER- tumors compared to ER+ tumors. In addition, above-median TDO2 expression had significantly shorter overall survival than patients with below-median TDO2 expression, suggesting that TDO2 expression may predict and/or contribute to poor prognosis in TNBC patients. Conclusions: The kynurenine pathway facilitates multiple characteristics of metastasis in TNBC, in vitro. Our findings provide the first preclinical data on the efficacy of targeting TDO2 in TNBC, which may offer a novel therapeutic strategy that could dramatically reduce TNBC mortality rates.

Poster Title: INHIBITION OF MER RECEPTOR TYROSINE KINASE WITH A NOVEL SMALL MOLECULE INHIBITOR IS EFFICACIOUS IN PRE-CLINICAL MODELS OF NON-SMALL CELL LUNG CANCER

Category: Cancer - Lung and Skin

Poster Location: Education 2 Bridge

Poster Number:59

Abstract: INHIBITION OF MER RECEPTOR TYROSINE KINASE WITH A NOVEL SMALL MOLECULE INHIBITOR IS EFFICACIOUS IN PRE-CLINICAL MODELS OF NON-SMALL CELL LUNG CANCER CT Cummings (M.D., Ph.D., MSTP)¹, KD Davies¹, GD Kirkpatrick¹, D DeRyckere¹, W Zhang², X Wang², S Frye², HS Earp², and DK. Graham¹ ¹ University of Colorado School of Medicine, ² University of North Carolina School of Medicine Mer is frequently overexpressed in non-small cell lung cancer (NSCLC). Genetic inhibition of Mer reduces NSCLC cell growth in vitro and tumor xenograft growth in vivo. Here, we examined anti-tumor effects mediated by a first-in-class Mer-selective small molecule tyrosine kinase inhibitor (TKI), in pre-clinical models of NSCLC. **Methods:** The effects on Mer activation and downstream signaling pathways were analyzed by immunoblot. Anti-tumor activity was determined in a panel of cell lines using soft-agar assays. Cells were stained with YoPro-1-iodide and propidium iodide dyes and induction of apoptosis was determined using flow cytometry. A subcutaneous murine xenograft model was employed to determine therapeutic effects in vivo. **Results:** The Mer TKI blocked autophosphorylation in numerous cell lines and was highly selective for Mer. Treatment inhibited downstream pro-survival signaling through the ERK1/2 and AKT pathways, resulting in apoptosis. Additionally, colony-forming potential was reduced in a large panel of NSCLC lines. Sensitivity was independent of driver oncogene status. RNAi mediated knock-down of Axl enhanced sensitivity to Mer TKI treatment. Finally, in animals treatment decreased tumor progression resulting in a significant decrease in tumor volume. **Conclusions:** This TKI is a novel and potent small molecule inhibitor that is selective for Mer. The data presented here indicate that Mer inhibition may be an effective strategy for treatment of lung cancer. Because sensitivity to the Mer TKI did not depend on driver oncogene status, development of Mer TKIs for clinical application may provide a molecularly-targeted treatment option for patients without known oncogenic mutations. In addition, since Axl inhibition sensitized NSCLC cells to treatment with Mer TKI, a functional and/or physical interaction between Mer and Axl is possible. In summary, the data presented here validate this Mer TKI as a potential treatment for NSCLC and provide critical data to support its continued development toward clinical application.

Poster Title: Geographically Constrained: An Examination of Emergency Contraception Accessibility in Colorado

Category: Health Care and Public Health

Poster Location: Education 2 Bridge

Poster Number:60

Abstract: Background Legal barriers to emergency contraception (EC) access disappeared Feb2014 when the FDA approved the unrestricted sale of all forms of levonorgestrel EC. Unwarranted barriers like age restrictions, and misinformation often remain. This survey of Colorado outpatient pharmacies quantifies commonly encountered barriers by individuals purchasing EC. **Methods** A pharmacy list was obtained from The Little Blue Book 2014, a phonebook for physicians. Only open pharmacies serving the general public were included. One of three female researchers phoned 690 listed pharmacies, and asked questions posing as a woman seeking EC. The script included questions about availability (in-stock), location of product, cost, weight-appropriateness, and age requirements. Completely accessible was defined as: in stock, on shelf, with no ID requirements. Geographic region were categorized as urban, rural, or frontier counties. Of 64 counties, 52 had less than 10 pharmacies, and 18 had none listed. Rates of in-stock, completely accessible, and weight-appropriateness were summarized with frequency and percent, and compared by county and pharmacy type using chi-square tests. **Results** Of 633 pharmacies, the majority were urban (85%) and chain (85%). Pharmacy technicians (60%) and females (71%) completed the survey most often. Most pharmacies stocked EC (87%), but only 23% had EC completely accessible. Neither EC stock nor completely accessible rate differed significantly by geographic region. Both EC stock and completely accessible rate differed across independent, chain and 24-hour type (p

