University of Colorado **Anschutz Medical Campus**

31st ANNUAL STUDENT RESEARCH FORUM

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DECEMBER 13th, 2016
ANSCHUTZ MEDICAL CAMPUS
Education 2, North and South

31st ANNUAL
UNIVERSITY OF COLORADO DENVER
ANSCHUTZ MEDICAL CAMPUS
STUDENT RESEARCH FORUM

Tuesday, December 13th, 2016

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

ANSCHUTZ MEDICAL CAMPUS
Education 2, North and South

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

The University of Colorado Denver
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Poster Session Judges

The organizing committee wishes to acknowledge their appreciation to the following serving as judges for the AMC Student Research Forum. Without their generous contribution of time and talent the forum would not be possible. Thank you!

2016 AMC Student Research Forum Award and Funding Donors

The organizing committee is especially grateful to the following schools, departments, divisions, and programs for their generous contribution of financial support for the forum and/or a $320 research prize awarded to the top scoring posters at the event.

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Primary Student Presenter: Nasser Alsaleh

Additional Presenter(s): N/A

Presenting School: Pharmacy

Degree Seeking: PhD

Year: 3rd

Mentor: Jared Brown

Poster Title: *Exposure to Silver Nanoparticles Induces Mast Cell Degranulation Through Activation of Calcium Signaling Without Inducing Major Cellular Toxicity*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

EXPOSURE TO SILVER NANOPARTICLES INDUCES MAST CELL DEGRANULATION THROUGH ACTIVATION OF CALCIUM SIGNALING WITHOUT INDUCING MAJOR CELLULAR TOXICITY

NB Alsaleh (Ph.D., GS), JM Brown. Dept. of Pharmaceutical Sciences, University of Colorado, Denver, CO

Nanoparticle-mediated toxicity often involves triggering immune responses. Mast cells regulate both innate and adaptive immune responses and they play an important role in allergy and inflammation (e.g. asthma, atopic dermatitis and anaphylaxis) as they have the ability to immediately release preformed mediators upon activation. Silver nanoparticles (AgNPs) are one of the most prevalent nanomaterials used in consumer products due to their antimicrobial properties (e.g. coating of medical devices, wound dressings, detergents, athletic apparel and food storage containers) leading to potential human exposure. We utilized bone marrow-derived mast cells isolated from C57Bl/6 mice. Previously, we have shown that AgNPs induce mast cell degranulation and we identified a role for scavenger receptor B1 (SR-B1). However, it is completely unknown how SR-B1 mediates mast cell degranulation and the intracellular signaling pathways involved. Our results demonstrate that AgNP-mediated mast cell degranulation is dependent on an influx of extracellular calcium, which appears to be at least partially mediated by the ORAI calcium channels. Upstream calcium regulators including PI3K and PLCγ are involved in degranulation of mast cells in response to AgNPs. Furthermore, mast cell exposure to AgNPs was not associated with apoptotic or necrotic cell death. Taken together, these results suggest that exposure to AgNPs may trigger an immune response, through activation of mast cells, without necessarily causing a direct damage to cells. Our findings provide new insights into AgNP-induced mast cell activation, which could be beneficial for designing novel nanomaterials that are devoid of immune system activation.

Primary Student Presenter: Madhurima Baliga

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Jelena Klawitter

Poster Title: *Identifying Biomarkers of Disease Progression in Pediatric Autosomal Dominant Polycystic Kidney Disease Patients*

Final Category: Pediatrics

Abstract:

IDENTIFYING BIOMARKERS OF DISEASE PROGRESSION IN PEDIATRIC AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE PATIENTS. M Baliga (M.D., SOM), A Karimpour-fard, J Klawitter, U Christians, M Cadnapaphornchai, and J Klawitter, Department of Anesthesiology, University of Colorado, Denver, CO.

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease. Though children with ADPKD show normal renal function and creatinine clearance prior to adulthood, rapid cyst development is occurring. We aimed to identify plasma biomarkers of disease progression in the pediatric ADPKD population. Plasma samples from 81 ADPKD patients aged 8-22 years were collected and samples from a cohort of healthy children (60 subjects, aged 1-3 years) served as a control. Metabolomic analysis of plasma was performed using liquid chromatography-mass spectrometry. Metabolites with a P value < 0.05 and an absolute fold change of 50% or greater were identified as significant. 117 metabolites were significantly changed between the ADPKD patients at baseline and healthy children controls, with 16 metabolites decreased in the ADPKD cohort and 101 increased. Of note, cardiovascular risk markers and intermediates of the methionine cycle (uric acid, allantoin, cysteine, S-adenosyl-homocysteine), intermediates of the Krebs cycle and glycolysis (pyruvate, α-ketoglutarate, D-glyceraldehyde-3-phosphate), and bile acids (deoxycholic and cholic acids) were increased in the ADPKD patients. An increase in renal insufficiency markers and tryptophan metabolites kynurenine and quinolinate was noted, with a decrease in kynurenine metabolite anthranilate. Hypoxanthine and nicotinamide were also decreased. In conclusion, we found several cardiovascular and renal risk markers to be increased in the pediatric ADPKD patients as compared to healthy subjects. Future work will involve targeted quantitation of these metabolites and their translation into studies of disease progression.

Primary Student Presenter: Kristina Barber

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Travis Heare

Poster Title: *Consideration of Limb Length Inequality in Treating Upper Extremity Pediatric Bone Sarcoma*

Final Category: Surgery, Cardiovascular and Other

Abstract:

CONSIDERATION OF LIMB LENGTH INEQUALITY IN TREATING UPPER EXTREMITY PEDIATRIC BONE SARCOMA. K Barber, (M.D., SOM), C Beebe, C Anderson, and T Heare, University of Colorado School of Medicine; Children's Hospital Colorado.

Reporting on treatment of pediatric upper extremity bone sarcoma is limited. Cases of upper extremity origin of this rare disease have generally been combined with lower extremity origin. However, combination disallows differentiation of unique surgical and functional outcomes for the upper extremities. Specifically, a need exists to delineate whether limb length inequality presents clinical and functional deficits in the upper extremity.

We retrospectively reviewed records of 15 patients at Children's Hospital Colorado after surgery and/or radiation therapy for sarcoma of the scapula, humerus, or clavicle from 2003 to 2014. Demographics, pathology, surgical procedure, chemotherapy, radiation, complications, and survival outcomes were collected.

Tumor locations included eight proximal, one distal, and two total humerus, three scapula, and one clavicle. With chemotherapy, 11 patients had surgery, three surgery and radiation, and one radiation. The few complications requiring further surgery were mostly nonunion of graft host junctions or shoulder instability. Desire for limb length equality led to instability and further surgery, while accepting inequality led to fewer complications.

Epiphyseal damage and shoulder instability occur with radiation and humeral resection. Instability worsens with greater force generated through limb lengthening resulting in further surgery. In fact, a short humerus in these patients with weak arm abduction is useful as it brings the elbow proximally for functions like hand to mouth motion. These cases suggest little importance of arm length equality. Thus, next steps will be to clinically measure arm lengths, functionality, and health related quality of life to improve recommendations for the future.

Primary Student Presenter: Alexander Barrett

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 4th

Mentor: Kirk Hansen

Poster Title: *Targeted proteomics and cross-linking analysis reveal alterations in the microenvironment of pancreatic tumors*

Final Category: Hematology and Oncology

Abstract:

   Pancreatic ductal carcinomas (PDAC) are characterized by progressive stiffening of the extracellular matrix (ECM) resulting in the formation of fibroses which contribute to patient mortality. Here we sought to use targeted ECM proteomics and cross-linking analysis to investigate ECM composition and tissue mechanics in three genetically engineered PDAC mouse models that vary in their degree of fibrosis. Although fibrosis is thought to be characterized by increased fibrillar collagen deposition and collagen cross-linking, our data show that fibrillar collagen abundance was unchanged between subtypes. Instead, we found that more aggressive PDAC tumors demonstrated significant increases in matricellular and FACIT collagen protein abundance. Additionally, we found that more aggressive PDAC tumors were less cross-linked - challenging the paradigm that stiffer tumors are a result of increased collagen cross-linking.

Primary Student Presenter: Colleen Bartman

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 3rd

Mentor: Tobias Eckle

Poster Title: *Illuminating a Circadian Link to Cario-Protective Metabolism*

Final Category: Surgery, Cardiovascular and Other

Abstract:

ILLUMINATING A CIRCADIAN LINK TO CARDIO-PROTECTIVE METABOLISM. CM Bartman (Ph.D., GS), L Khailova, and T Eckle, Department of Anesthesiology, Program in Cell Biology, Stem Cells, and Development

For over 4.5 billion years, life on Earth has evolved to consistent oscillations of sunlight. As a result, most organisms on our planet synchronize to a 24-hour cycle. This is called a circadian (Latin circa = around, and diem = day) rhythm. Modern humans evolved to sunlight as a powerful external stimulus of circadian rhythm. Today, we know that integration between sunlight and internal circadian rhythm does not simply regulate sleep–wake cycles but also influences the molecular biology of individual cells and organ systems, such as the heart. In fact, heart diseases such as ischemic myocardial infarction (MI), are circadian in their nature of onset. However, the role of circadian proteins in cardiac function and cardio-protection is not well understood.

The goal of our lab is to investigate the mechanism of circadian-mediated cardio-protection for preventative and therapeutic strategies in ischemic MI, which accounts for approximately one death every 42 seconds in the United States. In an initial screen from our lab to identify cardio-protective pathways induced by ischemic preconditioning, we found Period 2 (PER2) is most highly up-regulated. Intense light exposure to mice uncovered a time-dependent induction of cardiac PER2 and intense light exposure prior to in situ myocardial ischemia-reperfusion revealed reduced infarction size in wild-type mice but this protection was abolished in the Per2-/- mice exposed to intense light. Considering a hallmark of survival during ischemic MI is cardiac adaptation to hypoxia or ischemia, we hypothesize that PER2 regulates metabolic adaptation to produce energy by an 'oxygen efficient' mechanism. Indeed, we revealed a regulatory role for PER2 in the adaptive shift from mitochondrial respiration (an 'energy efficient' mechanism) to glycolytic metabolism (an 'oxygen efficient' mechanism) to produce ATP in hypoxia. Using in vitro, in vivo, and human studies, we identified a novel regulatory role of light-elicited PER2 in energy metabolism that may lead to using intense light as a preventative or therapeutic strategy in ischemic MI.

Primary Student Presenter: Thomas Beadnell

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 5th

Mentor: Rebecca Schweppe

Poster Title: *RPS6 Phosphorylation is a Predictive Biomarker of Response to Combined SRC and MAPK Pathway Inhibition in Thyroid Cancer*

Beadnell, TC, Wuensch, KE, Riffert, SM, Pozdeyev, N, Schweppe, RE. Department of Medicine

Final Category: Hematology and Oncology

Abstract:

Src is a promising therapeutic target in thyroid cancer. In addition, our lab recently demonstrated that combined Src and MEK1/2 inhibition results in enhanced anti-tumor responses in vitro and in vivo and improved survival in vivo. In this current study we hypothesized that by defining biomarkers of response, the efficacy of the combination therapy would be enhanced. Methods: Cell Titer-Glo assay, immunoblot analysis, and IHC. Results: Herein, we determined 11 thyroid cancer cell lines were sensitive to single agent dasatinib (<90 nm), and 25 were resistant. Interestingly, 3/3 dasatinib-sensitive and 3/6 dasatinib-resistant BRAF- and RAS-mutant cell lines tested demonstrated elevated apoptosis in response to combined Src/MEK therapy. However, no response was observed in response to the combination in the 3 PIK3CA-mutant cell lines tested. Interestingly, the downstream target of Src (pFAK-Y861) and MEK1/2 (ppERK1/2) were effectively inhibited by the combination treatment in all cell lines. Thus, we next analyzed PI3K pathway signaling responses. Surprisingly, BRAF- and RAS-mutant cell lines that were intrinsically resistant to dasatinib exhibited 5-6 fold higher baseline AKTS473 phosphorylation levels in comparison to the sensitive cell lines, and the levels were similar to those observed in the PIK3CA-mutant cell lines (4- and 8-fold). Interestingly, combined Src and MEK1/2 inhibition in the BRAF- and RAS-mutant cell lines effectively inhibited the PI3K pathway resulting in a synergistic (> 10-fold) reduction in pS6-S235 phosphorylation. Finally, RAS-mutant (Cal62) tumors treated with combined Src and MEK1/2 inhibitors exhibited a significant 1.5-fold reduction in S6-S235 phosphorylation in the combination treated group in comparison to the vehicle control (p = 0.041). In Conclusion, effective inhibition of S6 phosphorylation is a predictive biomarker for increased apoptosis and response to combined inhibition of Src and MEK1/2.

Primary Student Presenter: Sarah Black

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Nanette Santoro

Poster Title: *Reprometabolic Syndrome Mediates Subfertility in Obesity*

Final Category: Surgery, Cardiovascular and Other

Abstract:

INTRODUCTION: Studies of multiple measures of reproductive health in obese and normal-weight women show that reproductive dysfunction and obesity go hand-in-hand. In addition, previous research has identified dysregulation of the pituitary-ovarian axis as a possible cause for the observed decrease in fecundability of obese women.

AIM: To investigate whether experimentally controlled high levels of free fatty acids (FFAs) and insulin in normal women are necessary and sufficient to bring about a transient decrease in pituitary sensitivity to gonadotropin-releasing hormone (GnRH), similar to that seen in obese women.

