UNIVERSITY OF COLORADO DENVER
ANSCHUTZ MEDICAL CAMPUS

28TH ANNUAL STUDENT RESEARCH FORUM

AND

STUDENT RESEARCH AWARDS CONVOCATION

COLLEGE OF NURSING

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DECEMBER 17, 2013
ANSCHUTZ MEDICAL CAMPUS
EDUCATION 2 NORTH/SOUTH

28TH ANNUAL
UNIVERSITY OF COLORADO DENVER
ANSCHUTZ MEDICAL CAMPUS
STUDENT RESEARCH FORUM

Tuesday, December 17, 2013

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

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

ANSCHUTZ MEDICAL CAMPUS
EDUCATION 2 NORTH/SOUTH

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!

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ABSTRACTS

Adewumi, Joseph

Poster Title: CHARACTERIZATION OF PRDM15 EXPRESSION DURING RETINAL DEVELOPMENT

Category: Developmental Neuroscience and Brain and Behavior – Child

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 1304   Poster Number: 9

Abstract:

CHARACTERIZATION OF PRDM15 EXPRESSION DURING RETINAL DEVELOPMENT. Joseph Adewumi1, 2(M.D., MS), Ko Park2, Joseph Brzezinski2 1. University of Colorado School of Medicine, Aurora, CO 2. Department of Ophthalmology, UCSOM, Aurora, CO.   Diseases that result in retinal neuronal cell death cause vision loss in millions of people. This vision loss is irreversible because retinal neurons are incapable of regenerating. One promising approach is to use stem cells to create and transplant new neurons, thereby replacing the lost cells. To accomplish this, a thorough understanding of the mechanisms that govern retinal neuronal development is required. Here, we investigated the role of a poorly understood transcription factor, Prdm15, in retinal development. We spatially and temporally characterized Prdm15 expression in the murine retina using RT-PCR and immunohistochemistry. Mouse retinas were examined from embryonic (E) day 13.5 to mature adult stages. To determine which cell types express Prdm15, retinal sections were co-immunostained with multiple cell type-specific markers. We then performed an EdU pulse-chase experiment to determine when Prdm15 becomes upregulated in relation to terminal S-phase. Using RT-PCR, we determined that Prdm15 is expressed during embryonic retinal development and in the mature adult retina. Early in retinal development (E13.5) Prdm15 expression was sparse. Prdm15 progressively marked a larger fraction of the retina such that the entire adult neural retina was Prdm15 labeled. During embryogenesis, Prdm15+ cells co-labeled with early neuronal-specific markers, but not with proliferative progenitor cell markers. Post-natal analysis of the Prdm15 expression suggests that Prdm15 has different levels of expression at different times and appears highest in differentiated cells of the retina. We observed that Prdm15 expression onset correlated closely with the decision of proliferative progenitor cells to permanently exit the cell cycle and differentiate as retinal neurons. The EdU pulse-chase experiment suggested, however, that Prdm15 expression is not strictly on/off as we had predicted, but rather expressed in different levels in the cells at different time points. These data suggest that Prdm15 may still play a critical role in cell cycle differentiation in the retina, but not exactly as we had hypothesized. Future studies will look at gain- and loss-of-function analysis to observe the effect on cell cycle exit for retina cell types.

Akhavan, Jaleh

Poster Title: Comparison of QCT and Bone Attenuation Values to Assess Vertebral Bone Density in Cigarette Smokers

Category: Pulmonary and Critical Care

School: Medicine   Year: 1st

Poster Location: ED 2 North Room 2301   Poster Number: 80

Abstract:

COMPARISON OF QCT AND BONE ATTENUATION VALUES TO ASSESS VERTEBRAL BONE DENSITY IN CIGARETTE SMOKERS J Akhavan (MD, CUSOM), J Jaramillo, D Stinson, C Wilson, D Lynch, J Crapo, E Regan and the COPDGene Investigators; National Jewish Health, Denver, CO.   Rationale: Osteoporosis, or low BMD, in COPD is associated with vertebral fractures. DXA is commonly used for measuring lumbar spine and hip BMD. An alternative method, quantitative CT (QCT) BMD measurement is currently performed using a special calibration phantom and analysis software. The ability to determine BMD on volumetric CT scan without this extra equipment could increase diagnosis and treatment of osteoporosis in COPD patients. We investigated the correlation between CT bone attenuation values and BMD determined by QCT. Methods: 3331 subjects from COPDGene, including non-smokers, smoker controls and COPD cases, underwent volumetric chest CT with a calcium calibration phantom integrated into the scanner pad. Using quantitative bone density analysis software (Image Analysis, Lexington KY) we determined volumetric BMD at T6-L1. In a subset of 407 QCT subjects, scanned using 20 different scanners, we also determined the mean attenuation in Hounsfield Units (HU) (TeraRecon iNtuition, Foster City CA) in a region of interest of vertebral cancellous bone within T6-L1. Four readers independently measured the same 200 scans. Prediction equations were derived for BMD for each scanner based on QCT as a standard. Results: QCT measured BMD showed strong correlation with attenuation values (Figure 1)(R^2=0.86). Analysis stratified by scanner exhibited a generally close correlation between attenuation measures and QCT BMD with R^2 ranging from 0.64-0.96 (mean=0.81). The overall prediction equation is BMD[mg/cc]=-9.41[mg/cc]+0.758[HU^{-1}]*Mean Attenuation[HU] (R^2=0.86). Intra-reader correlations of QCT BMD measurements and mean vertebral attenuation are high (R^2=0.99 and 0.87 respectively). Inter-reader correlation of mean attenuation is strong (Figure 2, R>0.92). Conclusion: QCT determinations of thoracic BMD correlate well with mean attenuation values from the same thoracic vertebrae with acceptable observer agreement. These measurements can establish predictive equations for BMD based on CT attenuation values by scanner. Mean attenuation values of T6-L1 vertebral bodies were determined on the remaining 6612 subjects of the COPDGene cohort to estimate thoracic BMD as a predictor of osteoporosis and fracture risk.

Poster Title: Prevalence of Substance Use among Moroccan Adolescents and Its Association with Academic Achievement

Category: Developmental Neuroscience and Brain and Behavior – Child

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 1307   Poster Number: 11

Abstract:

Background: Little research has been done on adolescent drug and alcohol use in Arab countries. This study investigates the difference in association of drug and alcohol use on academic performance in male and female adolescents.   Methods: Data was gathered using an adapted form of the European School Project on Alcohol and Other Drugs survey administered to 2139 10th-12th graders in 36 urban public high schools in Morocco. Two multiple logistic regressions (one for boys and one for girls) were completed using grade average as a two-part outcome variable and drug use as a four-level categorical independent variable, with father's education level, mother's education level, and socioeconomic status as covariates.   Results: A total of 181 girls (16%) and 390 boys (40%) reported ever having used alcohol, hashish, or psychotropic drugs. Among the girls, drug use in the past 30 days was associated with an adjusted odds ratio (AOR) of 2.62 (95% CI 1.31-5.22) of having average or below average grades, and lifetime use with an AOR of 1.72 (1.07-2.77). The boys who had used in the past 30 days had an AOR of 2.08 (1.33-3.24) of average or below average grades; use in the last 12 months corresponded to an AOR of 1.74 (1.00-3.05). Any previous use with boys and previous 12 month use with girls did not show a statistically significant association with grades. Conclusion: Drug and alcohol use is prevalent among adolescents in Morocco, though the difference in use between genders is substantial. Use in the last 30 days was associated with lower grades among both genders.

Poster Title: DETERMINING THE ROLES OF MURINE FACTOR H-RELATED PROTEINS IN COMPLEMENT DYSREGULATION.

Category: Immunology and Autoimmune Diseases

School: Medicine   Year: 5th

Poster Location: ED 2 South Room 2304   Poster Number: 25

Abstract:

DETERMINING THE ROLES OF MURINE FACTOR H-RELATED PROTEINS IN COMPLEMENT DYSREGULATION. AH Antonioli, (MD/PhD, GS), JP Hannan, and VM Holers, Molecular Biology Department, University of CO, Denver, CO.   Immune-mediated diseases such as rheumatoid arthritis (RA), age-related macular degeneration (AMD), and atypical hemolytic uremic syndrome (aHUS) are chronic and costly illnesses that impact millions worldwide. Although the pathogenesis of each of these diseases is complex, it is known that dysregulation of the complement system plays an important role in each of these illnesses. Therefore, a better understanding of complement regulation and specific complement regulatory proteins is crucial for developing therapies that could improve the lives of many individuals. The overall objective of this work is to explore the interrelationships between the complement regulatory protein Factor H (FH) and a group of five closely related molecules called the Factor H Related (FHR) proteins. FH regulates complement activation on self-surfaces allowing the innate immune response to discriminate between self and pathogens. FH and the FHR proteins consist in their entirety of compact repeating domains known as short consensus repeats (SCRs). The FHRs share many structural and functional traits with FH including the capacity to bind complement component C3b and glycosaminoglycans (GAGs). However, few functional studies have been carried out on the FHR proteins, and they have not been studied in any in vivo models of inflammatory disease. We propose to test the hypothesis that FHR proteins compete with FH-mediated complement regulation in two animal models of complement-driven disease or injury. We propose to: 1) Generate recombinant forms of the murine homologs of the human FHR proteins and determine the capacity of each of these molecules to inhibit FH function, thus confirming our initial data that these molecules approximate well to their human counterparts. We will also compare the specificities and affinities of murine FH and the murine FHR proteins (mFHRs) for different surface ligands. 2) Determine the effects of mFHRs on complement activation on kidney cells and in a murine model of complement-mediated kidney injury and also on the onset, progression, and severity of disease in a murine model of human RA. The long-term objective of this work is to determine whether the FHR proteins are suitable therapeutic targets for the treatment of complement-driven diseases.