Poster Title: Physicians' Perceptions of Patient Safety Culture

Category: Health Care and Public Health

Poster Location: Education 2 Bridge

Poster Number:62

Abstract: PHYSICIANS' PERCEPTIONS OF PATIENT SAFETY CULTURE G. Fauchet, (seeking MD/MPH), M Mulvahill (MS), P Kneeland (MD), H Wald (MD/MSPH). Department of Medicine, University of Colorado, Aurora, CO. Background Physicians are key stakeholders in patient safety initiatives but are often difficult to engage. There is little understanding of physicians' perceptions of safety culture to inform engagement strategies. Purpose To identify determinants of physicians' overall perceptions of patient safety culture. Methods We performed a cross-sectional study using the Hospital Survey on Patient Safety Culture (HSOPSC) 2012 database that contained 10,756 eligible physician respondents from 512 unique hospitals. Linear mixed models were used to assess the relationship between physician specialty, staff position, years worked in current specialty, and the 11 HSOPSC domains to the primary outcome, the percentage of positive response for the overall perception of patient safety domain. Results Intensivists had the highest percentage of positive responses for perception of patient safety culture (66%), while emergency medicine specialists had the lowest percentage of positive responses (52%). Resident physicians were not significantly different from attending physicians in their perception of patient safety culture ($p=0.88$). Physicians who had worked the shortest and longest times in their current specialty had the highest perception of patient safety

Poster Title: DEATH CERTIFICATE INACCURACY COMPROMISES THE VALIDITY OF PUBLIC HEALTH STATISTICS Dylan Norton, (BA,MD), P Boyer, R Low, Department of Pathology, University of Colorado.

Category: Health Care and Public Health

Poster Location: Education 2 Bridge

Poster Number:64

Abstract: DEATH CERTIFICATE INACCURACY COMPROMISES THE VALIDITY OF PUBLIC HEALTH STATISTICS Dylan Norton, (BA,MD), P Boyer, R Low, Department of Pathology, University of Colorado. Death certificate data forms the basis for morbidity and mortality statistics. Errors in certificate completion threaten the accuracy of these statistics. Public health priorities are aimed at reducing morbidity and mortality from common diseases and risk factors. Reliance on flawed public health statistics may lead to misdirection of public health policies and interventions. **Purpose:** To assess the accuracy of public health statistics by comparing official death certification coding with data derived from certificates constructed following a review of autopsy findings and clinical records. **Methods:** Clinical and autopsy records were examined for 229 patients who died in 2010 and 2011 at a Denver area Hospital. Based on this data, a senior pathologist, blinded to the original cause of death determination, completed a post-autopsy death certificate. These revised certificates were then processed by the National Center for Health Statistics using Centers for Disease Control criteria for cause of death coding. A direct comparison was performed between the causes of death generated by the original death certificates and those identified using revised certificates. **Results/Outcomes:** There was a 47% disagreement between the original and revised underlying causes of death. Other significant conditions contributing to the patient's death were omitted or contained significant errors in 52% of cases. In no instance were autopsy results consulted prior to filing the original death certificate, and only two certificates (0.9%) were amended by the certifying clinician based on autopsy findings which disagreed with the original cause of death. **Conclusion:** The high rate of errors in death certification identified in this study calls into question the accuracy of vital health statistic data. These results suggest that population-based disease related morbidity and mortality data may be profoundly flawed. Although autopsy reports yield important information on the patient's cause of death, clinicians rarely wait for an autopsy to complete the death certificate or amend certificates based on autopsy findings. Measures should be taken to reduce errors in death certification and to improve the quality of the vital statistics data on which public health priorities are based.

Poster Title: Anti-cancer efficacy of silibinin and dehydrosilybin against basal cell carcinoma cells

Category: Cancer - Lung and Skin

Poster Location: Education 2 Bridge

Poster Number:66

Abstract: Basal cell carcinoma (BCC) is the most common cancer worldwide, and the cases of BCC are further rising due to the depleting atmospheric ozone layer, continuous sun exposure and lack of adequate protection against ultraviolet radiation. Current treatment options for BCC are insufficient and toxic; and surprisingly, chemopreventive efforts against BCC are lacking, suggesting the need for additional and novel preventive and therapeutic agents against BCC. Silibinin, a natural phytochemical derived from milk thistle plant has shown tremendous photoprotective and anti-cancer efficacy; however nothing is known about its potential efficacy against BCC. Herein, for the first time, we initiated studies with silibinin and its oxidation product dehydrosilybin (DHS) for their anti-cancer efficacy against BCC both in vitro and in vivo using ASZ (p53 mutated) and BSZ (p53 deleted) cell lines derived from a mouse BCC tumor. BCC cells were treated with DMSO (control), silibinin (25-100 μ M), or DHS (10-30 μ M) and analyzed for cell proliferation, clonogenicity, apoptosis, sphere formation, cell cycle distribution as well as for protein expression and/or DNA binding of major molecular regulators of BCC. Results showed that silibinin and DHS significantly reduced (more with DHS) the cell proliferation, clonogenicity as well as sphere formation, while induced cell cycle arrest and apoptosis in BCC cells. Furthermore, silibinin/DHS down regulated the expression and/or DNA binding of NF-kB, AP-1 and Gli1 in BCC cells. Importantly, in the ectopic allograft model, oral administration of silibinin and DHS (200 mg/kg body weight, 6 days per week) for 7 weeks strongly reduced the ASZ tumor volume by 44% (p