METHODS: We will recruit 10 regularly cycling, non-diabetic, normal-weight women. During the first week of their menstrual cycle, each will receive 1 of 2 treatments: either an infusion of free fatty acids and insulin (40mU/m2/min) OR normal saline (control) in random order. Infusions will last for 6hrs. Pituitary function will be assessed by measuring the frequency and amplitude of spontaneous LH and FSH pulsations for 4 hours as well as the response to a physiologic bolus of GnRH from hours 4-6.

RESULTS: Results are pending completion of the study. Women who have taken part so far have tolerated the experimental treatment well, and results from their frequent blood samples are currently being assayed for LH and FSH.

CONCLUSION: If hyperinsulinemia and elevated circulating FFAs are necessary and sufficient experimental conditions to elicit pituitary dysregulation in normal weight women, we expect to see a smaller response to the single dose of GnRH given at the 4hr point. In addition, as more participants complete our study, we hope to be able to analyze LH and FSH cycles over the first four hours of the study to look at characteristics like amplitude and frequency.

Primary Student Presenter: Amelia Bowman

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 4th

Mentor: TIllman Farley

Poster Title: *Communiversity: Bringing community members and healthcare professional students together to improve health*

Final Category: Education, Healthcare, and Public Health

Abstract:

C-STAHR (Community-Students Together Against Healthcare Racism) was founded in 2010 by medical students passionate about addressing racial disparities healthcare in collaboration with 2040 Partners for Health. C-STAHR's vision is "For students and community to work together to better understand perceived discrimination and design a feasible intervention to better equip future healthcare providers and community members to reduce its effects." In pursuit of this vision, the group adheres to a strict Community Based Participatory Research (CBPR) process where decision-making is shared equally between community members and students. C-STAHR, in partnership with the community, developed a problem tree to map out the problem of discrimination in healthcare as it is experienced by the Aurora/Denver community. Together, they identified breakdowns in provider-patient communication as a major factor contributing to discrimination. To address this issue, C-STAHR worked with community members to develop a communication tool that facilitates improved communication between patients and their providers. By facilitating community dialogue and developing this intervention, C-STAHR is a unique example of how sustainable partnerships can be created between academia and community, hence "communiversity."

Primary Student Presenter: Dylan Calame

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD/PhD

Year: 2nd

Mentor: Sana Karam

Poster Title: *Using Radiation Therapy to Prime the Immune System in Head and Neck Squamous Cell Carcinoma*

Final Category: Hematology and Oncology

Abstract:

Using Radiation Therapy to Prime the Immune System in Head and Neck Squamous Cell Carcinoma

D. Calame, A. Oweida, S. Lennon, S. Bhatia, J. Sharma, A. Griego, S. Karam

Purpose: Radiation therapy (RT) can have immune adjuvant-like effects that enable the body to fight off malignancies, and while the mechanism is unknown, it is thought to be antigen driven. We hypothesize that RT increases antigen presentation and immunogenicity of tumor cells, which can then activate CD8+ T cells. Understanding the immunomodulatory effects of RT could allow for better combination of traditional cancer therapy with immunotherapy.

Methods: HNSCC TCGA datasets were sorted into cytotoxic and exhausted CD8+ T cell groups. These groups were compared for expression of HLA genes.

LY2 HNSCC cells were plated and irradiated with 0, 4, 8, or 25 Gy X-rays at 24 hr. Tumor cells were harvested 24 hr after RT to assess expression of MHC I, CD80, and PD-L1 by flow cytometry.

For co-culture, mouse spleens were harvested and CD8+ T cells were purified using magnetic bead separation. T cells were incubated with 24-hr post-RT LY2 for 4 days. T cell IFN-γ and CD69 were assessed using flow cytometry.

Results: TCGA data showed higher HLA expression in the cytotoxic T cell group compared to the exhausted group. RT resulted in an increase in expression of MHC I in LY2 cells (p = 0.0001). CD80, a T cell co-stimulatory marker, showed a similar increase (p = <0.0001), however PD-L1, a T cell inhibitory marker, also increased (p = 0.0137). Co-culture of T cells with irradiated cells showed an increase in the percent of CD69+ and IFN-γ+ T cells compared to non-irradiated controls (p = 0.0005, p = 0.0035, respectively).

Conclusions: Cytotoxic T cell phenotypes are correlated with increased MHC I in TCGA datasets. RT increased expression of MHC I, CD80, and PD-L1 in a murine LY2 cells, and when these irradiated tumor cells were co-cultured with CD8+ T cells, the T cells displayed activated phenotypes.

Primary Student Presenter: Nzali Campbell

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 2nd

Mentor: Michael Morgan

Poster Title: *Integration of RNA Sequence Variant Detection, Differential Gene Expression, and Pathway Analyses Links ENOYL-COA Hydratase, Short Chain 1 and Dihydrolipoamide Branched Chain Transacylase E2 to Dilated Cardiomyopathy. N. V. Campbell, (Ph.D., SOM, Grad), M. G. Edwards, D. A. Weitzenkamp, I. L. Campbell, D. C. Irwin, J. J. Tentler, and M. J. Morgan, Clinical Science Ph.D. Program, Colorado Clinical and translational Sciences Institute, Anschutz Medical Campus, University of Colorado, Denver.*

Final Category: Surgery, Cardiovascular and Other

Abstract:

Background: Suppositions have been made that intermediates involved in the degradation of branched-chain amino acids and the fatty-acid beta-oxidation(FAB) pathways may initiate cardiac dysfunction. However, no study yet has directly linked these pathways to dilated cardiomyopathy(DCM) in unrelated patients. Methods: In this case-controlled study, we used a novel filtering approach in which we coupled RNA-sequence variant detection, and differential gene expression with pathway analysis using secondary data to determine genes carrying potential mutations, modifier genes, and pathways that predispose unrelated individuals to DCM. We used data from 6 unrelated DCM patients and 4 controls that were obtained from the Sequence Read Archive. Results: Data show that ECHS1(enoyl-CoA hydratase, short chain 1) (log2(foldchange)=1.63329), which carries 2 missense putative mutations, the rs10466126 and rs1049951 is associated with DCM(p=0.00135;q=0.013927). These variants are found in 3 catabolic pathways, the valine(p=2.04E-04) and isoleucine(p=7.68E-03) degradation 1, and the FAB pathways(p=2.99E-03), associated with DCM. Results also show that DBT(Dihydrolipoamide branched chain transacylase E2), which encodes a protein that forms the homo-24-meric dihydrolipoyl transacylase (E2) subunit of the branched-chain alpha-keto acid dehydrogenase complex was upregulated(log2(foldchange)=0.955072). This gene carries the rs12021720 mutation and is also associated with DCM(p=0.00545;q=0.0368792). Conclusion: Mutations in ECHS1 and DBT, involved in valine and isoleucine degradation and FAB, are associated with DCM. Disruption of these pathways may lead to ketoacidosis, propionic academia in cardiac mitochondria, with accumulation of long chain fatty acids in the cytoplasm. We present an effective filtering approach that has potential to lay a foundation for discovery of targets for therapeutic intervention and diagnosis that considers interplay between DNA, mRNA, and related pathways.

Primary Student Presenter: Heather Caulkins

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Natalie Serkova

Poster Title: *Glioblastoma Pseudoprogression Determined by T2 MRI*

Final Category: Hematology and Oncology

Abstract:

DISTINGUISHING GLIOBLASTOMA RECURRENCE FROM PSEUDOPROGRESSION WITH MAGNETIC RESONANCE IMAGING. _HK Caulkins, (MD, SoM)_, N Serkova, MD-PhD, Department of Anesthesiology, University of Colorado, Aurora, CO.

Glioblastoma multiform (GBM), the most common malignant brain cancer, has a 3.3% 2-year survival rate. The current standard of care – resection followed by radiotherapy (RT) and concurrent chemotherapy with temozolomide (TMZ) - causes inflammation called pseudoprogression (PsP), that appears as abnormal MRI signals and resolves within 6 months. Other imaging like DTI, PET, and SPECT have failed to differentiate PsP. Using superparamagnetic iron oxide nanoparticles (SPION) and specific metabolic signatures, we hope to determine whether T2 MRI and MRS can characterize PsP. We cultured two glioma cell lines. We tested cell survival after TMZ and after RT. We used MRS to evaluate metabolic changes after treatment. We injected U251 cells into the flanks of nude mice and GL261 cells into the flanks of wild type mice. We performed pre-treatment MRI with SPION and tumor blood volume. We treated the mice with oral TMZ or RT. We repeated the MRI imaging and harvested tissue for pathological testing. GBM survival declined linearly with TMZ and exponentially with RT. Glucose metabolism decreased with TMZ and RT. Baseline scans showed no SPION T2 signal reduction. Preliminary post-treatment scans showed SPION T2 signal reduction compared to control with RT. If macrophages take up iron and tumors do not, we expect SPION T2 signal reduction with PsP but not tumor growth. Macrophages on cytometry will confirm PsP, and iron should colocalize in macrophages but not tumor cells on histology. GBM cells are slightly resistant to RT. The greater metabolic effect of RT suggests more effect from RT than TMZ. If our results with the in vivo study are as expected, we can conclude that SPION T2 MRI can distinguish PsP from tumor growth non-invasively.

Nothing to disclose.

Primary Student Presenter: Christopher Covey

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 4th

Mentor: Martin Voskuil

Poster Title: *Iron Acquisition Affects Clofazimine Killing in Mycobacteria*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

The ability to access free iron is crucial to the effective growth of mycobacterial species which have evolved specialized mechanisms to bring in iron from their environment. While mycobacterial growth media is often replete with iron, it has been demonstrated that growing Mycobacterium tuberculosis in media from which the iron has been removed will render the bacteria more susceptible to several front-line antibiotics1. The anti-leprosy drug clofazimine(CFZ) has been shown to have some efficacy in vitro and in vivo (in certain circumstances) against M. tuberculosis, excellent killing in Mycobacterium leprae and other NTMs (non-tuberculosis mycobacteria) but limited action in Mycobacterium smegmatis as well poor efficacy in many animal models of tuberculosis. We noted that treatment in low-iron media reduced aerobic CFZ killing while high-iron media facilitated a period of growth during CFZ treatment followed by rapid death. The phenomenon repeated in M. tuberculosis and microarray analysis revealed increased expression of iron acquisition machinery, particularly those related to the production and trafficking of the siderophore mycobactin. A mutant strain defective for the iron regulator IdeR which overproduces mycobactin was showed increased resistance to CFZ compared to the wild-type and the addition of exogenous Mycobactin J to M. smegmatis cultures inhibited killing by CFZ, suggesting that the presence of mycobactin is detrimental to CFZ killing in mycobacteria. Finally, the availability of oxygen also appears to play a role in CFZ killing as it relates to iron and treatment with CFZ led to increased reduction of extracellular iron by M. smegmatis.

Primary Student Presenter: Kelly Crane

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Karen King

Poster Title: *Adenine Dose Study Modeling Chronic Kidney Disease for One Month in Older Male and Female BALB/C Mice*

Final Category: Surgery, Cardiovascular and Other

Abstract:

ADENINE DOSE STUDY MODELING CHRONIC KIDNEY DISEASE FOR ONE MONTH IN OLDER MALE AND FEMALE BALB/C MICE. KM Crane, (MD, SOM), WG Schroeder, RM Clark, & KB King, Department of Orthopaedics.

   Purpose: Chronic kidney disease causes mineral loss in bone but gain in cardiovascular and renal tissues. Our target patient population is mature adults; thus, we desire a method suitable for modeling CKD in older mice. Bone changes occur slowly; thus, we desire a model in which animal survival is robust. Adenine in the diet precipitates in the kidney, inducing damage. Adenine has been used to model CKD in young mice, but it has never been applied to older mice. This study tests different doses of adenine in the diet, given over a one-month period, in older male/female mice.

Methods: Male/female BALB/c mice were obtained from the NIH/NIA aged rodent colony at 24 wks old (analogous to ~30 yr-old humans). All animals received base casein diet for the first seven days. Then, four different doses of adenine (in casein diet) were administered in a 7-day induction phase followed by a 21-day maintenance phase. The four doses were 0.30% induction / 0.20% maintenance; 0.30% / 0.15%; 0.20% / 0.15%; and 0.20% / 0.10%. Control was base casein diet. Mice were individually housed (N = 10 total, 1 mouse/sex/diet). Body masses were measured 3x/wk until death or euthanasia. Kidneys were sectioned (5 μm) and analyzed via H&E, PAS, and von Kossa staining.

Results: All adenine mice lost body mass >30% and most died before study end. Females died faster. The lowest dose of adenine led to abnormal kidney histology, with dilated tubules/Bowman's spaces, peritubular leukocytes, and mineralization. Control mice did not lose body mass and had normal histology.

Conclusions: Adenine can be used to model CKD - via tubulointerstitial nephropathy - in older mice; however, a low dose of adenine should be used. 0.2% adenine for 7 days followed by 0.1% adenine for 21 days models CKD but may result in early death.