Beadnell, Thomas

Poster Title: Potential Mechanisms of Acquired Resistance to SRC Inhibitors in Thyroid Cancer

Category: Hematology and Oncology

School: Graduate   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 38

Abstract:

COMBINED MAP KINASE AND SRC IHIBITION IN THYROID CANCER. TC Beadnell (Ph.D., CANB) BE Bowers; C Chan; X Jing; LA Pike; J Tentler; J Kim; AC Tan; and RE Schweppe, Department of Endocrinology, University of Colorado, Aurora, CO   The MAPK pathway is constitutively active in a majority of papillary and anaplastic thyroid cancers (PTC and ATC). While MAPK-targeted therapies have been encouraging in other tumor types, clinical benefit has been limited in thyroid cancer. Our lab has shown Src is activated in PTC and ATC, and that the growth of a subset of thyroid cancer cells is susceptible to treatment with the Src inhibitors, dasatinib and saracatinib (Schweppe et al 2009; Chan et al 2012). Recently, we identified the MAPK pathway as a potential mediator of resistance in response to Src inhibition in an unbiased genome-wide synthetic lethal screen. We therefore hypothesized that inhibition of Src, using dasatinib or saracatinib, in combination with the MEK1/2 inhibitor, selumetinib, will enhance the anti-tumor effects of either pathway alone.   The effects of Src and MAPK pathway inhibition on thyroid cancer growth and apoptosis were tested in vitro, using the Sulforhodamine B and Caspase 3/7 assays, respectively, and signaling was evaluated by Western blotting. Therapeutic efficacy was tested in vivo using an orthotopic model.   For both the dasatinib + selumetinib and saracatinib + selumetinib combinations, the IC50 values were synergistically reduced 2.6 to 6.4 fold in both BRAF-mutant (BCPAP, SW1736) and RAS-mutant (C643) cell lines. Accordingly, apoptosis was enhanced 3.5 to 8.4 fold for the combinations compared to single agent treatments. As expected, both Src inhibitors effectively inhibited pY416Src and pY861FAK. Interestingly, treatment with dasatinib, but not saracatinib, resulted in a paradoxical increase in ERK phosphorylation, suggesting distinct mechanisms of drug action. We next tested the combinatorial effects of saracatinib (25mg/kg) and selumetinib (50mg/kg) in vivo using an orthotopic model. After 4 days of treatment, the combination therapy significantly reduced tumor growth in comparison to selumetinib or saracatinib alone (p=.039). Overall, the combination treatment was similar to selumetinib alone, resulting in a 2.1-fold increase in survival (p=.0076).   Combined Src and MAPK pathway inhibition results in enhanced anti-tumor effects, and may provide a new, more effective therapy for advanced thyroid cancer patients.

Poster Title: HEALTH-FAIR EVALUATIONS TO IDENTIFY SUBJECTS THAT ARE AT-RISK FOR FUTURE INFLAMMATORY ARTHRITIS AND RHEUMATOID ARTHRITIS

Category: Immunology and Autoimmune Diseases

School: Medicine

Year: 2nd

Poster Location: ED 2 South Room 2304

Poster Number: 27

Abstract:

Purpose of Study: It is established that there is a 'preclinical' period of rheumatoid arthritis (RA) when biomarkers including RF and anti-CCP are abnormal while joint exam is negative for RA. Furthermore, RF and CCP abnormalities are highly predictive of future classifiable RA. Most data regarding preclinical RA and prediction of future disease have been derived from retrospective studies of symptomatic patients, and little is known from prospective community-based studies. Therefore, in a community health fair we identified and subsequently followed subjects with elevated biomarkers but absent clinical RA to evaluate predictive factors for development of RA. Methods Used: Volunteers were tested for serum anti-CCP3 (INOVA) at a Colorado health fair from 2008-2012. Subjects with CCP3 positivity (≥20 units) without RA by physical examination were invited for biannual follow-up that included assessment of demographic factors, environmental exposures, joint symptoms, joint examination by a trained study physician or nurse, and testing of CCP3 and CCP3.1 (INOVA), CCP2 (Axis-Shield), RF by nephelometry (Dade-Behring) and specific isotypes IgG/M/A (INOVA), C-reactive protein (CRP), and the shared eptiope (SE).   Summary of Results: 7178 volunteers were initially evaluated, and 158 (2%) were CCP3(+) without IA; 47 of 158 (30%) invited subjects agreed to follow-up and were studied for a median of 27 months (range 1-52). Of these, 19/47 (40%) developed IA or RA in median of 5 months (2-30). The factor most strongly associated with the development of either IA or RA was CCP2 >3x normal plus positivity for any RF assay at any level at the baseline research visit (OR 6.0, 95% CI 1.1-34). Age, sex, smoking, family history of RA, baseline joint symptoms or examination tenderness, CRP and SE were not significantly associated with developing IA/RA.   Conclusions: A health fair evaluation is able to identify subjects at-risk for future RA. CCP2 >3x normal and RF positivity were most strongly associated with development of RA.

Poster Title: Gene regulation screen reveals neuroprotective mechanisms activated by phenylbutyrate to prevent the progression of Parkinson's disease

Category: Neuroscience and Brain and Behavior – Adult

School: Graduate   Year: 2nd

Poster Location: ED 2 North Room 2307   Poster Number: 86

Abstract:

We have discovered that the FDA-approved histone deacetylase (HDAC) inhibitor phenylbutyrate (PB) can increase DJ-1 concentrations both in vitro and in vivo. After administration to a transgenic mouse model of diffuse Lewy body disease, PB increased blood and brain DJ-1, stopped behavioral deterioration, and prevented age-related mutant alpha-synuclein deposition in brain (Zhou, W., et al., JBC, 2011). Based on these data, we initiated a Phase I clinical trial of PB in 12 patients with newly diagnosed idiopathic Parkinson's disease, Hoehn and Yahr stage 1 or 2 in the "off" state. Average age was 62 +/- 6 years. After 4 weeks of baseline evaluations, PB administration began with increasing doses at 4 week intervals over 24 weeks to 16 gm/day. Results showed that plasma alpha-synuclein levels increased in a dose-dependent way, suggesting that phenylbutyrate mobilized alpha-synuclein from brain into plasma, reducing the pathologic concentration of alpha-synuclein. Our transgenic mouse model of Parkinson's (Y39C-alpha-synuclein) has a mutant form of human alpha-synuclein which is expressed only in neurons under control of the Thy-1 promoter. In that animal, we found that brain alpha-synuclein is 50% human, 50% mouse. Plasma alpha-synuclein is also 50:50, indicating that plasma alpha-synuclein has come primarily from neurons, either central or peripheral. By contrast, red blood cell alpha-synuclein is all mouse in origin. Further studies in tissue culture, in mouse models, and in human plasma indicate that phenylbutyrate activates protein catabolic pathways including lysosomes and exosomes to enhance the removal of alpha-synuclein oligomers from cells. To evaluate whether other compounds can increase DJ-1 and promote dopamine neuron survival, we have tested a number of histone deacetylase inhibitors in N27 dopamine neurons in vitro. Results have shown that tricostatin-A, MS-275 and DPAH can increase DJ-1 and protect neurons from hydrogen peroxide toxicity in a way similar to PB. We conclude that phenylbutyrate can increase expression of the DJ-1 gene and protein and stop the progression of Parkinson's in a transgenic mouse model of the disease by enhancing clearance of abnormal brain proteins such as oligomeric forms of alpha-synuclein. Phenylbutyrate and other HDAC inhibitors may prove effective for slowing or stopping progression of Parkinson's disease in patients.