Poster Title: HYPERGLYCEMIA INCREASES INCIDENCE OF OSTEOPHYTE FORMATION IN A MOUSE MODEL OF OSTEOARTHRITIS

Category: Arthritis

Poster Location: Education 2 South 1308

Poster Number:7

Abstract: HYPERGLYCEMIA INCREASES INCIDENCE OF OSTEOPHYTE FORMATION IN A MOUSE MODEL OF OSTEOARTHRITIS. M McNulty (M.D. SOM), W Schroeder, M Duran, K King, Ph.D., Department of Orthopedics, University of Colorado, Denver. **Purpose:** Incidence of type 2 diabetes mellitus is rising worldwide, and it will cause increasing disability as the population ages. Recently published data identify an association between diabetes and increased incidence and severity of osteoarthritis (OA). However, little is known about the metabolic consequences of the diabetic environment in cartilage. We aim to determine if and how hyperglycemia affects cellular phenotype to promote increased OA progression.

Methods: The destabilized medial meniscus (DMM) model of OA was applied to a mouse model of type 2 diabetes. Seven 12 week old male mice with hyperglycemia (KKAy, blood glucose > 300 mg/dL) and 4 age-matched male mice without (KKaa) underwent DMM. At 8 weeks post-DMM, knee joints (stifle) were collected. Coronal sections were stained with safranin O/fast green and examined for differences in morphology. After an increase in osteophytes was noted, a follow up experiment was performed in which serial sections were stained with anti-BMP-2 polyclonal antiserum or anti-type X collagen monoclonal antibody. **Results:** The blood glucose of the hyperglycemic group at the time of DMM was 83% greater than the control group (438 ± 55 vs. 239 ± 33 , $P < 0.001$), and body mass was 9% greater (34.9 ± 1.8 vs. 31.9 ± 2.9 , $P = 0.01$). Histological analysis found that the percentage of mice with osteophytes was significantly greater in the hyperglycemic group (Table). Osteophytes were primarily located in the medial tibial articular cartilage. Both BMP-2 and type X collagen were located in or near osteophytes (Figure 1). **Conclusions:** BMP-2 and type X collagen production are characteristic of hypertrophic chondrocytes and may contribute to excess mineralization in OA. Our data suggest that high glucose conditions favor a change towards the hypertrophic phenotype. Ample evidence supports a similar change in human that is characteristic of OA chondrocytes. Our findings are in agreement with the recent clinical studies demonstrating accelerated OA progression in patients with diabetes. In summary, this study suggests that accelerated hypertrophy of articular chondrocytes is a result of hyperglycemia and may contribute to the progression of OA as previously seen in patients with diabetes.

Poster Title: Determining the Roles of Murine Factor H-Related Proteins in Complement Dysregulation.

Category: Arthritis

Poster Location: Education 2 South 1308

Poster Number:9

Abstract: DETERMINING THE ROLES OF MURINE FACTOR H-RELATED PROTEINS
Antonioli, AH; Kevin J. Marchbank; V. Michael Holers; Jonathan P. Hannan. Division of Rheumatology, University of Colorado School of Medicine, Denver, CO Immune-mediated diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are chronic illnesses that impact millions of lives. Although the pathogenesis of each of these diseases is complex, it is known that dysregulation of the complement system plays an important role. Therefore, a better understanding of complement regulation and specific complement regulatory proteins is crucial for developing therapies. The overall objective of this work is to explore the interrelationships between the complement regulatory protein Factor H (FH) and five closely related molecules known as the Factor H-Related (FHR) proteins. FH primarily regulates complement activation on self-surfaces allowing the innate immune response to discriminate between self and pathogens. FH and the FHR proteins consist in their entirety of compact repeating domains known as short consensus repeats (SCRs). The FHRs share many structural and functional traits with FH including the capacity to bind complement component C3b and self-surface markers such as glycosaminoglycans. Few functional studies have been carried out on the FHR proteins and these molecules have not been studied in any in vivo models of inflammatory disease. Our central hypothesis is that FHR proteins act as antagonists of FH function and increase complement deposition. Our preliminary data indicate that like their human counterparts, the murine FHR proteins act as antagonists of mouse FH and accordingly are excellent surrogates by which to interrogate the underlying mechanisms linking variations within the human CFH gene family and complement dysregulation. We also plan to compare the specificities and affinities of murine FH and the murine FHR proteins (mFHR A-D) for different known FH ligands and determine the effects of mFHR A-D on severity of disease in a murine model of human RA. As recent studies have shown that the FHR proteins modulate complement by competing with FH for binding to its major ligand, complement component C3b, likely disrupting FH-driven complement regulation on specific biological surfaces, our long-term objective is to determine whether the FHR proteins are suitable therapeutic targets for the treatment of complement-driven inflammatory diseases.