Primary Student Presenter: Ashley Denney

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: MD/PhD

Year: 4th

Mentor: Michael McMurray

Poster Title: *Mechanism for the Recessive Behavior of a Tumor-Derived P53 Mutant*

Final Category: Hematology and Oncology

Abstract:

MECHANISM FOR THE RECESSIVE BEHAVIOR OF A TUMOR-DERIVED P53 MUTANT

Ashley Denney (PhD Candidate, Graduate School), Michael McMurray, PhD

Cell and Developmental Biology

    p53 is a potent tumor suppressor that carries out anti-proliferative roles largely as a transcription factor. Mutations in TP53 are found in the majority of human cancers and in the inherited Li-Fraumeni syndrome. Mutant p53 can behave in a dominant-negative fashion, whereby co-expression of mutant p53 with wild type (WT) results in mixed mutant:WT tetramer formation and diminished WT activity. Interestingly, mutant p53 can also behave in a recessive fashion and factors that influence the degree of dominance or recessivity for p53 mutants is not well understood. The purpose of this study is to investigate the hypothesis that chaperones specifically impart a recessive phenotype to p53-V272M via sequestration of mutant p53 in cytoplasm, preventing the formation of dysfunctional mutant:WT tetramers in the nucleus. We use the eukaryotic model Saccharomyces cerevisiae to identify chaperone interactions specific to p53-V272M through a bimolecular fluorescence complementation (BiFC) approach, and we assess the functional impact of chaperone deletions on the dominance of p53-V272M co-expressed with WT in a strain carrying a p53 response element. Furthermore, we are building human p53 BiFC constructs to quantify mixed mutant:WT tetramer formation. Here we identify several chaperones — Ssa2, Ssb1, Hsp26, and Hsp104 — that interact with cytoplasmic p53-V272M and not WT. Assessment of p53-V272M dominance is currently underway in strains carrying Ssa2, Ssb1, Hsp26, or Hsp104 deletions, as are experiments to determine the extent of mixed mutant:WT tetramer formation in MCF7 cells. If our hypothesis is correct we expect increased dominance of p53-V272M in the context of specific chaperone inactivation, as well as minimal mixed tetramer formation for p53-V272M and WT relative to dominant-negative p53-R273H and WT.

Primary Student Presenter: Chidebele Duru

Additional Presenter(s): Jim Do

Presenting School: Public Health

Degree Seeking: MS

Year: 2nd

Mentor: Dominic Martinez

Poster Title: *Introducing Health Disparities, Health Equity, and Cultural Competency Through Online Learning Module*

Final Category: Education, Healthcare, and Public Health

Abstract:

Minority populations have poorer overall health than other U.S. residents which is attributed to lack of access to quality healthcare. Thus it is increasingly important for future healthcare providers to have a basic knowledge of health disparities, health equity, and cultural competency. Despite the interest in better understanding these topics, little time is available to further them during training. Thus, students and faculty hypothesized that a curriculum designed to introduce these topics before involvement in regular medical school curriculum could help them be more aware of issues involving health equity.

To assess and increase their knowledge we have developed a module composed of three units offered to students while on campus. The module is composed of three thematic subunits including an introduction to health disparities research and equity, introduction to the concept of cultural competency, and actual stories of individuals dealing with health disparities. Outcome measures will be based on comparison of survey data, pre and post, from participants before receiving the modules and after having completed the lessons online. The evaluation instrument will be the National Opinion Survey on Health and Health Disparities. Statistical testing we will be using is a paired T-test for numeric continuous data using the pre and post data comparison for each participant.

The purpose of this module is to understand if students entering careers in healthcare professions are aware of health disparities and the impact it has on their chosen field of study. This module will be used to assess its efficacy in delivering content through electronic methods. Additionally it will be used as a pre-entrance module to measure whether it is useful as an introduction to these complex topics. By assessing the knowledge base of the students using the module, we will be able to adjust the curriculum to better serve the educational path of the students.

Primary Student Presenter: Jaclyn Essig

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 3rd

Mentor: Gidon Felsen

Poster Title: *Functional Role of Inhibitory Superior Colliculus Neurons in Target Selection*

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

The superior colliculus (SC) is a midbrain structure critically involved in selecting targets for orienting movements. Multiple cell types are found comingled within the SC, but how these cell types function together to underlie target selection is not well understood. Approximately one-third of SC neurons are GABAergic and these cells have been proposed to mediate inhibition between competing motor plans. However, while GABAergic SC neurons have been studied ex vivo, their activity has not been directly examined in behaving animals. We have recently begun to examine GABAergic activity in the SC during head-fixed and freely- moving behavioral paradigms, each of which requires the mouse to select and initiate a leftward or rightward orienting movement in response to a stimulus cue in order to receive a water reward. In these contexts, the activity of principal output neurons of the SC increases as contralateral movements are selected. Given that GABAergic neurons are thought to inhibit these output neurons, we predict that the activity of GABAergic neurons will decrease during the selection of contralateral movements. We selectively expressed channelrhodopsin-2 (ChR2) in GABAergic neurons of the intermediate and deep (motor output) layers of the SC by injecting an AAV-mediated Cre-dependent ChR2 construct unilaterally into the SC of GAD2-Cre mice. The specificity of ChR2 expression to GABAergic neurons ultimately enables us to optically identify these cells in vivo so that we can record, and selectively manipulate, GABAergic activity during behavior. This approach will allow us to test whether and how GABAergic activity in the SC mediates competition between the circuits responsible for discrete motor plans. This is the first study to examine GABAergic activity in the SC in vivo and provides a platform for future studies to delineate how specific GABAergic cell types contribute to the functional circuitry underlying target selection.

Primary Student Presenter: Kevin Forey

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD/MBA in Health Administration

Year: 3rd

Mentor: Christine Waasdorp

Poster Title: *Outpatient Community-Based Treatment for Acute Malnutrition in the Pediatric Population of Leogane, Haiti.*

Final Category: Pediatrics

Abstract:

Background:

   In 2010, Children's Nutrition Program (CNP) of Haiti began its community-based management of acute malnutrition (CMAM). The program was created with the intention of reducing the burden of pediatric malnutrition in Léogâne, Haiti, which is estimated to have rates of chronic undernutrition as high as 23.3%. Because of financial constraints, CNP has been limited in its ability to evaluate the effectiveness of its CMAM therapy over the past six years.

Purpose:

   To determine if the CMAM therapy is an effective treatment for moderate and severe malnutrition in the pediatric population of Léogâne, as established by the international SPHERE Guidelines for Minimum Standards of Care. Other areas that will be investigated include the modifiable risk factors associated with poor therapy outcomes, and a comparison of outcomes in the rural plains to urban areas, highlighting the challenges of access-to-care in the remote villages.

Study Design:

   This is a retrospective cohort study of CNP's CMAM therapy outcomes from August 2010 to April 2016. Statistical analysis was performed using JMP software on the de-identified dataset containing more than 2,000 children 1-5 years of age that received CMAM therapy with albendazole, Vitamin A, and Plumpy'Nut supplementation.

Conclusion:

   Little is known about the effectiveness of CNP's CMAM therapy and the social factors that affect recovery rates. Furthermore, many of the staff members at CNP lack training and experience in project planning and program evaluation. By providing an independent, objective analysis of their CMAM therapy, these findings will help to improve the effectiveness, capacity, and coverage of future CMAM therapy.

Primary Student Presenter: Carolyn Foster

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 3rd

Mentor: Caroline LeClair

Poster Title: *Resident Perspectives on Curricula in Integrative Medicine*

Final Category: Education, Healthcare, and Public Health

Abstract:

RESIDENT PERSPECTIVES ON CURRICULA IN INTEGRATIVE MEDICINE: C Foster (MD, MS), C LeClair, L Corbin, and M Nuffer, Department of Medicine, University of Colorado Aurora, CO

Dietary and herbal supplement education is not required in US medical school curricula, per std 7 of the LCME (1). This is concerning as 38% of US adults use supplements and 72% do not report use to healthcare providers (2). In this study, family medicine (FM) residents participated in an hour-long curriculum covering basic concepts about supplements and completed pre and post surveys. Surveys assessed perceptions on adequacy of medical school education on supplements, opinions about efficacy and safety, and behaviors related to discussion of supplements with patients. 41% of Colorado FM residents (78 residents across 7 programs) participated.

Results show 88% of Colorado FM residents think they should have received more education on this topic than provided. Only 46% received required education on the topic, significantly less than the 73% who think this education should be required ($p<0.05$). The curriculum increased the number of residents planning to discuss or screen patient's supplements from 45% to 89% ($p<0.05$), frequency residents intend to ask about supplement use from "sometimes" to "often" ($p<0.05$) and improved resident perceptions on the efficacy of some supplements when used with physician guidance ($p<0.05$). Results confirming a lack of curricula on integrative medicine, desire amongst residents to receive education, and capability of a curriculum to provoke residents to discuss supplements with patients suggests that further education is needed and could make an impact on physician behavior and patient care.

1 LCME. "Functions and Structure of a Medical School." Standards for Accreditation of Medical Education Programs Leading to the M.D. Degree. (2015)

2 Eiseberg D, Davis R, Ettner S et al. Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. JAMA 280 (10), 1569-1575 (1998)

Primary Student Presenter: Tamara Garcia

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: MD/PhD

Year: 6th

Mentor: Christopher Porter

Poster Title: *Combined AZD1775 and Olaparib Treatment Synergistically Inhibits Acute Leukemia Cells*

Final Category: Hematology and Oncology

Abstract:

COMBINED AZD1775 AND OLAPARIB TREATMENT SYNERGISTICALLY INHIBITS ACUTE LEUKEMIA CELLS. TB Garcia, (M.D., Ph.D., GS), JC Snedeker, CC Porter, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO.

The goal of this study was to test the hypothesis that pharmacologic inhibition of WEE1 can sensitize acute leukemia cells to PARP1/2 inhibition. To test this hypothesis, human cell lines MV4;11 and Molm-13 (AML), Jurkat (T-ALL), and Reh (B-ALL) were treated with various concentrations of a WEE1 inhibitor (AZD1775) and a PARP1/2 inhibitor (olaparib) and counted by propidium iodide exclusion and flow cytometry. AZD1775 enhanced the anti-proliferative effect of olaparib in all cell lines, and this drug combination was synergistic as determined by Chou and Talay median effects analysis. Combined treatment with AZD1775 and olaparib significantly enhanced apoptosis induction as evidenced by an increased Annexin-V+ cells and caspase 3 cleavage. Comet assays and western blots for γH2AX confirmed that combined AZD1775 and olaparib treatment resulted in more DNA damage than either drug alone. Daily AZD1775 and olaparib treatment enhanced leukemia control and improved survival in mice injected with a murine MLL-ENL, FLT3-ITD+ AML cell line. Combined AZD1775 and olaparib treatment reduced proliferation, enhanced apoptosis induction, and decreased colony formation in methylcellulose in three AML patient samples. In conclusion, combined treatment with AZD1775 and olaparib results in greater inhibition of AML, T-ALL, and B-ALL cell proliferation and enhances DNA damage and apoptosis compared to either drug alone. Combined inhibition of WEE1 and PARP1/2 enhances survival in a murine AML model and is effective in reducing colony formation in AML patient samples. These preliminary studies raise the possibility of rational combinations of targeted agents for leukemia in patients for whom conventional chemotherapeutics may not be effective or well tolerated.

Primary Student Presenter: Jennifer Gile

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Tobias Eckle

Poster Title: *The Impact of Midazolam on the Expression of the Circadian Rhythm Protein PER2*

JG Gile, (M.D., SoM), D Sehrt, B Scott, T Eckle

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

Delirium occurs in 30% of critically ill patients, and the risk of dying during admission doubles in those patients. Molecular mechanisms causing delirium are unknown, however, critical care units consistently disrupt patients' circadian rhythms which is highly associated with the occurrence of delirium. Exposure to benzodiazepines (e.g. midazolam) is a major contributor to the development of delirium. Thus we tested the effects of midazolam on the regulation of the circadian rhythm protein Per2 in the mouse brain. We analyzed the effects of midazolam on Per2 mRNA expression in wild-type mouse brains and found a robust and significant downregulation of Per2 transcript levels. Using midazolam in a T-maze alternation model, in open field studies (line crossing/center square entries) or in novel recognition tests, we were able to establish a novel mouse model for delirium. Following studies using midazolam in a T-maze alternation model, we found 0.5 h, 24h and 72 h after midazolam treatment that mice exhibited significant deficits in a T-maze alternation model with significant downregulation of Per2 protein in the hippocampus and the SCN. Based on these preliminary studies we hypothesize that Per2 plays a major role in the pathogenesis of delirium and that Per2 stabilization in the brain attenuates delirium. Future studies using gene target mice for Per2 will further elucidate Per2 mechanisms in the development of delirium.

Primary Student Presenter: Amanda Glickman

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Brian Berman

Poster Title: *Eye Muscle Spasms Co-Activate with Cerebellar and Sensorimotor Cortical Regions in Blepharospasm*

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

EYE MUSCLE SPASMS CO-ACTIVATE WITH CEREBELLAR AND SENSORIMOTOR CORTICAL REGIONS IN BLEPHAROSPASM. A Glickman (MD, SOM), E Shelton, and BD Berman, Department of Neurology, University of Colorado, Denver, CO

   Purpose of Study: Blepharospasm (BSP) is a focal dystonia of the orbicularis oculi. Previously considered a motor disorder of the basal ganglia, dystonia is now viewed as a network disorder with widespread dysfunction. However, it is unclear what regions play key roles in BSP.

   Methods Used: Collected functional MRI (fMRI) data on 15 patients with BSP (4M:11F; mean age 62.2±8.0 y; disease duration 8.4±7.3 y) during 8-minute resting state with eyes open. Spasm severity was modeled using amplitude of orbicularis oculi contractions recorded by surface electromyography (EMG-Amp) and included in multiple regression fMRI analysis using SPM8. Primary outcome was within BSP group blood-oxygen-level dependent (BOLD) activations that co-varied with EMG-Amp (individual voxel-level threshold $p \leq 0.005$; cluster size threshold 50 voxels). Secondary analyses included Spearman's rank correlation testing ($p < 0.01$) of imaging findings and BSP duration/severity.

   Summary of Results: fMRI data were excluded for 1 subject due to excessive movement. EMG-Amp co-activated with bilateral sensorimotor regions of the cerebellum (lobule 6) and postcentral gyri. Activity in the postcentral gyri negatively correlated with disease severity: UDRS (R/L:$R^2=0.60$, $R^2=0.48$), BFM (R/L:$R^2=0.74$, $R^2=0.71$) and GRS (R/L:$R^2=0.66$, $R^2=0.67$). BFM negatively correlated with left cerebellar activity ($R^2=0.37$). Disease duration did not correlate with fMRI.