Poster Title: CAN PREOPERATIVE SMOKING CESSATION INTERVENTIONS GENERATE LONG-TERM CESSATION? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Category: Health Care and Public Health

School: Medicine   Year: 4th

Poster Location: ED 2 South Room 2201   Poster Number: 34

Abstract:

CAN PREOPERATIVE SMOKING CESSATION INTERVENTIONS GENERATE LONG-TERM CESSATION? A SYSTEMATIC REVIEW AND META-ANALYSIS. CM Cutter (M.D., SOM), NL Berlin, MM Desai. Yale School of Public Health, Yale University, New Haven, CT. Background: Smoking is the leading cause of preventable death worldwide. In the United States, approximately ten million tobacco smokers undergo surgical intervention each year. Surgery is an event that precipitates spontaneous uptake of risk-reducing health behaviors and, therefore, presents an opportunity to promote smoking cessation. The efficacy of preoperative cessation programs at three and six months postoperatively is well established in the literature. The aim of this review is to examine published randomized controlled trials (RCTs) and quasi-experimental studies that evaluate the association between preoperative smoking cessation programs and long-term smoking cessation (≥12 months). Methods: A systematic review was performed utilizing MEDLINE, EMBASE, CINAHL, PSYCHinfo and COCHRANE databases. All RCTs and quasi-experimental studies of smoking-cessation interventions initiated preoperatively, with cessation measured at twelve months postoperatively, were identified. A meta-analysis was performed using pooled RCT results. Results: Four RCTs and two quasi-experimental studies were included in this review. Two RCTs demonstrated a statistically significant association between preoperative smoking cessation interventions and cessation at twelve months. Another RCT demonstrated a similar, though non-significant, trend. Additionally, the quasi-experimental studies demonstrated cessation rates of 48% to 56% at twelve months postoperatively. In a fixed-effects model, preoperative cessation interventions were associated with a greater likelihood of cessation at twelve months (relative risk, 1.60, 95% CI 1.11-2.32, P=0.01), although this effect was no longer significant after applying a random-effects model (relative risk, 1.79, 95% CI 0.91-3.53, P=0.09). Conclusions: The results of this review suggest that preoperative smoking cessation programs can generate long-term (≥12 months) smoking cessation. Further research is needed to explore this association. Additional studies should seek to identify approaches that optimize preoperative smoking cessation programs in the promotion of short-, as well as long-term, cessation.

Poster Title: Understanding the contribution of the microenvironment in parity-induced protection against breast cancer

Category: Hematology and Oncology

School: Graduate   Year: 3rd

Poster Location: ED 2 South Bridge   Poster Number: 40

Abstract:

Title: Understanding the contribution of the microenvironment in parity-induced protection against breast cancer. Authors: C Betts1,2, O Maller3, K Hansen4, V Borges1,5,6, P Schedin1,5,6 Affiliations: 1 Division of Medical Oncology, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO 80045. 2 Graduate Program in Cells, Stem cells, and Development (CSD), University of Colorado Anschutz Medical Campus, Aurora, CO 80045. 3 Department of Surgery and Center for Bioengineering and Tissue Regeneration, University of California, San Francisco, CA 94143. 4 Department of Biochemistry and Molecular Genetics, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO 80045. 5 University of Colorado Cancer Center, Aurora CO 80045 6 Young Women's Breast Cancer Translational Program, University of Colorado Anschutz Medical Campus, Aurora, CO 80045.   Abstract: Epidemiological studies have identified that parity induced by a full-term pregnancy is protective against a woman's life-long risk of developing breast cancer. Understanding how parity induces protection may allow for therapeutic interventions that aim at mimicking this natural state in high risk women. There is a strong precedence that tissue stroma is capable of "reverting" the phenotype of malignant cells. The Schedin lab has identified that extracellular matrix isolated from the mammary glands of parous rodents is sufficient to reduce tumor growth and revert the invasive phenotype of mouse mammary tumor cells. We have extended this finding and discovered that mouse mammary tumor cells (D2.OR and D2.A1), human mammary tumor cells (MCF10DCIS.com), and normal mouse mammary epithelial cells (Eph4) all respond similarly to matrix that resembles the parous mammary gland by becoming rounded and non-invasive, which is in contrast to the invasive phenotype the cells adopt when on nulliparous matrix (from a rat that has never had a pregnancy). In addition, cells on the parous matrix differentially regulate many immune genes, compared to cells on nulliparous matrix. Of the 25 most differentially regulated genes,11 are involved in regulating dendritic cell phenotype and/or function. We have validated many of these gene changes by qPCR analysis, and furthermore we have characterized the timing of these gene changes. These data support the hypothesis that parous extracellular matrix modulates tumor cell immune cytokine production to result in the induction of anti-tumor dendritic cell functions, and furthermore that this may be one mechanism of parity-induced protection from breast cancer.

Poster Title: Nopal as a Therapeutic for Dry Eye

Category: Pharmacology and Physiology

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2301   Poster Number: 78

Abstract:

NOPAL AS A THERAPEUTIC FOR DRY EYE. L Bidikov (MD, SOM), M Pedler, J Diego, E McCourt, J Kennedy, and M Petrash. Department of Ophthalmology, University of Colorado, Denver, CO. Background Dry eye is a prevalent disease. Many treatments exist; however, they do not work in all cases. One treatment which has not been tested for dry eye is application of derivative of Nopal, a prickly-pear cactus consumed widely in Mexico. Methods Female mice were treated with 5µl benzalkonium chloride (BAK) twice a day for seven days to induce dry eye. Various extractions were administered to the eye four times a day for an additional seven days. The extracts were PBS (n=15), cyclosporine (n=5), nopal extract (n=10), nopal (n=5) filtered through a .2 µm, methanol extract of nopal (n=5, and ethyl acetate extract of nopal (n=5). BAK application, twice a day, continued during both the induction and treatment periods. The primary outcome was resolution of damage caused by the BAK treatment as measured by three parameters: (1) Zone-Quick tests, to measure tear volume production, and (2) punctate staining, to assess degree of epithelial damage, and (3) the corneal epithelium thickness, measured after the eyes were enucleated, fixed, and stained. Results The eyes induced with BAK had a thinner corneal epithelium than the untreated eyes (p

Poster Title: PERSISTENT RAS/MAPK ACTIVATION PROMOTES LACTOTROPE DIFFERENTIATION, WHEREAS THE PI3K PATHWAY REGULATES PROLIFERATION OF GH4 PITUITARY SOMATOLACTOTROPE TUMOR CELLS

Category: Metabolism and Endocrinology

School: Graduate

Year: 2nd

Poster Location: ED 2 North Room 2102

Poster Number: 61

Abstract:

PERSISTENT RAS/MAPK ACTIVATION PROMOTES LACTOTROPE DIFFERENTIATION, WHEREAS THE PI3K PATHWAY REGULATES PROLIFERATION OF GH4 PITUITARY SOMATOLACTOTROPE TUMOR CELLS. A Booth (Ph.D., GS), T Trudeau, C Gomez, and A Gutierrez-Hartmann; Department of Endocrinology, University of Colorado Denver, Aurora, CO. Pituitary somatotropes and lactotropes expressing growth hormone (GH) and prolactin (PRL), respectively, retain plasticity allowing for rapid cell expansion to meet physiological demands. Somatolactotropes expand into lactotropes during pregnancy and into somtatotropes with exercise, but little is known about signaling events that instruct these cells to terminally differentiate or proliferate. Activation of growth factor-Ras-MAPK signaling in lactotropes in vivo promotes hyperplasia. In GH4 and GH3 rat pituitary somatolactotrope tumor cell lines, activated pMAPK is necessary for short-term proliferation and differentiation in vitro, and the duration of pMAPK activation may dictate distinct responses. However, these short-term (6-24 hrs) assays did not address the role of Ras/MAPK in durable lactotrope proliferation and differentiation. The role of PI3K signaling, an alternate downstream target of Ras, has not been addressed in either of these cellular events. We developed GH4 clonal cell lines expressing doxycycline (Dox)-inducible HA-tagged V12Ras. MAPK and PI3K inhibitors were used; constitutively active PI3K (PI3KCA) was overexpressed using a retroviral protocol; cell proliferation, 2D colony formation, and soft agar colony formation were assessed. GH4 cells with Dox-inducible Ras were flank injected into female nude mice; Dox was added to drinking water. Activation of V12Ras over 6 days in serum-starved GH4 cells promoted a switch to the lactotrope phenotype with no effect on proliferation. Soft agar colony number and xenograft tumor size in nude mice were reduced. Cycling GH4 cells treated with low-dose MEK inhibitor surprisingly showed an increased proliferative response, while higher dose MEK inhibitor only modestly reduced proliferation, clonogenicity, and soft agar growth. In contrast, PI3K inhibitor resulted in a dose-dependent, complete inhibition of proliferation, clonogenicity, and soft agar growth. Overexpression of PI3KCA in cycling GH4 cells increased proliferation and colony formation. The MAPK pathway regulates differentiation into the lactotrope phenotype, whereas the PI3K pathway governs somatolactotrope proliferation.

Poster Title: THINNING OF THE LEFT ROSTRAL ANTERIOR CINGULATE AND LEFT MEDIAL ORBITOFRONTAL CORTICES IN ADOLESCENT FEMALES WITH ANTISOCIAL SUBSTANCE DEPENDENCE

Category: Developmental Neuroscience and Brain and Behavior – Child

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 1303   Poster Number: 8

Abstract:

Purpose of Study: Some individuals have onset of substance use disorders early in adolescence, develop multiple substance use disorder diagnoses, and have severe persistent courses. Youths in this population are likely to have a number of precursors, associated cognitive deficits, and characteristic co-morbidities such as conduct disorder. We have previously termed this Antisocial Substance Dependence. Although such youths exhibit more impulsivity, risk-taking, and problems of inhibition, relatively little is known about brain differences seen in such youths. This is especially true among adolescent females. Methods Used: We recruited 22 patients from a university-based treatment program for youths with serious substance and conduct problems and 21 community controls, all female and aged 14-19 years. We obtained T1 structural brain images using a General Electric 3T MRI scanner and assessed for group differences in cortical thickness across the entire brain using FreeSurfer's QDEC program and for three regions-of-interest bilaterally (total of 6 comparisons). These regions of interest were defined by the Desikan's atlas, chosen based on a priori predictions from the literature, and included: 1) medial orbitofrontal cortex; 2) rostral anterior cingulate cortex; 3) middle frontal gyrus. Age and IQ were entered as nuisance factors for all analyses. Summary of Results: Using a vertex-level threshold of $p < 0.005$ and Monte Carlo Simulation-determined cluster threshold we demonstrated on whole-brain analyses that one region, including the left rostral anterior cingulate cortex and extending into the left medial orbitofrontal region (355.84 mm2 in size) was significantly thinner in patients. Region-of-interest analyses showed no significant difference in any of the 6 regions. Conclusions: Adolescent females with Antisocial Substance Dependence have significantly thinner left rostral anterior cingulate and left medial orbitofrontal cortices. These regions have been hypothesized to be associated with poor behavioral control in past studies.

Bui, Quan

Poster Title: Secondary Analysis of The Take Heart™ Austin TAKE10 Program

Category: Cardiovascular

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 1203   Poster Number: 1

Abstract:

SECONDARY ANALYSIS OF THE TAKE HEART™ AUSTIN TAKE10 PROGRAM. QM Bui, (MD, SOM), L Gonzalez, P Hinchey, J Cabanas, B Eigel, C Sasson, MD,MS, Department of Emergency Medicine, University of Colorado School of Medicine, Denver, CO.   Background: The Take Heart™ Austin TAKE10 Program is a community-based bystander cardiopulmonary resuscitation (CPR) educational training program. TAKE10 stands for "take 10 minutes to learn compression-only CPR." The underlying premise of the TAKE10 Program is to train facilitators in compression-only CPR, who can check-out a kit containing all the necessary materials, including eight inflatable mannequins, to then train others.   Objective: To conduct a secondary analysis of prospectively collected data through the Take Heart™ Austin TAKE10 Program implemented in July 2008 through September 2013 in order to investigate the program's geographical impact in the communities and to elucidate a future framework for implementing a successful CPR educational training program.   Methods: A descriptive analysis of summary data was conducted using Stata v13.0 (Redlands, California). Trends were then plotted to assess the change over time in the numbers of trainers and trainees that were trained using a train-the-trainer model. Home zip codes of trained individuals were sorted and consequent GIS mapping were formed, allowing visualization of the program's geographical outreach.   Results: From July 2008 to September 2013, a total of 404 persons were trained as TAKE10 program trainers, who then trained an additional 18,777 participants in compression-only CPR. The overall mean for the program was 46.5 trainees per facilitator. The geographical impact of the program encompassed 879 zip codes. Participants were trained at 28 various location categories with the top five being elementary and secondary school (29.5%), government general office building (14.1%), hospitals/clinics/health care facilities (7.67%), fair ground (7.31%), and university/college (6.72%). The total cost for the program was $25,000, for a return on investment of $1.33 dollars per person trained.   Conclusion: The TAKE10 Program was a successful program that illustrates the benefits of a train-the-trainer approach to community CPR training. Participants were distributed across 879 zip codes and trained at 28 various location categories. Further research will need to be conducted in other cities to see if this novel method for training community members can be replicated.

Poster Title: Autoimmune Disease Recurrence and Islet Allograft Rejection Differ in Requirements for Graft Cell MHC Expression but Converge on Similar TCR Utilization

Category: Immunology and Autoimmune Diseases

School: Graduate   Year: 5th

Poster Location: ED 2 South Room 2305   Poster Number: 20

Abstract:

Autoimmune Disease Recurrence and Islet Allograft Rejection Differ in Requirements for Graft Cell MHC Expression but Converge on Similar TCR Utilization In the setting of pancreatic islet transplantation, it is unclear whether the pathways of autoimmune disease recurrence are similar to or distinct from allograft immunity. To determine whether islet donor MHC expression is required for disease recurrence or allograft destruction in spontaneously diabetic NOD mice, we grafted NOD mice with either syngeneic NOD islets or allogeneic C57BL/6 islets that were genetically deficient in MHC class I, MHC class II, or both MHC class I and II. NOD MHC I-deficient or MHC I/II-deficient islets had greatly prolonged survival in untreated NOD mice (MST 121 days and 87 days, respectively). In stark contrast, B6 islet allografts deficient in MHC class I, MHC class II, or both MHC were uniformly rejected in NOD mice in

Poster Title: Community-Based, Targeted CPR Education to Improve Survival from Out-of-Hospital Cardiac Arrest in High-Risk Neighborhoods

Category: Health Care and Public Health

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 2207   Poster Number: 32

Abstract:

COMMUNITY-BASED, TARGETED CPR EDUCATION. T Califf (MD, SOM), T Tran (MD, SOM), C Sasson, M Tran, M Carmona, and A Nassel, Department of Emergency Medicine, University of Colorado, Aurora, CO.   Background: High-risk neighborhoods, defined as having a low prevalence of bystander CPR and high incidence of out-of-hospital cardiac arrest (OHCA), may be targets for community-based interventions. The HANDDS Program is a novel intervention to increase awareness of OHCA symptoms and provision of hands-only CPR in these neighborhoods.   Objective: To conduct a pilot, community-based hands-only CPR trial for residents of high-risk neighborhoods in Denver.   Methods: Design: Prospective community-based clinical trial. Setting: Targeted high-risk neighborhoods in Denver, CO metropolitan area. Population: Convenience sample of 344 residents were recruited during the 12-week study period. Intervention: Participants completed a demographic survey and pre-test to assess baseline knowledge of CPR. Subjects then completed a group hands-only CPR training lasting 1 hour using the CPR Anytime kit, which included an educational DVD and hands-on skills training with an inflatable mannequin. After the intervention, participants were asked to complete the same 5-question survey to assess their retention of knowledge. They were also asked to use these kits to train other community members over a 2-6 week period. A $10 incentive was given for participation in the study. Two-sample t-tests were conducted to assess for differences in hands-only CPR knowledge pre- and post-CPR training.   Results: Demographics are given in Table 1 for 344 participants. Participants were Asian (50.0%) and black (35.6%), female (68.0%), had completed high school (26.8%), and had an annual income of less than $30,000 (37.1%). After the intervention, the mean number of questions about CPR answered correctly increased (Table 2). Most participants (84.6%) felt comfortable performing hands-only CPR after the intervention. One hundred forty-nine (43.4%) participants returned trainee data at the end of the study, with an additional 812 people trained.   Conclusion: With 344 CPR Anytime Kits, we trained 1156 members of high-risk neighborhoods in hands-only CPR (average of 3.36 people/kit). Participants demonstrated increased knowledge of CPR and enthusiasm to train others. A targeted, community-based CPR intervention is a feasible way to increase bystander CPR training in high-risk neighborhoods.

Poster Title: Investigating regulation of sodium current through use of the macho mutant zebrafish

Category: Developmental Neuroscience and Brain and Behavior – Child

School: Graduate   Year: 6th

Poster Location: ED 2 South Room 1304   Poster Number: 10

Abstract:

INVESTIGATING REGULATION OF SODIUM CURRENT THROUGH USE OF THE MACHO MUTANT ZEBRAFISH. V Carmean (PhD, GS), AB Ribera. Neuroscience Program and Department of Physiology & Biophysics, University of Colorado, Aurora, CO   The structural subunits of voltage-gated sodium channels have been identified, however less is known about mechanisms that regulate their function in vivo. In the zebrafish touch-insensitive mutant macho (mao), sensory neurons have reduced sodium current amplitudes. In previous work, we found that the mao mutation is not linked with sodium channel α-subunit or β-subunit genes, indicating that the lesioned gene does not code for a structural subunit. Here, we report that mao mutants carry a genetic lesion within the pigk gene, consisting of a T to C substitution in the start codon. The pigk gene codes for the protein Pigk, an transposase critical to attaching glycosylphosphatidylinositol (GPI) anchored proteins (GPI-AP) to their GPI-anchor and allowing the GPI-AP to be tethered to the extracellular cell surface. Over expression of wildtype pigk mRNA in mao mutants resulted in mao mutants with a touch response, indicating the pigk mutation underlies the mao phenotype. This result was surprising as sodium channel subunits are not GPI-anchored. Using qPCR, we assessed pigk mRNA levels during embryogenesis and found that it is both maternally and zygotically expressed, and present throughout the first 48 hours post fertilization. Using RNA in situ hybridization we characterized the spatial expression pattern of pigk during early development and found that the gene is ubiquitously expressed in the dorsal spinal cord, where the sensory neurons reside. The implication of this gene in the mao mutant identifies a potentially novel mechanism for regulation of sodium current (INa) amplitude. Further studies can distinguish the mechanisms in which this gene specifically attenuates the INa amplitude in order to better understand the physiological relevance of this mutation.