   Conclusions: Co-activation of postcentral gyri and cerebellum is consistent with known sensory and motor dysfunction in BSP and supports the network disorder model. Negative correlation of disease severity with sensorimotor activity may indicate that greater network impairment manifests as increased symptom severity.

Primary Student Presenter: Dawn Goral

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 3rd

Mentor: Austin Heare

Poster Title: *Intramedullary Implant Choice and Cost in the Treatment of Pediatric Diaphyseal Forearm Fractures*

Final Category: Pediatrics

Abstract:

INTRAMEDULLARY IMPLANT CHOICE AND COST IN THE TREATMENT OF PEDIATRIC DIAPHYSEAL FOREARM FRACTURES

D Goral (MD, GS), A Heare MD, M Belton MD, C Beebe MS, J Stoneback MD

University of Colorado School of Medicine and Children's Hospital of Colorado - Departments of Orthopedic Surgery

Elastic stable intramedullary nailing (ESIN) of pediatric forearm fractures has been described utilizing various implant designs and materials with a significant variation in implant cost. The aims of this study were to determine if there was a difference in outcome between three commonly used intramedullary implants: titanium elastic nails (TENs), stainless steel elastic nails (SENs) or standard Kirschner wires (K-wires). Furthermore, this study aimed to elucidate whether a statistically significant cost difference exists between these devices.

This study retrospectively examined pediatric patients with diaphyseal forearm fractures (OTA 22A & 22B) treated with intramedullary fixation at a single institution over a 10-year period. Patients received single or both bone fixation with TENs, SENs, or K-wires. Data was collected on time to radiographic union, complications, surgical time, and actual cost of the implants for each patient. Statistical analysis was used to determine whether any significant differences existed between the groups.

100 patients met inclusion criteria for the study. 31 patients were treated with TENs, 30 with SENs, and 39 with K-wires. There was no statistically significant difference in time to radiographic union, complication rate, or surgical time between the 3 types of fixation. Average time to union was 9.4 weeks ± 5.4 weeks and complication rate was 12.9% for TENs, 10.0% for SENs, and 12.8% for K-wires. There was however a significant difference in cost per implant, with an average cost of $591, $158 and $22 for TENs, SENs, and K-wires respectively (p<0.001).

The present study demonstrates no difference between TENs, SENs, and K-wires in the treatment of pediatric diaphyseal forearm fractures with regards to outcome, time to union, surgical time or

complication rates. Given the significant cost difference between these implants, we recommend surgeons consider modifying their implant selection to help mitigate cost.

Primary Student Presenter: Kaitlin Gorman

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Paul Wischmeyer

Poster Title: *Quantifying Antibiotic Pressure Scores to Determine Impact on Oral and Fecal Microbiome in Critically Ill Patients*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

Purpose

Antibiotic interventions in ICU patients have potentially adverse effects on the microbiota, termed dysbiosis. We observed dysbiosis in oral and fecal microbiome samples from ICU patients. The impact of antibiotics on dysbiosis is not well understood. Quantifying effects of antibiotic pressure on the microbiome composition of ICU patients will help identify potential restorative therapeutic options.

Methods

Fecal and Oral swabs were collected from 149 participants in five ICUs within 48 hours of ventilation in the ICU and again within 10 days of discharge. Antibiotic pressure was measured before admission (n=121), between admission and discharge (n=75), and following discharge (n=79) using a novel method to capture pressure scores over time. Extending ranks (1-4) previously developed by Braykov et al, the spectrum of activity was weighted based on length administered for 48 discrete antibiotics spanning 381 administrations (scores ranged from 0.00 to 86.63). Expected microbial community was compared with observed community.

Summary of Results

Higher antibiotic pressure negatively correlated with a lower proportion of the expected community type. Oral communities in individuals with a high antibiotic pressure were significantly different then in patients with lower antibiotic pressure. In oral samples, discharge pressure and in-between time point pressure differed (r=-0.48). This effect was not statistically significant in fecal communities.

Conclusions

The negative correlation between higher antibiotic pressure scores and the structure of the oral microbial communities may suggest that oral communities are more sensitive than fecal ones to stronger antibiotic pressure. Further research is needed to determine if antibiotic pressure is an important metric in understanding the antibiotic impact on dysbiosis in ICU patients or if critical illness itself is responsible for previously observed fecal dysbiosis in ICU.

Primary Student Presenter: Eitan Halper-Stromberg

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Russel Bowler

Poster Title: *Circulating Lymphocyte Sub-Populations Define Molecular Subtypes of COPD*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

Rationale: Chronic obstructive pulmonary disease (COPD) is associated with systemic inflammation and alterations in circulating immune cell populations. While many studies have reported COPD-associated alterations in CD4+/CD8+ ratio, there have been few comprehensive studies of alterations in circulating lymphocyte subpopulations in COPD. In addition, little is known about how cell type alterations relate to distinct subtypes of COPD. Cell type deconvolution methods can infer cell type proportions from genome-wide gene expression of tissue samples of mixed cellular composition, such as blood. These approaches enable a broader perspective on circulating immune cell alterations in large COPD cohorts with available blood gene expression data.

Objective: To study the relationship between circulating immune cell sub-populations in COPD and in molecular subtypes of COPD by applying cell-type deconvolution methods to genome-wide gene expression data from peripheral blood in smokers.

Methods: Using genome-wide microarray gene expression data from two cohorts of smokers enriched for COPD, we applied three cell-type deconvolution methods to gene expression data from 229 subjects from the ECLIPSE Study, and we validated our results in 135 subjects from the COPDGene Study. We evaluated our cell type deconvolution results using measured CBC data from the ECLIPSE subjects.

Results: Inferred cell type proportions were highly correlated with measured proportions of neutrophils and lymphocytes (r=0.75 and 0.76, respectively, $p<2.2 \times 10^{-16}$). Subjects with COPD had a lower proportion of CD4+ resting memory, activated natural killer, and naïve B cells compared to non-COPD smokers. COPD molecular subtypes determined by blood gene expression showed more pronounced alterations in these cell types and were also characterized by significant changes in helper T-regulatory cells, T-follicular cells, T-gamma-delta, and B memory cells ($p<0.05$).

Conclusion: Cell type deconvolution methods infer proportions of neutrophils and lymphocytes in smokers with reasonable accuracy. Analysis of inferred cell type proportions identified that the proportion of CD4+ cells, natural killer cells, and B-cells are associated with more severe forms of COPD. Previously reported COPD molecular subtypes are characterized by alterations in many lymphocyte sub-populations.

Primary Student Presenter: Brigit-Alexandra High

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD/PhD

Year: 1st

Mentor: Manisha Patel

Poster Title: *Selective Neuronal Vulnerability in SOD2 Deficient Mice*

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

Temporal lobe epilepsy (TLE), one of the most common types of epilepsy, is characterized by chronic, recurrent seizures. There is evidence demonstrating a relationship between seizures and mitochondrial dysfunction among patients with TLE. SOD2 is part of the family of superoxide dismutases responsible for catalyzing the conversion of superoxide to hydrogen peroxide within the mitochondria. Previous work demonstrated that neuronal-specific deletion of SOD2 in mice results in seizures and mitochondrial dysfunction culminating in death around 2 months of age. Here, we characterize neuronal loss and determine a time course of brain pathology in a SOD2-NexCre mouse model. We performed immunofluorescence staining and demonstrated that SOD2 deficiency, neuronal degeneration, and astrogliosis occur progressively throughout the short lifespan of these mice. Additionally, we characterized locomotion via rotarod testing and demonstrated motor impairment at both 3 weeks and 6 weeks of age. Taken together, the data suggest that neuronal-specific SOD2 deficiency results in progressive brain pathology from 3 to 6 weeks of age and persistent locomotor deficits.

Primary Student Presenter: Johnny Hoang

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Jeffrey Olson

Poster Title: *A Novel Approach to Treating Macular Degeneration with Polyacrylonitrile.*

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

A NOVEL APPROACH TO TREATING MACULAR DEGENERATION WITH POLYACRYLONITRILE. JM Hoang (M.D., SOM), JL Olson, and MG Pedler.

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly. There are two forms of the disease: non-exudative (dry) and exudative (wet). The wet form accounts for 10% of AMD and is characterized by choroidal neovascularization. The dry form accounts for 90% of cases, with 10-50% of those developing into the wet form. It is characterized by lipoprotein deposits called drusen that cause atrophy to the retinal pigment epithelium. The pathogenesis of dry AMD is unclear, and thus treatment options are limited. The alternative complement pathway has been implicated to play a role in dry AMD progression in previous studies, in particular complement factor D (CFD). The purpose of this study is to determine if polyacrylonitrile (PAN) membranes are capable of adsorbing CFD are biocompatible to prevent and treat dry AMD.

PAN fibers were incubated with CFD solution to demonstrate adsorption. CFD concentration in the remaining solution after incubation was analyzed using ELISA. Biocompatibility studies were initiated by inserting the PAN membranes into the vitreous cavity of Brown Norway Rats. Electroretinograms (ERGs) and histology were to be obtained to assess for any signs of retinal toxicity.

Incubation of CFD solution with PAN fibers led to significantly lower CFD concentration compared to controls. Biocompatibility studies are still pending. The baseline ERGs are normal and will be compared to final ERGs to determine if there is any retinal toxicity caused by the PAN fibers. Histology will be obtained to assess for any signs of inflammation and ocular damage.

We can conclude from this study that PAN membranes are capable of adsorbing CFD at high levels. Theoretically, this raises the possibility of utilizing PAN to prevent and treat dry AMD.

Primary Student Presenter: Monica Johnson

Additional Presenter(s): N/A

Presenting School: Pharmacy

Degree Seeking: PhD

Year: 6th

Mentor: Jared Brown

Poster Title: *Systems Biology Analysis Reveals Novel Non-Ige Mechanisms of Silver Nanoparticle-Induced Mast Cell Degranulation*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

SYSTEMS BIOLOGY ANALYSIS REVEALS NOVEL NON-IGE MECHANISMS OF SILVER NANOPARTICLE-INDUCED MAST CELL DEGRANULATION

Monica Johnson (Ph.D., Toxicology), Laura Saba, Jared M. Brown

Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO

   Mast cells represent a crucial cell type in host defense; however, maladaptive responses are contributing factors in the pathogenesis of allergic diseases. Previous work in our laboratory has shown that silver nanoparticle (AgNP) exposure causes mast cell degranulation via a non-immunoglobulin E (IgE) mechanism. In this study, we utilized a systems biology approach to identify novel genetic factors playing a role in AgNP-induced mast cell degranulation compared to the classical activation by antigen-mediated FcεRI crosslinking. Mast cell degranulation was assessed in bone marrow-derived mast cells (BMMCs) isolated from 23 strains of mice following AgNP and antigen-mediated (DNP) activation. Utilizing strain-dependent phenotype data, we performed a genome-wide association study (GWAS) using single nucleotide polymorphisms (SNPs) characterized in 23 strains of mice and identified 3 chromosomal regions that were significantly associated with mast cell degranulation by AgNP and one non-overlapping region associated with DNP-mediated degranulation. Two of the AgNP-associated regions (TRAC2 on chromosome 1 and TRAF6 on chromosome 2) correspond to genes previously reported to be associated with allergic disorders and a non-annotated gene identified on chromosome 1 (FAM126B) may contribute to mast cell degranulation. Second, we performed RNA-seq on mast cells from the high and low responder strains which revealed 3754 and 34 differentially expressed genes that were unique to DNP and AgNP exposures, respectively. Select candidate genes include a G-protein coupled receptor (PTGER4) and multifunctional adaptor protein (TXNIP) that may be driving mast cell degranulation by AgNP. Together, we identified novel target genes contributing to non- IgE mediated mast cell activation as potential therapeutic targets in the treatment of mast cell-linked disorders.

Primary Student Presenter: Wallace Jones

Additional Presenter(s): Nathaniel Dusto, William Silkworth

Presenting School: Medicine

Degree Seeking: MD

Year: 3rd

Mentor: Benzi Kluger

Poster Title: *Central Visual Oscillopsia: Case Report and Review*

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

Objective: The aim of this study was to present a case of central visual oscillopsia caused by traumatic brain injury, review current literature, and investigate whether repetitive Transcranial Magnetic Stimulation (rTMS) applied over primary visual cortex or area V5/MT could improve the oscillopsia.

Presentation of case: A 57-year old man suffers from visual oscillopsia due to a traumatic brain injury. Symptoms are presumed to have a central origin as the patient demonstrated normal eye movements and peripheral vestibular function and reported oscillopsia with visual imagery with eyes closed. Occipital lesions and/or damage to white matter connections were suspected to be the cause of the oscillopsia.

Review of the literature: Central oscillopsia without nystagmus or vestibular-ocular dysfunction is rarely reported in the literature. Proposed etiologies of reported cases include neuromyelitis optica spectrum disorder, stroke, arterial dissection, migraine without infarction, and psychological trauma.

Methods: rTMS was applied in successive rounds of therapy to visual area left V5/MT, bilaterally to visual area V5/MT, and bilaterally to visual area V1. Response to therapy was evaluated with static and dynamic visual acuity testing.

Results: The patient reported symptomatic improvement in large amplitude oscillations but stated that smaller amplitude oscillations were not affected.

Results from static and dynamic visual acuity testing suggest oscillopsia in this patient was refractory to rTMS.