Poster Title: Selective Detoxification of Hypothiocyanous Acid by Mammalian Thioredoxin Reductase: A Missing Link in Innate Immunity and Antioxidant Defense

Category: Microbiology and Infectious Diseases

School: Graduate   Year: 5th

Poster Location: ED 2 North Room 2106   Poster Number: 65

Abstract:

The endogenous oxidant hypothiocyanous acid (HOSCN) inhibits and kills pathogens but paradoxically is well tolerated by mammalian host tissue. Mammalian thioredoxin reductase (H-TrxR) is evolutionarily divergent from bacterial thioredoxin reductase (L-TrxR), expressing selenocysteine (Sec) and having broadened substrate reactivity. Recombinant and purified H-TrxR1 and 2 from rat and mouse selectively turned over HOSCN with high affinity (mean $K_m=31.9\pm10.3$ µM) but were inactive against hypochlorous acid (HOCl). Replacing or removing Sec decreased affinity and turnover of HOSCN by H-TrxR. In contrast, recombinant E. coli L-TrxR was potently inhibited by HOSCN ($IC50=2.75$ µM). Similarly, human bronchial epithelial cell (16HBE) lysates metabolized HOSCN but E. coli and P. aeruginosa lysates were largely inactive. 16HBE cells, E. coli and P. aeruginosa were then exposed to HOSCN or HOCl. HOSCN selectively produced toxicity in bacteria while HOCl was non-selectively toxic to bacteria and 16HBE. Treatment with the H-TrxR inhibitor auranofin inhibited HOSCN metabolism in 16HBE lysates and significantly increased HOSCN-mediated cytotoxicity. These findings demonstrate both the detoxification of HOSCN by mammalian H-TrxR and the potent inhibition of bacterial L-TrxR yielding resistance to HOSCN in mammals and sensitivity in bacteria. These data support a novel detoxification mechanism of host defense in mammals in which HOSCN formation simultaneously inhibits pathogens and protects host tissue.

Poster Title: ALDOSE REDUCTASE INHIBITION PREVENTS ENDOTOXIN-INDUCED INFLAMMATORY RESPONSES IN RETINAL MICROGLIA

Category: Microbiology and Infectious Diseases

School: Pharmacy   Year: 3rd

Poster Location: ED 2 North Room 2106   Poster Number: 67

Abstract:

ALDOSE REDUCTASE INHIBITION PREVENTS ENDOTOXIN-INDUCED INFLAMMATORY RESPONSES IN RETINAL MICROGLIA. KC Chang1, 2 (Ph.D., TXCL), DV. LaBarbera1, and JM Petrash*1, 2, 1Department of Pharmaceutical Science; 2Department of Ophthalmology, University of Colorado, Denver, CO.   Purpose: Activated microglia and inflammation are involved in degenerative retinal diseases. Among other effectors, aldose reductase (AR) has been linked to ocular inflammation in the endotoxin-induced uveitis (EIU) model. Retinal microglia (RMG) have been demonstrated to play a pathogenic role in experimental uveitis. The purpose of this study is to investigate whether AR inhibition or deficiency is against various inflammatory responses in RMG. Methods: The detection of inflammatory cytokines was investigated by ELISA assay. Primary mouse RMG were isolated from wild type or AR knockout mice and confirmed by staining with specific marker, Iba-1. Images were detected by fluorescence microscopy. Cell migration was measured using a transwell assay. Active MMP-9 was detected by gelatin zymography. Apoptosis of ARPE-19 cells were conducted by co-cultured system. Results: AR inhibition or deficiency prevented LPS-induced cytokines secretion in macrophages and RMG. AR inhibition or deficiency also attenuated LPS-induced cell migration. We further elucidated that AR inhibition or knockdown reduces activation of MMP-9. Additionally, AR inhibition or deficiency rescues activated RMG-induced apoptosis in ARPE-19 cells. Conclusion: These results suggest that AR inhibition may be useful as a therapeutic agent against inflammatory diseases in the eye by mediating RMG inflammatory responses.

Poster Title: The Effect of Route of Administration on the Immunogenicity of Recombinant Murine Growth Hormone Protein Aggregates

Category: Immunology and Autoimmune Diseases

School: Pharmacy   Year: 5th

Poster Location: ED 2 South Room 2305   Poster Number: 22

Abstract:

THE EFFECT OF ROUTE OF ADMINISTRATION ON THE IMMUNOGENICITY OF RECOMBINANT MURINE GROWTH HORMONE PROTEIN AGGREGATES. M Christie(Ph.D., GS) and JF Carpenter, University of Colorado, Denver, CO.   Purpose: Protein products are routinely prescribed for a number of indications—sometimes as the only treatment option. Even though they have been in use for decades, much is still unknown about the major risk factors that impact patient safety. Consequently, evaluation and mitigation of the risk of immunogenicity to protein aggregates remains a primary concern for drug developers and regulatory agencies. In order to investigate a risk potential factor, we used a self-protein in a mouse model to determine the effect of the route of administration on the immunogenicity to recombinant murine growth hormone (rmGH) protein aggregates.   Methods: We created protein aggregates by subjecting rmGH to freeze-thaw stress and quantified the nano- and micro-sized particles via SEC, particle tracking analysis, resonant mass measurement and flow imaging. We also created a population of nanosized particles by ultra-centrifuging the freeze-thawed protein at 110,000g for 1 hour at 4°C. Protein aggregates were injected on days 2 and 23 into CB6F1 mice via subcutaneous, intraperitoneal and intravenous (via tail vein) routes. Submandibular blood draws were performed on days 1, 22 and 36. The production of anti-rmGH IgG antibody isotypes were monitored with ELISA to determine immunogenicity.   Results: Compared to the ultra-centrifuged protein, the freeze-thaw protein injections contained much higher quantities of micro-sized protein particles. No major difference in immunogenicity could be ascertained between the freeze-thaw stressed and ultracentrifuged rmGH protein injections. However, the intravenous route was the most immunogenic of the three tested; which is surprising considering the current popular viewpoint in vaccine immunology dictates the subcutaneous route to be more immunogenic than intravenous.   Conclusions: Both nano- and micro-sized protein aggregates have the capacity to elicit an immune response. The route of administration is a major factor impacting the immunogenicity of protein aggregates. Based on the results of this study, protein aggregates injected via the intravenous route elicit a more pronounced immune response compared to the subcutaneous and intraperitoneal routes, contrary to the prevalent beliefs on this issue.

Poster Title: Endoribonuclease Cleavage Sites in Host and Viral RNAs

Category: Microbiology and Infectious Diseases

School: Graduate   Year: 5th

Poster Location: ED 2 North Room 2106   Poster Number: 69

Abstract:

Ribonuclease L (RNase L) is a well-studied antiviral endoribonuclease; however, its numerous cleavage sites within host and viral RNAs are poorly defined. We developed 2', 3'-cyclic phosphate cDNA synthesis and Illumina sequencing methods to comprehensively define the frequency and location of endonuclease cleavage sites in host and viral RNAs. Metal ion-independent endonucleases like RNase L and RNase A cleave single-stranded RNA, producing RNA fragments with terminal 2', 3'-cyclic phosphates. Arabidopsis thaliana tRNA ligase, which specifically recognizes RNA fragments with 2', 3'-cyclic phosphates, can be used to generate cDNA libraries (Schutz et al., 2010). Illumina sequencing and bioinformatic analyses of the data reveal the location and frequency of endonuclease cleavage sites in host and viral RNAs. We optimized and validated the methods using viral RNAs cleaved with RNase L, viral RNAs cleaved with RNase A, and RNA from uninfected and poliovirus (PV)-infected HeLa cells that over-express either wild-type or dominant-negative forms of RNase L. We observed that hepatitis C virus (HCV) and PV RNAs were cleaved predominantly at sites in the structural genes. The data indicate that positive-strand RNA virus genomes assume secondary and tertiary structures that render some regions of the genome largely resistant to single-strand specific endonucleases. Other regions of the genome, like the portion of HCV RNA encoding the hyper-variable regions of the E2 protein, are more susceptible to single-strand specific nucleases. In addition to our analyses of viral RNA, we identified the frequency and location of RNase L-dependent and RNase L-independent cleavage sites in ribosomal RNAs, and we discovered 2', 3'-cyclic phosphate termini on a subset of functional host RNAs.

Poster Title: INHIBITION OF MER TYROSINE KINASE BY A NOVEL SMALL MOLECULE INHIBITOR IS EFFICACIOUS IN NON-SMALL CELL LUNG CANCER

Category: Hematology and Oncology

School: Medicine   Year: 5th

Poster Location: ED 2 South Bridge   Poster Number: 42

Abstract:

INHIBITION OF MER TYROSINE KINASE BY A NOVEL SMALL MOLECULE INHIBITOR IS EFFICACIOUS IN NON-SMALL CELL LUNG CANCER. CT Cummings* (MD, PhD; MSTP), KD Davies*, J Carrico*, D DeRyckere*, W Zhang^, X Wang^, S Frye^, HS Earp**, and DK Graham* *Department of Pediatrics, University of Colorado, Aurora, CO. ^Center for Integrative Chemical Biology and Drug Discovery, **Department of Medicine, Lineberger Cancer Center, University of North Carolina, Chapel Hill, NC. Background: Mer tyrosine kinase is frequently overexpressed and activated in non-small cell lung cancer (NSCLC). In addition, its genetic inhibition reduces NSCLC cell growth in vitro and tumor xenograft growth in vivo. Here, we examine effects of a first-in-class Mer-selective small molecule tyrosine kinase inhibitor (TKI), in pre-clinical models of NSCLC. Methods: The effects of the Mer TKI on activation of Mer and the related TAM-family members, Axl and Tyro3, and on downstream signaling, were analyzed by immunoblot. Activity was assessed in a panel of NSCLC cell lines using soft-agar and clonogenic assays. Induction of apoptosis was determined using flow cytometry. Finally, a subcutaneous murine xenograft model was used to determine effects in vivo. Results: The Mer TKI blocked Mer phosphorylation at sub-micromolar concentrations and was highly selective for Mer over Axl and Tyro3. Treatment also inhibited downstream signaling through the ERK1/2 and AKT pathways, resulting in induction of apoptosis and reduced colony formation. Sensitivity was independent of driver oncogene status, as cell lines positive for EGFR mutations, KRAS mutations, and gene fusions all responded to treatment. Interestingly, RNAi mediated knock-down of Axl enhanced sensitivity to Mer TKI treatment. Finally, in mice treatment resulted in a significant decrease in tumor volume. Conclusions: This Mer TKI is a novel and potent inhibitor that is selective for Mer over other TAM family kinases. Treatment resulted in decreased pro-oncogenic signaling, increased apoptosis, decreased colony formation, and decreased tumor growth in vivo. Sensitivity did not depend on driver oncogene status. Mer TKIs may therefore provide a targeted treatment option for patients without known oncogenic mutations. In addition, Axl inhibition sensitized cells to Mer TKI treatment, suggesting an interaction between Mer and Axl. In summary, these data validate the Mer TKI as a potential treatment for NSCLC and support its development toward clinical use.

Poster Title: CAN PREOPERATIVE SMOKING CESSATION INTERVENTIONS GENERATE LONG-TERM CESSATION? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Category: Health Care and Public Health

School: Medicine   Year: 4th

Poster Location: ED 2 South Room 2201   Poster Number: 34

Abstract:

CAN PREOPERATIVE SMOKING CESSATION INTERVENTIONS GENERATE LONG-TERM CESSATION? A SYSTEMATIC REVIEW AND META-ANALYSIS. CM Cutter (M.D., SOM), NL Berlin, MM Desai. Yale School of Public Health, Yale University, New Haven, CT. Background: Smoking is the leading cause of preventable death worldwide. In the United States, approximately ten million tobacco smokers undergo surgical intervention each year. Surgery is an event that precipitates spontaneous uptake of risk-reducing health behaviors and, therefore, presents an opportunity to promote smoking cessation. The efficacy of preoperative cessation programs at three and six months postoperatively is well established in the literature. The aim of this review is to examine published randomized controlled trials (RCTs) and quasi-experimental studies that evaluate the association between preoperative smoking cessation programs and long-term smoking cessation (≥12 months). Methods: A systematic review was performed utilizing MEDLINE, EMBASE, CINAHL, PSYCHinfo and COCHRANE databases. All RCTs and quasi-experimental studies of smoking-cessation interventions initiated preoperatively, with cessation measured at twelve months postoperatively, were identified. A meta-analysis was performed using pooled RCT results. Results: Four RCTs and two quasi-experimental studies were included in this review. Two RCTs demonstrated a statistically significant association between preoperative smoking cessation interventions and cessation at twelve months. Another RCT demonstrated a similar, though non-significant, trend. Additionally, the quasi-experimental studies demonstrated cessation rates of 48% to 56% at twelve months postoperatively. In a fixed-effects model, preoperative cessation interventions were associated with a greater likelihood of cessation at twelve months (relative risk, 1.60, 95% CI 1.11-2.32, P=0.01), although this effect was no longer significant after applying a random-effects model (relative risk, 1.79, 95% CI 0.91-3.53, P=0.09). Conclusions: The results of this review suggest that preoperative smoking cessation programs can generate long-term (≥12 months) smoking cessation. Further research is needed to explore this association. Additional studies should seek to identify approaches that optimize preoperative smoking cessation programs in the promotion of short-, as well as long-term, cessation.

Poster Title: REVITALIZATION OF BONE ALLOGRAFT WITH HUMAN INDUCED PLURIPOTENT STEM CELLS

Category: Surgery

School: Medicine   Year: 2nd

Poster Location: ED2 North Room 2102   Poster Number: 62

Abstract:

REVITALIZATION OF BONE ALLOGRAFT WITH HUMAN INDUCED PLURIPOTENT STEM CELLS. Davis, B (MD, UCSOM); Sauque, M; Baldini, T; Bilousova, G; Patel, V; Payne, K; University of Colorado, Aurora, CO.   The aim of this study was to determine whether human induced pluripotent stem cells (iPSCs) could adhere, remain viable, and undergo osteogenic differentiation on a human cancellous bone allograft.   Human fibroblasts were reprogrammed to iPSCs and differentiated towards the mesenchymal lineage (iPSC-MSC). iPSC-MSCs were evaluated for mesenchymal markers CD90, CD73 and CD105 by flow cytometry. Bone marrow-derived mesenchymal stem cells (BM-MSC) were the positive control. Osteogenic differentiation potential in monolayer culture was evaluated by stimulating iPSC-MSCs with either complete culture medium (CCM) or osteogenic medium (OSM). At 4 weeks, calcium deposition was evaluated by Alizarin Red stain. iPSC-MSCs were seeded onto 4.8mm x 4.8mm decellularized cylindrical cancellous bone cores obtained from cadaveric humeral head. Scaffolds were seeded with 1.2 x 106 cells and cultured in OSM or CCM. An unseeded group was cultured in OSM. Viability and attachment was evaluated using the LIVE/DEAD assay at 3 hours, 3 days, and 28 days. Histological samples were obtained after 28 days, decalcified, paraffin embedded and stained with Hematoxylin and Eosin (H&E).   During mesenchymal induction, iPSCs began to display a fibroblast-like morphology usually seen with MSCs. iPSC-MSCs also expressed mesenchymal cell surface markers CD90, CD73 and CD105 (Fig. 1). iPSC-MSCs cultured in OSM in monolayer stained positive for Alizarin Red indicating their ability to undergo osteogenic differentiation (Fig. 2). The LIVE/DEAD assay revealed that cells attached and were viable up to 28 days regardless of media type (Fig. 3). These live cells were mainly seen around the outside edge of the construct. H&E staining showed variability in the porosity of the bone allografts and indicated that cells were present at 28 days. The resulting tissue appeared denser in the scaffolds cultured in OSM.   Human iPSCs were able to attach and remain viable on a human bone allograft, suggesting that they have potential to revitalize tissue. The lack of cells in the center of the scaffold suggests that future experiments may require a perfusion system. The greater tissue formation in the scaffold seeded with iPSCs and cultured in OSM suggests that iPSCs can be stimulated to form matrix within bone.

Poster Title: Care Coordination Rounds

Category: Humanities and Bioethics

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 2301   Poster Number: 30

Abstract:

CARE COORDINATION ROUNDS R De Andrade Pereira, (MD UC-SOM), M Rovira, (MD UC-SOM) S Groves, D Medrano, M Muszelik, M Ross, J Sweigart MD, D Tad-Y MD, R Peirce MD, Division of General Internal Medicine, University of Colorado, Aurora, CO.   Well-designed multidisciplinary rounds (MDRs) have been shown to decrease stroke mortality. Thus, hospitals hoping to become Centers of Excellence have been charged by JAHCO (Joint Commission: Accreditation, Health Care and Certification) to implement disease-specific MDRs. However, at the University of Colorado Hospital, a JAHCO Stroke Center of Excellence, the current state stroke MDRs, based on frontline staff feedback, are one that interferes with interprofessional communication and patient-care coordination, which results in an increased patient length of stay. In an effort to decrease the length of stay of ischemic stroke patients, a redesign of the current MDRs gave rise to the Care Coordination Rounds (CCRs). This redesign hopes to enable efficient quality conversation between all neurology teams involved by way of an improved [CCR] platform for the exchange of patient information. In doing so, end goals of the new CCRs are three-fold: Decrease the length of stay of ischemic stroke patients, decrease the amount of work experienced by each neurology personnel, and to produce an overall increase in patient satisfaction and education. Future goals for the project aim to achieve CCRs that function off both face-to-face rounding combined with a facilitation tool for both ease of information access and the ability for Stroke Team Members to be "present in absentia". The Stroke Team Care Coordination Rounds are currently in the first phases of implementation at UCH. Initial feedback has shown promising reviews from staff and patients alike.