Conclusions: The patient's symptomatic improvement was not reflected in dynamic visual acuity testing results. Oscillopsia without nystagmus or peripheral vestibular dysfunction may be refractory to rTMS therapy, or dynamic visual acuity testing may have failed to detect a treatment effect.

Primary Student Presenter: Kevin Kim

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Jason Hoppe

Poster Title: *A Comparison of Three Screening Tools for Aberrant Opioid Drug-Related Behavior in the Emergency Department*

Final Category: Education, Healthcare, and Public Health

Abstract:

A COMPARISON OF SCREENING TOOLS FOR ABERRANT OPIOID DRUG-RELATED BEHAVIOR IN THE EMERGENCY DEPARTMENT. K Kim (MS2), J Hoppe (DO), S Weiner (MD, MPH), E Kiemele (MS2) Department of Emergency Medicine, University of Colorado, Denver, CO; Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA.

   The recent rise in opioid related drug deaths has paralleled the increased availability of opioid analgesics (OA). OAs are commonly prescribed from the emergency department (ED). Sadly, ED physicians do not have the benefit of validated tools to identify patients at risk of aberrant opioid use. This project evaluated three validated, office based OA risk-screening tools in the ED: Screener and Opioid Assessment for Patients with Pain - Revised (SOAPP-R), Drug Abuse Screening Test (DAST-20) and Opioid Risk Tool (ORT).

   This observational study included a convenience sample of ED patients ≥18 years old with a painful condition in 2 academic hospitals for whom the clinician considered prescribing an OA. Prescription Drug Monitoring Program (PDMP) was accessed as part of routine care. The pre-defined at-risk scores for the screeners were analyzed relative to aberrant behavior, defined as ≥4 OA prescriptions and ≥4 different prescribers for scheduled medications in the prior 12-months.

   A total of 154 patients were approached and 121 patients were enrolled from two hospitals (109 from site A, 12 from site B). Median age of subjects was 35 years old (IQR: 27-48), 60% were female. Past OA use was reported by 68% (104/121) and 23% (28/121) reported opioid use within the past 7 days. SOAPP-R was the only significantly associated with identifying aberrant opioid behavior: OR 2.8 (95%CI 1.04-7.4), compared with ORT (OR 1.2 (95%CI 0.5-3.4)) and DAST-20 (OR 0.6 (95%CI 0.1-4.9). SOAPP-R had the highest sensitivity (SN) of 33% (95%CI 17-54%), specificity (SP) of 85% (95%CI 76-91% and positive predictive value (PPV) of 39% (95%CI 20-61%). ORT had SN 22% (95%CI 9-40%), SP 82% (95%CI 72-89%) and PPV 30% (95% CI 13-53%). DAST-20 had SN 10% (95%CI 1.0-37%, SP 79% (95%CI 69-86%) and PPV 8.7% (95% CI 1.1-28%) for aberrant OA related behavior.

Compared with DAST-20 and ORT, we found that SOAPP-R has superior test characteristics for detecting aberrant opioid drug-related behavior by PDMP criteria in ED patients where OA treatment was considered.

Primary Student Presenter: Janet Kim

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Marilyn Coors

Poster Title: *Adolescent Cannabis Use Disorder and Male Sex Predict Medical Cannabis Card Status in Young Adulthood*

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

ADOLESCENT CANNABIS USE DISORDER AND MALE SEX PREDICT MEDICAL CANNABIS CARD STATUS IN YOUNG ADULTHOOD. J Kim (MD., MS), JT Sakai, SE Young, K Raymond, CJ. Hopfer, TL. Wall, ME. Coors, University of Colorado School of Medicine, Denver CO, University of California San Diego, San Diego CA

   Purpose of Study: To examine if a substance use disorder (SUD), especially cannabis use disorder, and conduct disorder diagnosis in adolescence predict future medical cannabis card status. Methods: Data collection occurred in Denver and San Diego. We recruited adolescents, with or at high risk for SUD (hereafter probands) and their siblings (n=665). Baseline (Wave 1) assessments took place between 1999 and 2008, and follow-up (Wave 2) assessments took place between 2010 and 2013. In initial bivariate analyses, we examined whether cannabis abuse or dependence, other substance use disorders, and conduct disorder (along with other potential predictors) were associated with possessing a medical cannabis card in young adulthood. Significant predictors were then included in multiple regression analyses. Results: About 16% of the sample self-reported having a medicinal cannabis card at follow-up in young adulthood. Bivariate analyses demonstrated that: male sex, cannabis abuse or dependence, total number of SUD diagnoses, a higher number of cannabis SUD symptoms, conduct disorder, ADHD diagnosis, race and proband status significantly predicted Wave 2 medical cannabis card status. In multiple regression analyses, only cannabis abuse or dependence and male sex significantly predicted card status in young adulthood. Conclusions: Cannabis abuse/dependence and male sex positively predicted future medical cannabis card holder status among a high-risk sample of youths. Future cannabis policies should consider high-risk adolescent populations as they may be more impacted than the general population.

Primary Student Presenter: Alex Kretowicz

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Theodore Alkousakis

Poster Title: *Gender Differences Among Melanoma Prognostic Factors*

Final Category: Hematology and Oncology

Abstract:

GENDER DIFFERENCES AMONG MELANOMA PROGNOSTIC FACTORS

AM Kretowicz (M.D., SOM)1; JS Mounessa, BS1; T Braunberger, MD1; JV Caravaglio, BA3; BB Khallouq, MA4; K Wells, MD5; RP Dellavalle, MD, PhD, MSPH1; D Norris, MD1; T Alkousakis, MD1

University of Colorado School of Medicine, Department of Dermatology1.University of North Dakota School of Medicine, Department of Dermatology2. University of Central Florida College of Medicine, Department of Dermatology3.University of Central Florida College of Medicine, Department of Statistics4.University of Colorado School of Medicine, Department of Cutaneous Oncology5.

Over the last decade, the incidence of melanoma has steadily risen in the United States. Although studies have explored gender differences in the incidence and prognosis of melanoma, limited research on this topic exists. This study investigated gender differences in Breslow's depth, mitotic rate, ulceration, presence of metastases, and anatomic location of melanoma. Using data compiled from patient electronic medical records at UCH, this retrospective chart review study analyzed the categorical data using Pearson's Chi Square and Fisher's Exact Test. Age was analyzed using Independent t-test. Comparing the initial melanoma of men (N=644) and females (N=492), we found that men were five years older at time of diagnosis (mean age: 59 vs. 54, respectively; t (1134) = 5.116). Moreover, men were more likely to present with metastases (32% vs. 21%, respectively; odds ratio (OR) (confidence interval (CI)) = 0.589 (0.449-0.774)), ulceration (24% vs. 31% in males; OR (CI) = 0.731 (0.554-0.964)) and mitotic rates of 5.00-9.99mm2, 10.00-19.99mm2, and ≥20mm2 (11%, 6%, 3% and 15%, 12%, 4%, respectively). We further found significant differences in anatomical body sites, occurring greatest on the lower and upper extremities of women and on the head/neck and posterior trunk of men. The evidence presented here suggests males are more likely than females to present with more aggressive melanomas and later stage of disease, which can directly impact survival rates. Our study identifies gender differences in melanoma prognostic factors that clinicians may consider when screening their patients. Special attention to areas such as the head/neck and posterior trunk is needed in males versus the extremities in females. Increased efforts to educate on early detection of melanoma may decrease the risk of advanced stage disease in men.

Primary Student Presenter: Nazanin Kuseh Kalani Yazd

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 3rd

Mentor: Carol Stamm

Poster Title: *Physicians and Pharmacists on Over-The-Counter Contraceptive Access for Women*

Final Category: Education, Healthcare, and Public Health

Abstract:

PHYSICIANS AND PHARMACISTS ON OVER-THE-COUNTER CONTRACEPTIVE ACCESS FOR WOMEN

Recently, legislation has been proposed nationally to provide easier access to oral contraceptive pills. The proposed legislation entitled Allowing Greater Access to Safe and Effective Contraception Act seeks to allow "routine-use contraceptives" to be sold over-the-counter (OTC). This legislation would increase women's access to contraception; however, it could also increase out-of-pocket cost because the Affordable Care Act contraception provision only covers prescription contraception. Alternative legislation entitled Affordability Is Access Act requires health insurance to cover costs of oral contraception when it becomes OTC. California and Oregon have transitioned to allow access to oral contraception through pharmacist provision. Undeniably, political and healthcare leaders are investigating alternative methods of access to oral contraception. The goal of this study was to assess and compare the perceptions of Colorado physicians, pharmacists, and pharmacy technicians on OTC access to progestin-only oral contraception in order to identify specific concerns among health professionals to inform future policy and to guide effective provider education.

METHODS: A physician-specific survey was created for faculty physicians in internal medicine, family medicine, and obstetrics and gynecology at the University of Colorado School of Medicine and emailed to faculty members. A pharmacist and pharmacy technician specific survey was created for pharmacists and pharmacy technicians practicing in Denver County outpatient pharmacies. Two student researchers visited 74 randomly selected pharmacies on the list of Denver pharmacies, and they attempted to obtain responses from one pharmacist and one pharmacy technician at each site. Survey responses were compared among respondent groups using chi-square and Fisher's exact tests.

RESULTS: Responses were collected from 56 physicians, 58 pharmacists, and 43 pharmacy technicians. There was a statistically significant relationship between profession (physician, pharmacist, and pharmacy technician) and how confident the survey participant felt about patients correctly using the progestin-only contraception without prior consultation (p-value=0.0318). Surveyed physicians, pharmacists, and pharmacy technicians "somewhat agree" that OTC progestin-only contraception will have a positive impact on women's health (58.93%, 56.14%, and 41.64% respectively), and there was no statistically significant difference among groups (p-value=0.142). However, there was a significant

difference on top concern of OTC access of progestin-only contraception (p-value <0.001). The biggest concern of physicians was efficacy of progestin-only contraception (35.71%), while pharmacists and pharmacy technicians both responded that patient self-assessment of contraindications was their top concern, (35.09% and 23.82% respectively).

CONCLUSION: Our study has shown that there are differing views among healthcare professionals on OTC provision of progestin-only contraception. This study builds upon previous literature including the work of Daniel Grossman et. al that indicates that most women are able to self-assess for contraindications using simple checklists. Given recently proposed legislation, it is crucial to seek the perspectives of primary stakeholders, including physicians and pharmacists. Legislators should address the concerns of healthcare professionals before moving forward with OTC provision. While provider/physician prescribing is a barrier to contraceptive access and adherence, moving oral contraception to OTC status may create unforeseen barriers including removing insurance copays and increasing direct costs to women. Affordable prices, assured insurance reimbursement, and clear packaging may alleviate some concerns.

Primary Student Presenter: Dillon Le

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Aik-Choon Tan

Poster Title: *Developing A Computational Method for Drug Repurposing and Repositioning*

Final Category: Surgery, Cardiovascular and Other

Abstract:

Purpose:

To develop a novel computational method to predict drugs and drug combinations based on a query of gene lists, and to deploy a web interface that allows users to utilize this connectivity map in their research.

Methods:

Utilizing publicly available gene expression data obtained from the NCBI Gene Expression Omnibus (GEO), we collected human gene chip microarray data from different studies assessing drug treatment on various cell lines. We included data from three different microarray platforms: Affymetrix, Illumina, and Agilent. Gene chip series were selected based on availability of supplementary raw data. Within each series, we filtered samples that met the criteria of available drug treatment data, including cell line treated, drug name, dosage, and time treated. Cell lines with insufficient or absent data regarding treatment time and dosage were excluded. Samples that shared these criteria were aggregated into groups; aggregated treatment groups were thus compared to aggregated control groups. This data was then normalized on a Log2 scale to compare treatment versus control gene expression data.

After manually curating and normalizing the data, we developed Python scripts for inserting the data into the MySQL tables. We specifically used PyMySQL, which is a enables Python to execute MySQL statements.

Results:

From the three gene chip microarray platforms, we collected 599 series, of which there were 772 cell lines and 1978 unique compounds. Within these cell lines and compounds, 4480 comparisons of treatment versus control groups were made. This data is visually represented by a web site that queries and displays the MySQL database.

Conclusion:

We developed a novel database that represents a collection of gene sets based on drug-induced gene expression that can be used as a resource for gene set enrichment analyses. The website

implementation allows users to search and retrieve drug-induced gene expression data in a meaningful visual representation.

Primary Student Presenter: Jeffrey Lee

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Maria Albuja-Cruz

Poster Title: *Using Adenoma Weight and Volume to Predict Multigland Disease in Primary Hyperparathyroidism*

Final Category: Surgery, Cardiovascular and Other

Abstract:

USING ADENOMA WEIGHT AND VOLUME TO PREDICT MULTIGLAND DISEASE IN PRIMARY HYPERPARATHYROIDISM. J Lee (MD, SOM), MB Albuja-Cruz, C Burton, CD Raeburn, R McIntyre, University of Colorado School of Medicine, GI, Tumor, and Endocrine Surgery, Denver, CO.

Intraoperative parathyroid hormone (ioPTH) monitoring is the current gold standard for intraoperative determination of multi-gland disease (MGD) in patients with primary hyperparathyroidism (pHPT). The purpose of this study is to determine if the weight or volume of the first resected adenoma can serve as a reliable predictor of MGD.

Retrospective review of prospectively collected data of 469 consecutive patients who underwent initial parathyroidectomy for pHPT at a single tertiary medical center from January 2010 to June 2015 was performed. ioPTH monitoring was used in all cases and intraoperative cure was defined by a >50% drop of the preoperative PTH at 10 minutes after excision and a PTH value within normal limits. 185 patients met criteria for inclusion in this study. Data was analyzed for patient demographics, operative procedure, first resected adenoma weight and volume, presence of MGD, complications, cure, and persistent disease.