Poster Title: HUMAN MILK AS A THERAPEUTIC FOR DRY EYE

Category: Vision

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 2302   Poster Number: 29

Abstract:

HUMAN MILK AS A THERAPEUTIC FOR DRY EYE. JL Diego (M.D., School of Medicine), JM Petrash, M Pedler, Department of Ophthalmology, University of Colorado, Denver, CO.   The purpose of this study was to investigate if human milk shows efficacy in the treatment of dry eye. Induction of dry eye was accomplished by treating twice daily with topical administration of 5µl PBS or 0.2% benzalkonium chloride (BAK) for 4 days. We monitored the mice for dry eye with fluorescein staining on a slit lamp microscope and zone quick for tear volume. After 4 days we treated the eyes four times a day with 5µl of PBS, milk, or cyclosporine for an additional 7 days. All eyes were enucleated at day 11, fixed, and imaged to measure corneal thickness. Fluorescein staining demonstrated punctates and possibly even corneal burns at day 4 which healed by day 11 . Punctates were most severe in the dry eye group. Tear volume demonstrated an overall increasing trend over the 11 day period in all groups. This is attributed to the over production of tears to compensate for the induction of dry eye. Corneal thickness was the most striking data showing significant improvement with whole milk, aqueous milk and cyclosporine compared to dry eye model induced by BAK. In conclusion, whole human milk and the aqueous phase of human milk show efficacy as a therapeutic for dry eye.

Poster Title: MICRORNA-424 INHIBITS TUMOR CELL GROWTH YET PROMOTES BREAST CANCER METASTASIS

Category: Hematology and Oncology

School: Graduate   Year: 6th

Poster Location: ED 2 South Bridge   Poster Number: 44

Abstract:

MICRORNA-424 INHIBITS TUMOR CELL GROWTH YET PROMOTES BREAST CANCER METASTASIS. DJ Drasin, (Ph.D., GS), AL Guarnieri, D Neelakantan, J Kim, P Gasparini, L Cascione, K Huebner, AC Tan, HL Ford, Program in Molecular Biology, Department of Pharmacology, University of Colorado Anschutz Medical Campus, Aurora, CO.   PURPOSE: The epithelial-to-mesenchymal transition (EMT) is a normal and dynamic developmental process that has been implicated in metastasis. Regulation of this oncogenic EMT, as well as cellular processes that are altered downstream, need to be better understood to guide therapeutic development.   During an EMT, epithelial cells lose their tight cell-cell adhesion in favor of looser focal cell-cell contacts, in addition to changes in a number of epithelial and mesenchymal proteins that can identify which state cells are in. Importantly, the mesenchymal state increases cellular migration and invasion, traits that can facilitate metastasis. Carcinoma metastases are typically epithelial, though, thus tumor cells that metastasize through an EMT are hypothesized to undergo a reverse mesenchymal-to-epithelial transition (MET) at the secondary site. This ability of tumor cells to shift back and forth along the EMT continuum is a reflection of cellular plasticity that tumor cells possess, making regulation of EMT-MET a critical facet of progression. While much is known of how the epithelial half of the EMT program is repressed, regulation of the mesenchymal half is largely unstudied.   METHODS: MicroRNA (miR) and protein-coding genes were over-expressed in normal and tumorigenic human mammary epithelial cell lines and assayed by real-time PCR, immunoblotting, migration and stemness assays and next generation sequencing. Immunocompromised mice were used for tumor-initiation and metastasis assays.   RESULTS: MiR-424 increases mesenchymal properties while maintaining epithelial characteristics, yielding an intermediate EMT mediated by TGFBR3. MiR-424 increases motility and decreases matrix adhesion, but decreases tumor initiation, while metastatic cells are able to down-regulate miR-424. Patient breast tumors have high miR-424 versus normal breast, yet patient metastases have low miR-424 versus primary tumors.   CONCLUSIONS: These findings suggest that miR-424 plays a dual role in cancer progression, facilitating the early stages of metastasis, but repressing outgrowth at secondary sites, supporting the need for MET in macrometastatic disease.

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

Category: Cardiovascular

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 1209   Poster Number: 3

Abstract:

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

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

Category: Hematology and Oncology

School: Medicine   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 46

Abstract:

In the search for regulators of chromosome segregation, a variety of genome-wide approaches have been utilized. One such remarkable study, a mutagenesis screen in Schizosaccharomyces pombe, utilized the intensity of nuclei signal as a readout of successful chromosome segregation which identified novel regulators of chromosome segregation. Here we use a preliminary qualitative assessment of a genome-wide RNA interference (RNAi) screen of the Male-specific Lethal 1 protein (MSL1) in Drosophila S2 cells to identify novel regulators of chromosome segregation. Knockdowns of these factors, by RNAi, led to multiple MSL1 foci per nucleus, in contrast to the wild-type phenotype of a single MSL1 focus per nucleus. We denoted this as the "fragmented MSL1 phenotype," reflecting an incorrect number of X chromosomes that have accumulated due to chromosome mis-segregation. Computational analysis of this RNAi screen yielded a total of 374 positive genes. Five identified novel genes, CG30020, NEK2, His4r, CG5880, and CG2865 were confirmed to display severe chromosome mis-segregation after RNAi knockdown. Thus, this computational approach of associating an easily discernible "fragmented MSL1 phenotype" with chromosome mis-segregation was successful in identifying novel regulators of chromosome segregation in Drosophila melanogaster. Additional cellular assays, such as investigating whether these novel factors co-localize and interact with known centromere proteins at the centromere locus, will shed light into their specific roles in the process of chromosome segregation.

Duran, Michael

Poster Title: A NEW ANIMAL MODEL FOR DETERMINING THE EFFECTS OF DIABETES ON OSTEOARTHRITIS

Category: Surgery

School: Medicine   Year: 3rd

Poster Location: Ed 2 North Room 2102   Poster Number: 64

Abstract:

Attached in email to coloradoresearchtrack@ucdenver.edu

Dyamenahalli, Kiran

Poster Title: Photoactive shape memory polymer – gold nanocomposite materials for transcatheter medical devices

Category: Materials and Basic Processes

School: Graduate   Year: 4th

Poster Location: ED 2 North Room 2212   Poster Number: 77

Abstract:

Photoactive shape memory polymer – gold nanocomposite materials for transcatheter medical devices. K Dyamenahalli, (MD/PhD, GS), and R Shandas, Department of Bioengineering, University of Colorado, Denver, CO. Modern trans-catheter devices (TCDs), such as vascular stents and embolic coils, are generally fabricated using metal alloys. While these materials are durable and radiopaque, their bulk mechanical, imaging, and surface characteristics are static, resulting in biocompatibility and device performance issues. We aim to develop a highly-tunable composite material for TCD design, which combines the characteristics of shape-memory polymers (SMPs) and gold nanoparticles (GNPs). With adequate thermal energy, SMPs can recover from large deformations, a useful property for catheter-based storage and delivery. GNPs are expected to confer x-ray visibility, significantly extend the spectrum of attainable mechanical properties, and allow for precise control of thermal transitions with visible light energy absorption. Here, we present the initial results of our effort to disperse GNPs in acrylate SMPs through targeted surface-functionalization and study the resulting composite material properties. GNPs were synthesized chemically via the reduction and capping of hydrogen tetrachloroaurate(III) trihydrate with oleylamine at elevated temperature, followed by ligand exchange with dodecanethiol. X-ray photoelectron spectroscopy of GNP films was used to confirm surface thiolation. Surface-stabilized GNPs were then suspended, up to 1 wt%, by sonication, in a mixture of two acrylate monomers: 80 wt% tert-Butyl acrylate and 20 wt% poly(ethylene glycol) dimethacrylate (Mn 550). This mixture was polymerized in the presence of thermal initiators. UV-Vis spectroscopy and transmission electron microscopy of the resulting composite materials revealed well-dispersed clusters of 10-15 nm GNPs. The composites demonstrated higher moduli and improved shape recovery characteristics, including free strain recovery and shape recovery sharpness. Moreover, the glassy-rubbery transition was successfully induced by 500 mW/cm2 532 nm light in a spatially-controlled manner, opening up the possibility of using green laser light to deploy polymeric TCDs. To improve the quality of the composite, future work will introduce heterogeneity in molecular weight and hydrophobicity to the GNP surface brush. Transport phenomena, including electrical and thermal conduction, will also be assessed.