Of the 185 patients, 74% had a single adenoma and 26% had MGD. The mean weight for the single adenoma group was 846 mg compared to 461mg for the MGD group ($P < 0.05$). A weight of $\geq$ 200mg was used as a cutoff to distinguish a single adenoma from MGD (SEN 87%, SPE 28%, PPV 76%, NPV 45% and ACC 71%; $P = 0.73$). The mean volume for the single adenoma group was 1.12cm^3 compared to 0.56cm^3 for the MGD group ($P < 0.05$). A volume of $\geq$ 0.2cm3 was used as cutoff to differentiate a single adenoma from MGD (SEN 83%, SPE 35%, PPV 78%, NPV 44% and ACC 71%; $P = 0.82$).

The weight and volume of the first resected adenoma is not a reliable predictor of MGD in patients with pHPT. Surgeon judgment and ioPTH monitoring remains paramount in the operative management of this patient population.

Primary Student Presenter: Katie Mishall

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 4th

Mentor: Rebecca Schweppe

Poster Title: *Activation of the AKT/mTOR Pathway Promotes Resistance to the Src Inhibitor, Dasatinib*

Final Category: Hematology and Oncology

Abstract:

Our lab has shown Src is a key mediator of tumorigenesis in thyroid cancer. However, Src inhibitors have limited efficacy in the clinic. To more effectively target Src, our lab generated 4 thyroid cancer cell lines resistant to dasatinib (Beadnell, 2016). We have shown the dasatinib-resistant (DasRes) cells are also resistant to saracatinib, but sensitive to the Src inhibitor bosutinib, suggesting unique off-targets of bosutinib play an important role in mediating dasatinib resistance. We used compound centric chemical proteomics to identify bosutinib specific kinases (BSKs). Using the STRING database we identified mTOR as a potential network breaker among the BSKs.

Treatment with the AKT/p70S6 inhibitor, AT7867, or the mTOR inhibitor, everolimus, inhibited growth of control and DasRes cells. Interestingly, maintaining the DasRes cells in dasatinib increased the sensitivity to AT7867 3-8 fold, but did not affect sensitivity to everolimus. Accordingly, immunoblot analysis showed that sensitivity to the combination of AT7867 and dasatinib completely inhibited S6 ribosomal protein, while single agent treatment only partially inhibited S6. Single agent mTOR inhibition with everolimus was sufficient to shut down S6, correlating with no increase in sensitivity when the DasRes cells are maintained in dasatinib. Increased activation of AKT and ERK was observed in response to everolimus or AT7867 treatment, suggesting that inhibition of this pathway promotes a feedback loop to try to activate the MAPK pathway. Thus, combinatorial inhibition of AKT/mTOR and MAPK pathways may be the most effective way to overcome dasatinib resistance.

These results indicate that activation of S6 may be a biomarker of Src inhibitor resistance, and provides important information on how targeting different components of the AKT/mTOR pathway affect bypass signaling mechanisms in DasRes cells.

Primary Student Presenter: Angela Mitchell

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 5th

Mentor: Andrew Fontenot

Poster Title: *CD4+ T Cell Receptor Repertoire in Sarcoidosis Patients*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

CD4+ T CELL RECEPTOR REPERTOIRE IN SARCOIDOSIS PATIENTS. AM Mitchell (PhD, GS)1, Y Kaiser2, MT Falta1, J Grunewald2, AP Fontenot1, 1University of Colorado, Denver, CO; 2Karolinska University Hospital, Stockholm, Sweden.

Sarcoidosis is a multisystem disorder which most commonly affects the lungs and involves granuloma formation and the accumulation of CD4+ T cells at the sites of disease. The etiology of the disease is unknown, and the lack of a known antigen has hindered the study of disease pathogenesis. However, there is considerable evidence that CD4+ T cells are involved in the initiation and perpetuation of sarcoidosis. Previous work by our lab and others has demonstrated that particular T cell clones within the bronchoalveolar lavage (BAL) are preferentially expanded in patients with sarcoidosis. These oligoclonal T cell populations accumulate within the lung and disappear with disease resolution. Correlations have been observed between the expansions of CD4+ T cells expressing the T cell receptor (TCR) α-chain variable (V) region Vα2.3 and the presence of the HLA-DRB1*0301 (DR3) allele in sarcoidosis patients. We hypothesize that sarcoidosis-specific CD4+ T cells accumulate and expand in the lungs of sarcoidosis patients in response to a specific antigen. To determine whether these expanded CD4+ T cell clones play a pathogenic role in disease progression, as well as to address their antigen specificity, the TCRs of these clones have been identified utilizing iRepertoire analysis and a novel technique known as emulsion PCR. HLA-DR3+ sarcoidosis patients had expansions of CD4+ T cells utilizing Vα2.3 and Vβ22.1. In addition, CDR3 motifs were found exclusively in HLA-DR3+ sarcoidosis patients (the motifs were not found in DR3- or DR3+ healthy control patients), suggesting a public TCR repertoire in this subset of patients. These TCRs will be cloned into murine hybridoma cells to determine the disease-initiating antigens that drive sarcoidosis.

Primary Student Presenter: Michelle Nelsen

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 7th

Mentor: Ronald Gill

Poster Title: *Innate Immune Stimulation Contributes to T-Cell Resistance to Tolerance and Pancreatic Islet Allograft Rejection*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

INNATE IMMUNE STIMULATION CONTRIBUTES TO T-CELL RESISTANCE TO TOLERANCE AND PANCREATIC ISLET ALLOGRAFT REJECTION. MK Nelsen (Ph.D., GS), KS Beard, A McMahon, R Kedl, and RG Gill, Department of Immunology & Microbiology, University of Colorado Anschutz Medical Campus, Aurora, CO.

   Even with intensive insulin therapy, type 1 diabetics often cannot control their blood glucose. Better disease management can be achieved through transplantation of insulin-producing pancreatic islet cells. However, islet transplants can be rejected by the immune system, so recipients must be treated with immune suppressive drugs. The drugs can have substantial long-term toxicity, so a preferable alternative is to induce immune tolerance. Durable donor-specific tolerance can develop after brief treatment with tolerance-promoting agents, but as host tolerance to the islet graft evolves, the process is vulnerable to disruption by microbial infections. This susceptibility may be due either to innate immune stimulation driven by pathogen-associated molecular patterns, or to interference from pathogen-specific memory T cells. In this study, we sought to determine which immune response is a greater barrier to allograft tolerance. We modeled pathogen exposure through host immunization with egg-white protein (ovalbumin) and an innate immune stimulant (adjuvant) that mimics the inflammation induced from viral infection. Our results indicate that only innate immune stimulation triggers rapid islet allograft rejection despite treatment with tolerance-promoting therapies. Importantly, this disruption of tolerance is time-dependent: Early (day 2 post-transplant) but not late (day 60) adjuvant treatment inhibits tolerance. T-cell bioassays show that the adjuvant blocks the therapy's initial restraint of graft-reactive T cells. Thus, innate immune stimulation impairs the early outcome of graft-reactive cells, inducing immunity rather than tolerance following treatment with tolerance-promoting agents.

Primary Student Presenter: Caroline Nguyen

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Eoin McNamee

Poster Title: *Small molecule inhibition of the chemokine receptor CXCR3 attenuates experimental Crohn's disease*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

CHARACTERIZING CXCR3 IN INFLAMMATORY BOWEL DISEASE: SMALL MOLECULE INHIBITION OF CXCR3 ATTENUATES EXPERIMENTAL MODEL OF CROHN'S DISEASE. CN Nguyen (MD, SOM) O Jensen, P Jedlicka, ME Gerich, FR Byrne, EN McNamee. Mucosal Inflammation Program, School of Medicine, University of Colorado, Denver, CO.

Inflammatory bowel disease (IBD) is a group of disorders characterized by idiopathic chronic inflammation of the intestine. Though IBD affects millions of individuals in the US and is responsible for billions of health care dollars, there is very limited treatment and no cure for the disease. Previous investigators have implicated the importance of the chemokine receptor CXCR3 in the propagation of IBD, as evidenced by the increased expression of its ligands in diseased tissue. Our work aims to discover the expression profile of CXCR3 and its ligands CXCL9, CXCL10, and CXCL11 and whether a small molecule inhibitor of CXCR3, AM487, can attenuate the murine model of Crohn's disease, a subset of IBD.

Mice to be treated with the small molecule inhibitor received once daily subcutaneous injections of the drug for 10 days. Real time PCR, flow cytometry, ELISA, FACs sorting, and histology were used to evaluate the expression profile of CXCR3 and its ligands, the cytokine phenotype of the cells expressing CXCR3, and the extent of disease.

CXCR3 is expressed preferentially by inflammatory T cells in the gut, and these CXCR3+ T cells, and its ligands, are significantly increased in disease, at the site of inflammation. The small molecule inhibitor AM487 is capable of attenuating the severity of disease in the murine model of Crohn's disease.

CXCR3+ T cells play an important role in potentiating inflammation in the gut. Better understanding of its expression profile will allow for more specific and effective methods of treating Crohn's disease. We show that small molecule inhibition of CXCR3 is capable of mitigating disease severity in our model of IBD.

Primary Student Presenter: Phuong Nguyen

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Brian Berman

Poster Title: *Interaction Between the Basal Ganglia and the Cerebellar Circuits in Parkinsonian Resting Tremor*

Final Category: Neuroscience--Brain, Behavior, and Vision

Abstract:

INTERACTION BETWEEN THE BASAL GANGLIA AND THE CEREBELLAR CIRCUITS IN PARKINSONIAN RESTING TREMOR. P Nguyen (M.D., SOM), E Shelton, and B Berman, Department of Neurology, University of Colorado, Denver, CO.

Parkinson disease is characterized by the depletion of dopamine in the basal ganglia. However, this pathologic hallmark alone can not account for resting tremor, a prominent symptom of the disease. The role of the cerebellar circuit and its interaction with the basal ganglia have been indicated in the pathophysiology of resting tremor. This study is aimed to determine the distinct contribution of the basal ganglia and the cerebellar circuits in generating resting tremor.

Concurrent surface EMG and BOLD fMRI data were collected from 24 PD patients in resting state to determine the brain activity covarying with the tremor. The EMG waveform was processed to extract its amplitude at the peak tremor frequency. Temporal derivative of EMG data was calculated to represent tremor onset and offset. Tremor amplitude and tremor onset/offset were then correlated with fMRI signal.

Preliminary data shows different patterns of brain activity corresponding to tremor amplitude and to tremor onset/offset, with some degree of overlapping. With both tremor amplitude and tremor onset/offset, brain activation is seen predominantly in the contralateral motor cortex and thalamus, and ipsilateral cerebellum. However, tremor onset/offset is also correlated with activation of the globus pallidus (part of the basal ganglia).

Activation of the cerebellum, correlated with both tremor amplitude and tremor onset/offset, indicates the involvement of the cerebellar circuit. Activation of the pallidal part of the basal ganglia is associated with tremor onset/offset but not tremor amplitude, suggesting its role in initiating tremor, but not in driving it. This result is in agreement with a single prior study. Analysis at the population level will be done to strengthen this finding.

Primary Student Presenter: Molly Nowels

Additional Presenter(s): N/A

Presenting School: Public Health

Degree Seeking: MS

Year: 3rd

Mentor: David Nowels

Poster Title: *Healthcare System Interactions Influence Engagement in Advance Care Planning in Developed Countries*

Final Category: Education, Healthcare, and Public Health

Abstract:

Background: Many factors may influence individuals' participation in advance care planning (ACP). The potential impact of access to high quality primary care on ACP is unknown, especially given healthcare systems variability across countries.

Objective: To explore individual and healthcare system-based factors associated with ACP across 11 developed countries.

Research Design: Analysis of 2014 Commonwealth Fund International Health Policy Survey of adults aged 55 and older in 11 developed countries with a multilevel Poisson regression model.

Measures: Self-reported completion of at least one of three indicators of ACP (having discussed treatment preferences, documentation of healthcare wishes, or documenting a surrogate decision maker), socio-demographic variables, and a composite index of access to quality primary care.

Results: 13,409 (53%) respondents (N=25,530) reported any ACP. Those who participated in ACP had a higher multi-morbidity (1.6 vs 1.2), were more likely to be a caregiver (21% vs 19%), and were less likely to be men (38% vs 48%, p<0.001). Those with ACP were also more likely to have had an inpatient hospitalization (26% vs 20%) and emergency department visit (35% vs 28%) in the past 2 years (p <0.001). Multilevel Poisson regression (N=25,486) showed that hospitalization (rate ratio [RR]1.18), multimorbidity (RR 1.16), informal caregiving (RR 1.13), education level (RR 1.14), access to quality primary care (RR 1.16), ED visits (RR 1.04), and income (RR 1.06) were positive predictors of participating in ACP. Male sex (RR 0.85) and higher perceived health status (RR 0.96) were negative predictors.

Conclusions: In this international study, we found that multiple socio-demographic and healthcare utilization factors predict completion of ACP. Individuals with greater interaction with the healthcare system through hospitalization, multimorbidity, and caregiving were more likely to have completed ACP. Access to quality primary care was positively associated with ACP, albeit not strongly.

Primary Student Presenter: Bryan Nycz

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Daniel Frank

Poster Title: *Evaluation of Clostridium difficile Infections, Bloodstream Infections, and the Microbiome in Pediatric Oncology Patients*

Final Category: Pediatrics

Abstract:

Development of bloodstream infections (BSI) and Clostridium difficile infections (CDI) in pediatric populations with underlying malignancies are frequent complications associated with significant morbidity and mortality. The relationship between the development of these infections and changes in the gastrointestinal microbiome have not been studied in great detail. The purpose of this study was to explore possible associations between microbiome composition and the development of BSI and CDI in a small, convenient cohort of pediatric oncology patients. As part of a CDI outbreak investigation, stool samples were collected from all patients admitted to the pediatric oncology floor from Oct – Dec 2012. Stool samples were tested for the C. difficile toxin B gene by PCR. Bacterial profiles from patient stools were determined by broad-range PCR of bacterial 16S rRNA genes and phylogenetic sequence analysis. Differences in microbiome composition were assessed by a non-parametric multivariate analysis of variance (PERMANOVA) test using the Bray-Curtis index to assess microbiome dissimilarity. Differences in the relative abundances of specific taxa were tested using a Wilcoxon rank based test. At admission, 9 of 42 patients (21%) were colonized with C. difficile, and 24% (n=10) previously had or developed a BSI. In a univariable analysis, differences in overall microbiome composition were significantly associated with cancer type ($p < 0.008$), reason for admission or admission type ($p < 0.05$), subsequent BSI ($p < 0.001$), and subsequent CDI ($p < 0.04$). Within this pediatric population, our results suggest that differences in microbiome composition may be predictive of subsequent bloodstream and C. difficile infections. A prospective study is required to further explore these relationships.

Primary Student Presenter: Zoe O'Donoghue

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 3rd

Mentor: Jeffrey Kieft

Poster Title: *Exploration and Characterization of Disease Associated RNA Structures in Flaviviruses*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

EXPLORATION AND CHARACTERIZATION OF DISEASE ASSOCIATED RNA STRUCTURES IN FLAVIVIRUSES

O'Donoghue, Z. G. (Ph.D. G.S.), MacFadden, A. R., and Kieft, J.S.

Department of Biochemistry & Molecular Genetics, University of Colorado Anschutz Medical Campus

Flaviviruses like Dengue, Zika, and West Nile infect millions of people every year, making them prominent global health threats. Broadly speaking, the family flaviviridae contains viruses that are vector borne & enveloped, and have positive sense, single stranded RNA genomes. Throughout infection viral replication produces large quantities of genomic RNA, but the accumulation of smaller regions of the highly structured viral 3'UTR is also observed. These subgenomic Flaviviral RNAs (sfRNAs) are made via incomplete degradation of the viral genome by the host 5' to 3' exonuclease Xrn1, and previous studies show that sfRNA formation is dependent upon the presence of highly structured and conserved regions of the 3'UTR called Xrn1 resistant RNAs (xrRNAs). sfRNAs have been shown to be necessary for both cytopathicity and pathogenicity during WNV infection. Using a reconstituted in vitro study system, we have been able to demonstrate that several alternate members of the flaviviridae family, including Murray Valley Encephalitis (MVEV), Modoc (MODV), Montana Myotis Leukoencephalitis (MMLV), Cell Fusing Agent (CFAV), and Tick Borne Encephalitis (TBEV) viruses, also produce sfRNAs following Xrn1 degradation. This observation carries implications for a generalized role for sfRNAs during flavivirus infections and currently we are working to more fully characterize the location(s) of enzyme halting in these alternate virus 3' UTRs. Additionally, we have found that the halt sites in the 3'UTR of WNV are capable of stopping other enzymes as well, including bacterial enzyme RNase J1. Future studies will shift to include infection models and manipulations of xrRNAs in the Dengue Virus 3'UTR to explore the structure and mechanisms of sfRNA function during infection in both mosquito vector and vertebrate host models.

Primary Student Presenter: Danielle Ostendorf

Additional Presenter(s): N/A

Presenting School: Public Health

Degree Seeking: PhD

Year: 4th

Mentor: Victoria Catenacci

Poster Title: *Association Between Baseline Fitness and Exercise Adherence*

Final Category: Education, Healthcare, and Public Health

Abstract:

ASSOCIATION BETWEEN BASELINE FITNESS AND EXERCISE ADHERENCE: DM Ostendorf (Ph.D., EPI), Z Pan, SA Creasy, E Seyoum, K Bing, LT Wayland, EL Melanson, and VA Catenacci, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

Few studies have examined the relationship between baseline fitness and exercise adherence in adults with overweight/obesity during a comprehensive behavioral weight loss program (BWLP). Our aim was to examine the association between baseline fitness and exercise adherence during a 26-week supervised exercise program. The 26-week supervised exercise intervention consisted of moderate intensity exercise (65-75% max HR), 3 supervised sessions/week, progressing from 20 to 60 min/session by week 13. Baseline fitness (VO2 max) was categorized based on age and sex norms. Logistic regression was used to examine the association between baseline fitness and a) attrition and b) exercise adherence (attended ≥80% of supervised sessions). The association with adherence was assessed over the entire program (weeks 1-26) and during discrete intervals (weeks 1-4, 5-8, 9-14, 15-20, and 21-26). 69 participants (BMI 41±9.7 kg/m2, age 34±3.8 years, 87% female) were enrolled in the BWLP. Participants were classified based on baseline fitness level: 29% very poor, 48% poor, 19% fair, 3% good, and 1% superior. 78% (n=54) completed the 26-week supervised exercise intervention. Baseline fitness category was not associated with attrition, nor was it associated with adherence over the entire program (weeks 1-26) or at weeks 1-4, 5-8, 9-14, and 15-20. However, there was a positive association between baseline fitness category and adherence during weeks 21-26. Participants categorized as poor or above were 9.4 times more likely to attend ≥80% supervised sessions as compared to those categorized as very poor (95%CI: 1.1-78.5; p=0.039). Baseline fitness levels in our study population were surprisingly low. Those starting an exercise program with very poor fitness may struggle with adherence over time as the exercise volume reaches higher levels and may require more coaching during this phase of the program.

Primary Student Presenter: Daniel Paz de Araujo

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Robert Meguid

Poster Title: *Preoperative Capture of American Society of Anesthesiology Class and Functional Health Status for the Surgical Risk Preoperative Assessment System*

Final Category: Surgery, Cardiovascular and Other

Abstract:

PREOPERATIVE CAPTURE OF AMERICAN SOCIETY OF ANESTHESIOLOGY CLASS AND FUNCTIONAL HEALTH STATUS FOR THE SURGICAL RISK PREOPERATIVE ASSESSMENT SYSTEM. DN Paz de Araujo (MD, SOM), JS Holtrop, MR Bronsert, KE Hammermeister, WG Henderson, RA Meguid, Department of Surgery, University of Colorado, Denver, CO.

This study seeks to develop novel methods for preoperative capture of American Society of Anesthesiology Physical Status Classification (ASA) and American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Functional Health Status (FHS) allowing use in the Surgical Risk Preoperative Assessment System (SURPAS). SURPAS is a surgical risk prediction system that utilizes 8 preoperative variables (including FHS and ASA) to predict risk of 8 clinically meaningful postoperative outcome clusters. ASA Class is a metric that assesses the health status of patients prior to surgery while FHS is a metric that assesses the independence of patients prior to surgery. ASA class and FHS are not routinely assigned by surgeons in the preoperative clinic visit limiting their use with SURPAS which limits the system's utility for guiding patient/provider decision making, informed consent, and preoperative interventions. This study uses focus groups with anesthesiologists and ACS NSQIP surgical clinical reviewers to develop guidelines for surgeons to make ACS and FHS determinations. Patient cases from the ACS NSQIP dataset representative of a variety of ASA/FHS determinations will be assigned a consensus ASA class and FHS by anesthesiologists and surgical clinical reviewers. By asking surgeons to then make ASA and FHS determinations with these cases we will demonstrate surgeons can be trained to consistently assign ASA/FHS with a high degree of concordance with the clinicians that traditionally assign these scores as an important step to bringing SURPAS into clinical use. This study is on-going and will report results at the Annual Student Research Forum.

Primary Student Presenter: Tuong Phan

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 3rd

Mentor: Lynn Vanderweilen

Poster Title: *Student Run Free Clinic Volunteer Attitudes on Interprofessional Care*

Final Category: Education, Healthcare, and Public Health

Abstract:

STUDENT RUN FREE CLINIC VOLUNTEER ATTITUDES ON INTERPROFESSIONAL CARE. T Phan (MD, SOM), M Baliga, J To, S Gordon, D Hecht, A Stahly, K Mader, J Johnson, L Vanderweilen, University of Colorado, Denver, CO.

   Student run free clinics (SRFCs) offer health services to underserved communities and unique education opportunities to students. Literature regarding the impact of volunteering at an SRFC on student attitudes is limited. We aimed to assess student volunteers' attitudes towards interprofessionalism at our local SRFC, the DAWN Clinic in Aurora, CO. DAWN is open two nights a week and staffed by students of various health professions with preceptor supervision. The clinic sees an average of 12 patients a night and offers flu shots, health education classes, and specialty consults (e.g. ophthalmology). DAWN sees a population that is 66.9% Hispanic, 19.3% Black, and 8.7% White and 93% of patients are uninsured. Student volunteers were surveyed before volunteering at DAWN and again after having volunteered for 1 year. Surveys were administered through RedCap from March 2015 to August 2016 and participation was anonymous and voluntary. Questions were adapted from the Readiness for Interprofessional Learning Scale, Student Perceptions of Interprofessional Clinical Education Revised, and Medical Student Attitudes Toward the Underserved surveys. 26 volunteers participated and following a year of service at DAWN, volunteers agreed or strongly agreed that learning with other students and professionals will make them more effective members of a health and social care team (p = 0.04). Volunteers also agreed or strongly agreed that trust and respect are required for successful small-group learning (p = 0.02). In conclusion, SRFCs positively impact student attitudes towards other professions and towards interprofessional care. Future work includes assessing the attitudes of a larger cohort of volunteers and also assessing their attitudes on underserved and primary care.

Primary Student Presenter: Howe Qiu

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Robert Meguid

Poster Title: *Understanding Attitudes Towards and Techniques of Preoperative Risk Asessment*

Final Category: Surgery, Cardiovascular and Other

Abstract:

Purpose of Study: Surgical risk is an integral component of informed consent and shared decision-making between physicians and patients. While current literature indicates the importance of shared-decision making as a factor in building a trusting patient-physician relationship, there are no published standards for surgical preoperative risk assessment. Risk assessment ranges from a "best guess" on likelihood of outcomes by the surgeon, to citation of literature on risk associated with specific procedures, to use of formal online risk assessment tools characterizing individual patient outcomes based on their specific risk factors. This study aims to understand the current trend in assessment of preoperative surgical risk values among surgeons.

Methods Used: In order to understand attitudes towards and techniques of surgical risk assessment utilized in current practice, a survey was designed for administration to surgeons. The survey has 20 questions, and will be administered to up to 200 surgical faculty at the University of Colorado School of Medicine. In addition to understanding the current attitudes towards surgical risk assessment, data from this survey will be used to optimize a formal surgical risk assessment tool currently being developed, to facilitate implementation and utilization.

Primary Student Presenter: Thomas Rogers

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 5th

Mentor: Jennifer Richer

Poster Title: *Loss of miR-200c Regulates Tryptophan Catabolism in Triple-Negative Breast Cancer*

Final Category: Hematology and Oncology

Abstract:

Background: Epithelial to mesenchymal transition (EMT) is utilized by carcinoma cells to facilitate metastasis. The microRNA-200 family are potent suppressors of EMT, and loss of miR-200 contributes to the aggressiveness of triple-negative breast cancer (TNBC). Increasing evidence supports a tumor promotional role of the tryptophan catabolism pathway in many solid tumor types, including breast cancer. Tryptophan-2,3-dioxygenase (TDO2) is a rate-limiting enzyme that catabolizes tryptophan into kynurenine (Kyn). Kyn promotes metastasis and immune suppression. We reported that TDO2 is highly expressed in TNBC, and is further upregulated in forced suspension, leading to increased intracellular and secreted Kyn. Kyn activates the aryl hydrocarbon receptor (AhR) in cancer cells via an autocrine loop promoting metastasis by providing a survival signal for tumor cells in transit. We hypothesize that TDO2 is regulated both at the transcriptional level by NFkB and the post-transcriptional level by miR-200c and that TDO2 is inappropriately allowed to be expressed as consequence of miR-200c loss in TNBC.

Methods and Results: Restoration of miR-200c to TNBC cells via miRNA mimics or a doxycycline-inducible vector, significantly decreased TDO2 mRNA and protein. Further, miR-200c decreased activity of a luciferase reporter containing the 3'UTR of TDO2 containing the predicted miR-200c binding site (P<0.01). Restoring miR-200c also reduced intracellular and secreted Kyn (P<0.01), as measured by UPLC-MS. This decrease in Kyn reduced AhR transcriptional activity (P<0.01), as measured by AhR luciferase reporter activity.

Conclusions: We identify a novel mechanism of TDO2 regulation through targeting by miR-200c. Loss of miR-200c during breast cancer progression may lead to upregulation of TDO2 and subsequent increase in Kyn production, contributing to the ability of TNBC to survive anchorage-independent conditions, suppress the immune system, and rapidly metastasize.

Primary Student Presenter: Eric Sasine

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Kathrin Bernt

Poster Title: *RNF20 Overexpression May Confer Chemotherapy Resistance in Acute Lymphoblastic Leukemia*

Final Category: Hematology and Oncology

Abstract:

RNF20 OVEREXPRESSION MAY CONFER CHEMOTHERAPY RESISTANCE IN ACUTE LYMPHOBLASTIC LEUKEMIA

E Sasine, G South, MD, and K Bernt, MD

University of Colorado, Department of Pediatrics, Hematology/Oncology/BMT

Study Purpose: Although there have been advances in the treatment of pediatric acute lymphoblastic leukemia (ALL), relapsed ALL remains a top cause of childhood mortality. Cancer is the second-leading cause of death in children 1 to 14, and leukemia causes the most cancer deaths. There is thus an urgent need to identify pediatric ALL drug targets.

More than 60% of relapsed ALL presents with mutations in epigenetic genes. This prompted us to subject ALL samples to paired diagnosis and relapse histone profiling by mass spectrometry. One pair showed loss of H3K79 monomethylation and increased dimethylation at relapse. Histone dimethylation requires ubiquitination of H2B. Transcriptome analysis of this sample revealed increased expression of the H2B ubiquitin ligase RNF20 at relapse, suggesting that increased RNF20 expression causes drug resistance. RNF20 has previously been shown to be required in MLL-rearranged leukemias. This sample lacked MLL rearrangement, pointing to a generalizable mechanism.

We hypothesize that overexpression of RNF20 confers chemotherapy resistance in ALL. If true, this would support the development of RNF20 inhibitors in non-MLL-rearranged ALL.

Methods: Lentiviral vectors with RNF20-GFP and empty-GFP (for control) were transduced into ALL cell lines. Following transduction. Upregulation of RNF20, H2B-ub, and H3K79me2 in experimental cells was verified by Western blot. Growth rate and chemotherapy response were compared between cell groups.

Results: We have created the experimental and control viruses and are now transducing the viruses into ALL cells.

Conclusions: Should our data demonstrate that RNF20 overexpression confers chemotherapy resistance in ALL cells, this would support the development of RNF20 inhibitors for ALL therapy.

Primary Student Presenter: Taylor Soderborg

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: MD/PhD

Year: 5th

Mentor: Jed Friedman

Poster Title: *Maternal Obesity and Gestational Diabetes Alters 2 Week Human Infant Microbiome and Drives Metabolic Processes in Germ-Free Mice*

Final Category: Pediatrics

Abstract:

Maternal Obesity and Gestational Diabetes Alters 2 Week Human Infant Microbiome and Drives Metabolic Processes in Germ-Free Mice

T. Soderborg, D. Lemas, K. Kuhn, A. D'alessandro, D. Frank, R. Janssen, B. de la Houssaye, L. Barbour, K. El kasmi, J. Friedman.

Background: We hypothesized that a critical component of non-alcoholic fatty liver disease (NAFLD) risk is maternal influence on infant gut microbiome (MB) colonization. **Objective:** 1. Characterize the MB from 2wk infants born to normal weight (NW) or obese mothers (Ob) 2. Characterize phenotype differences between germ-free mice (GFM) colonized with the infant NW MB or Ob + gestational diabetes mellitus (GDM) MB. **Methods:** GFM were orally inoculated with pooled stool samples from 2wk infants born to NW or Ob/GDM mothers and colonized for 21d. **Results:** MB from infants born to Ob mothers had a significant reduction in pioneering γ-proteobacteria (P=0.03) and a trend for elevated short-chain fatty acids (P<0.06). Mice colonized with Ob/GDM MB had no difference in food intake or weight gain, but a trend for increased fat mass (P<0.09), suggesting a shift in energy storage. The Ob/GDM MB increased liver ER stress XBP-spliced (P<0.01), Ppara (P=0.04), Pparg1/2 (P=0.006) expressions, and a trend for elevated hepatic portal vein (HPV) insulin (P=0.09), perhaps a compensatory response to hepatic inflammation. The Ob/GDM MB reduced liver T regulatory cells (P=0.04), concomitant with MB induced inflammation. Lastly, Ob/GDM MB significantly increased liver expression of bile acid (BA) synthesis rate limiting enzymes Cyp7a1 (P=0.02) and Cyp8b1 (P=0.04), BA receptor Fxr (P=0.05), and secondary BA deoxycholic acid in the HPV (P=0.01), suggesting that Ob/GDM MB alters BA metabolism. **Conclusion:** This is the first evidence that early MB changes due to maternal Ob/GDM may affect liver metabolism and immunity through alteration of gut-derived signals that act on the liver, contributing to NAFLD risk during a susceptible life period.

Primary Student Presenter: Christina Spandler

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 2nd

Mentor: Ravi Mahalingam Ph. D.

Poster Title: *Development of Recombinant VZV Containing Regulatable CRISPR-CAS9*

Final Category: Microbiology, Immunity, and Autoimmunity

Abstract:

Authors: Christina Spandler and Ravi Mahalingam Ph. D.

Institutional affiliations: University of Colorado School of Medicine-Department of Neurology

Purpose of study: Primary Varicella Zoster Virus (VZV) causes varicella (chickenpox) and becomes latent in the trigeminal and dorsal root ganglia and reactivates decades later to produce zoster (shingles) in the elderly. The VZV vaccine uses a live attenuated virus that also becomes latent and can reactivate later on in the life and cause shingles and associated serious neurological complications. VZV affects more than 1 million people in the U.S. annually. The goal of this project is to control the expression of genes necessary for host reinfection by using the Crispr-Cas9 system. We will use the Cas-9 protein and guide RNA sequence to edit the VZV genome, specifically VZV open reading frame (ORF) 63 which is present as duplicate copy in ORF70. Expression of ORF63/70 is necessary for virus replication, and without them the virus cannot reactivate to produce Shingles. By using the CRISPR-Cas9 system to edit the latent VZV genome in the host, we can control the expression of genes essential for virus reinfection. This study will be used as the basis for future studies aimed at preventing Shingles.

Methods used: 1. Prepare a CRISPR-Cas9 expression vector in which sequence encoding Cas9 is fused to destabilization domain, (rendering the stability of the protein dependent on the common antibiotic trimethoprim), and recombine the modified CRISPR-cas9 sequences into VZV genome. The guide RNA will be driven by the human U6 promoter and Cas9 expression will be driven by VZV IE63/70 promoter.

2. Test the efficiency of editing VZV genomes in VZV-infected cells using mutant VZV expressing VZV-specific gRNA.

Summary of results: Briefly describe the details of what you have done till now. The destabilization domain has been cloned into the N-terminus and C-terminus of Cas9. These clones were characterized using DNA sequencing and Cas9 was found to be in reading frame. We successfully transfected Cas9 into Kidney epithelial cells (Vero cells) and detected the presence of Cas9 by western blot.

Conclusion: After we recombine these clones and gRNA for ORF 63/70 into the VZV genome we hope to see that genes necessary for host reinfection can be controlled by Cas9 in a regulatable dose dependent manner using TMP.

Primary Student Presenter: Eline van den Broek

Additional Presenter(s): N/A

Presenting School: Public Health

Degree Seeking: PhD

Year: 3rd

Mentor: Adam Atherly

Poster Title: *The Effect of Restrictions on Provider Access in Health Plans on Total Health Care Expenditure*

Final Category: Education, Healthcare, and Public Health

Abstract:

Purpose of Study

The objective of this study is to estimate the effect of restricted network health insurance designs on total health care spending. Restricted network plans have proven popular on the health insurance exchanges. Numerous recent policy proposals have been advanced to regulate network design without a clear understanding of the impact of restricted networks on health care spending.

Methods Used

Using a two stage residual inclusion instrumental variable approach, the unconditional total health expenditures are estimated using a generalized linear model with log link. A modified park test established gamma family for the variance distribution. The validity of the instrument was tested using two stage least squares regression using the log of total expenditure. The results of the exogenous GLM model were compared to the estimates of the endogenous two part model, estimating total conditional expenditures.

Data were drawn from the Medical Expenditure Panel Survey 2013 full year consolidated and medical condition files, a nationally representative survey. The study sample excluded individuals under age 18 and above 64; the uninsured and those enrolled in public plans.

Summary of Results

We found that enrollees of plans that cover care outside the network have $426.53 (12.8%) higher predicted total expenditures than those in plans with closed networks. Results from the IV-GLM and the endogenous two part models vary both in magnitude and significance. The effect is not significantly different among patients with various chronic and acute conditions. The study findings suggest that health plans without restrictions on provider access have significantly higher predicted total expenditures than restricted plans.

Conclusions Reached

This study provides insight for policy makers focusing on bridging the price gap between restricted network plans and plans with provider choice in order to avoid regional concentration of "managed care designs" and stimulate competition. One of the first established trends after the opening of the Affordable Care Act (ACA) in October 2013 is the re-emergence of "managed care designs" (McKinsey, 2014). Consumers seeking plans "with provider choice" find far fewer of those plans offered on the marketplace this year. (KHN, 2015) Also, premiums for plans "with choice" (open networks) are rising faster than for plans "without choice" (closed networks). (KHN, 2015)

The study findings suggest that health plans without restrictions on provider access have significantly higher predicted total and outpatient expenditures than restricted network plans. These results are relevant for policymakers in the various counties and states in which insurers have started to restrict their network of providers.

This study aims to impact health policies promoting price competition and informing consumers about price and provider choice trade-offs. The gap in premium between plans with choice and those without choice may result from shifts in demand, but may also result from lower costs of care. Carriers who discontinued their open network-plans have argued that the cost of the product makes it impossible to affordably price on the exchange. (RWJ Foundation, 2015). This could potentially distinguish the recent shift in demand from the developments in the 1990s.

Primary Student Presenter: Seth Welsh

Additional Presenter(s): N/A

Presenting School: Graduate

Degree Seeking: PhD

Year: 6th

Mentor: Jim Hagman

Poster Title: *Fusion of Early B Cell Factor One to Platelet Derived Growth Factor Receptor Beta in Leukemia Disrupts Functions Necessary for Normal B Lymphopoiesis*

Final Category: Hematology and Oncology

Abstract:

FUSION OF EARLY B CELL FACTOR ONE WITH PLATELET DERIVED GROWTH FACTOR RECEPTOR BETA IN LEUKEMIA DISRUPTS FUNCTIONS NECESSARY FOR NORMAL B LYMPHOPOIESIS SJ Welsh (Ph.D., GS) Churchman, M2, CG Mullighan2, and J Hagman1,3. 1Molecular Biology Program, University of Colorado School of Medicine, Aurora, CO. 2Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN. 3Department of Biomedical Research, National Jewish Health, Denver, CO.

Kinase-activating chromosomal rearrangements are hallmarks of Philadelphia-like leukemias, and are associated with poor treatment outcomes and relapse. Kinase inhibitors, while effective, risk of increased selection for drug-resistant clones. This warrants alternative drug targets. The purpose of this study was to identify the mechanisms contributing to a novel form of B cell leukemia in which early B cell factor 1 (EBF1) is fused to platelet-derived growth factor receptor beta (EBF1-PDGFRB). EBF1 is required for normal B lineage specification, commitment and development. Here, we use biochemical, fluorescent microscopy, and cell-based assays along with mouse models to demonstrate that EBF1-PDGFRB results in loss of EBF1 function, constitutive tyrosine kinase activity, IL-7 independent proliferation and a fully penetrant leukemia in vivo. Fusion of EBF1 to PDGFRB results in cytoplasmic mislocalization that is dependent on the transmembrane (TM) motif of PDGFRB. Deletion of the TM domain restores normal EBF1 function and IL-7 dependence. Thus, a single chimeric fusion protein drives leukemogenesis through loss of transcription factor activity and gain of cell proliferation. We demonstrate that mislocalization is kinase-independent, requires the TM domain, and that EBF1 function and cytokine dependence are rescued by TM deletion. Given that the TM domain is retained in the vast majority of PDGFRB rearrangements in both AML and ALL, our data suggest it is an appealing target to complement current therapies.

Primary Student Presenter: Thomas Wong

Additional Presenter(s): N/A

Presenting School: Medicine

Degree Seeking: MD

Year: 3rd

Mentor: Mary Jesse

Poster Title: *Upsloping Lateral Sourcil: A Novel Radiographic Finding in Clinically Unstable Hips*

Final Category: Surgery, Cardiovascular and Other

Abstract:

UPSLOPING LATERAL SOURCIL: A NOVEL RADIOGRAPHIC FINDING IN CLINICALLY UNSTABLE HIPS. TY Wong, (MD, CUSOM), MK Jesse, O Meidan, Departments of Musculoskeletal Radiology and Sports Medicine, University of Colorado, Denver, CO.

   Hip dysplasia is a phenomenon where insufficiency of the acetabular roof results in pain, hip instability, and early osteoarthrosis. While radiographic findings of frank dysplasia are well defined, there is a lack of diagnostic criteria for patients with radiographically "normal" hips who have borderline morphologic deficit and clinical instability. In this study, we evaluate the upsloping lateral sourcil as a novel radiographic finding in the evaluation of these patients. 316 patient charts were reviewed, including the earliest possible AP-pelvis radiographs with confirmed standard quality parameters. Lateral center edge angles (LCE) were measured bilaterally, upsloping lateral sourcils were documented, and clinical instability was elucidated from notes provided by a hip preservation surgeon. Patients were segmented into the following subgroups: dysplastic (LCE<20 degrees), borderline dysplastic (LCE=20-25 degrees), normal (LCE=25-40 degrees), and pincer (LCE >40 degrees). Chi-square statistical analysis was performed to evaluate the association of the radiographic upsloping lateral sourcil with the degree of dysplasia and the presence of clinical hip instability. Our review consisted of 104 males (32.9%) and 212 females (67.1%), with a mean age of 34y. 49 patients were excluded from analysis due to lack of imaging or for having gross dysplastic deformity, such as femoral head subluxation. Of the hips displaying upsloping sourcils, 77.9% had clinical instability (p-value = 0.0258). This finding demonstrated an 89.0% specificity for hip instability. The upsloping sourcil is a novel radiographic finding that may be useful in identifying patients with borderline hip dysplasia and hip instability. We feel that incorporation of this finding into the assessment of the painful hip will allow for an earlier and more accurate identification of at-risk patients and help to guide treatment.