Poster Title: THE EFFECTS OF INTERFERON GAMMA RECEPTOR 1 DOWN REGULATION ON MACROPHAGES DURING BACTERIAL INFECTION.

Category: Immunology and Autoimmune Diseases

School: Graduate   Year: 3rd

Poster Location: ED 2 South Room 2305   Poster Number: 24

Abstract:

THE EFFECTS OF INTERFERON GAMMA RECEPTOR 1 DOWN REGULATION ON MACROPHAGES DURING BACTERIAL INFECTION. EM Eshleman (Ph.D., GS), SJ Kearney, and LL Lenz. Integrated Department of Immunology, National Jewish Health and University of Colorado, Denver, CO.   Type I and type II interferons (IFNs) are both important regulators of the immune response; yet they signal through different receptor systems and in some cases have opposing or antagonistic effects. The biological consequences of antagonistic crosstalk between these two IFN response pathways remain elusive. Our laboratory previously demonstrated that one mechanism by which type I IFNs suppress responsiveness to type II IFN (IFNγ) is through down regulation of its receptor, IFNGR. This down regulation occurs predominantly in myeloid cells. We hypothesized that such down regulation normally decreases pro-inflammatory activation of macrophages and thus increases susceptibility to bacterial infections. To test our hypothesis, we developed a transgenic mouse model, fGR1, in which a functional flag-tagged IFNGR1 is expressed in myeloid cell types using the type I IFN-unresponsive csfr1 promoter. The fGR1 and control C57BL/6 mice were infected with Listeria monocytogenes, a bacterial pathogen that induces infected host cells to produce type I IFN. Consistent with our hypothesis, we observed increased surface expression of the IFNGR and increased expression of IFNγ-induced activation markers such as MHC II, CD64, and CD80. The fGR1 mice also displayed significantly increased resistance as indicated by decreased bacterial burdens in the livers and spleens. These results suggest that preventing the down regulation of IFNGR in macrophages increases their activation during a Listeria monocytogenes infection and improves clearance of this pathogen.

Poster Title: SCREENING HISTONE DEACETYLASE INHIBITORS TO UPREGULATE DJ-1 GENE EXPRESSION TO PREVENT DOPAMINE NEURON DEATH IN PARKINSON'S DISEASE

Category: Pharmacology and Physiology

School: Graduate   Year: 2nd

Poster Location: ED 2 North Room 2301   Poster Number: 79

Abstract:

SCREENING HISTONE DEACETYLASE INHIBITORS TO UPREGULATE DJ-1 GENE EXPRESSION TO PREVENT DOPAMINE NEURON DEATH IN PARKINSON'S DISEASE. Brent Fitzwalter (Ph.D., GS), J. Cummiskey Ph.D, W. Zhou Ph.D, Curt Freed MD. Department of Pharmacology, University of CO, Denver, CO.   Parkinson's disease is a common neurodegenerative disorder characterized by the death of dopamine neurons in the substantia nigra, leading to slow movement, muscle rigidity, and tremors. People with mutations in the DJ-1 gene develop autosomal recessive, early onset Parkinson's disease. Overexpression of the DJ-1 gene and protein has been shown to prevent the death of rat dopamine neurons in tissue culture and to preserve motor and cognitive function in transgenic mice that are genetically programmed to get a form of Parkinson's.   We have discovered a way to pharmacologically upregulate DJ-1 gene expression, protecting dopamine neurons from cell death. Phenylbutryate is a histone deacetylase inhibitor (HDACi) that can upregulate DJ-1 protein levels by 300% in rat dopamine neuron cell culture experiments and can rescue these neurons from cell death induced by oxidative stress. To search for additional HDAC inhibitors that may be able to protect dopamine neurons, we have developed a screening method using N27 rat dopamine neurons and HEK293 cells with the DJ-1 promoter linked to a luciferase reporter. Results from a series of HDAC inhibitors showed increases in DJ-1 protein levels that ranged from less than 5% (valproic acid) to 300% (phenylbutyrate). Intermediate levels were achieved with DPAH 90%, MGCD 60%, Trichostatin A 50% , Vorinostat 20%, Tubastatin 50%, and MS-275 25%. The ability to pharmacologically upregulate the DJ-1 gene may prevent the death of dopamine neurons in patients and halt the progression of Parkinson'

Francomano, Jesse

Poster Title: Chronic Physical and Mental Health Conditions Among Homeless Adolescents and Young Adults

Category: Health Care and Public Health

School: Nursing   Year:

Poster Location: ED 2 South Room 2208   Poster Number: 31

Abstract:

CHRONIC PHYSICAL AND MENTAL HEALTH CONDITIONS AMONG HOMELESS ADOLESCENTS AND YOUNG ADULTS. L Hellerova (BSN), J Francomano and S Harpin, College of Nursing, University of Colorado, Aurora, CO.   The purpose of this study was to examine the characteristics of the homeless adolescent and young adult population living with chronic physical and mental health conditions, as well as to highlight correlates of chronic mental and/or physical health conditions in this population. Research regarding homeless adolescents and young adults suggests that this population has significantly higher rates of, and is at higher risk for developing, chronic physical and/or mental health conditions due to numerous predisposing factors as well as environmental and socioeconomic circumstances. While the data suggests that many in the population have access to healthcare and qualify for health insurance, most of them are not receiving continuous or consistent care, which further deteriorates their potential ability to escape the cycle of homelessness. An anonymous, cross-sectional survey of 1555 homeless youth and young adults ages 12-28 was collected one October evening in 2009 across Minnesota. Volunteer surveyors canvassed participants primarily in shelters and on the streets. Univariate frequencies were used to describe our sample. Crosstabulation tables were used to further describe prevalence of chronic physical and health issues by age strata. In our unweighted sample, the majority of respondents were 18 years or older (91%), female (62%) and educated (71%). 98% of the population reported having a history of being placed in foster care, a group home, halfway house, or transitional home. 293 (19%) of those surveyed reported having a chronic physical health condition, with 73% of those reporting asthma or other respiratory conditions, followed by hypertension, diabetes, and STIs/HIV in order of prevalence. 40% of the sample reported having a mental health condition, nearly one third reporting major depression, followed by bipolar disorder, PTSD and personality disorders as most common diagnoses. Prevalence of chronic physical health conditions was highest among those 18-21 years (22%), while the prevalence of mental health conditions increased steadily from a low of 25% among those under 18 to a high of 44% among those 22-28 years. We present the following correlates of health: education, employment, history of abuse/neglect, out-of-home status, insurance coverage, emergency services use, barriers to health care, and place of health care. Our research helps to confirm previous studies on the physical and mental health status of homeless youth in America. Our findings are limited in they are from a single state at a single point-in-time, and a geographic location (Minnesota) that has a history of well-funded social programs for its vulnerable citizens. Despite high rates of education, employment and health coverage in our sample, these

indicators of health still lag behind those seen in the general population. Healthcare institutions would benefit from training their staff to understand the typology of the homeless youth in an effort to not only provide better treatment when it is sought, but attempt to develop new methods of outreach and preventative care options particularly among those living with chronic physical or mental health conditions.

Poster Title: Investigating a role for liver involution in postpartum breast cancer metastasis

Category: Hematology and Oncology

School: Graduate   Year: 3rd

Poster Location: ED 2 South Bridge   Poster Number: 48

Abstract:

INVESTIGATING A ROLE FOR LIVER INVOLUTION IN POSTPARTUM BREAST CANCER METASTASIS.   E Goddard, (Ph.D., GS), O Maller, V Borges, P Schedin Department of Medical Oncology, University of Colorado Anschutz Medical Campus   Women with postpartum breast cancer, defined as a breast cancer diagnosis within 5 years of giving birth, have a significantly increased risk for metastasis and a reported 3-fold reduced survival when compared to age-matched nulliparous breast cancer patients. In preclinical models, the Schedin lab has identified mammary gland involution as a key event that drives this increased risk for metastasis. During involution, triggered by a cessation of lactation or by birth if there is no lactation, the mammary gland undergoes tissue remodeling to return the lactation-competent breast to a non-secretory state. Postpartum mammary gland involution is characterized by epithelial cell death, an influx of immunosuppressive immune cells, and extensive stromal remodeling, all of which are predicted to contribute to breast cancer progression. In rodent models of postpartum breast cancer we observe larger tumors and increased metastasis compared to nulliparous controls. The question of whether physiologic tissue remodeling occurs in organs besides the mammary gland in the postpartum period, and escalates breast cancer metastasis, has not been previously explored. Work I have done in the Schedin lab revealed the novel finding that the maternal rodent liver undergoes weaning-induced regression and stromal remodeling during the window of postpartum mammary gland involution. Based on these findings we hypothesize that postpartum liver involution results in a pro-metastatic microenvironment that supports breast cancer metastasis. The establishment of a pro-metastatic microenvironment in the postpartum liver would identify a novel mechanism by which liver metastasis occurs and might explain the increase in metastasis in postpartum breast cancers.

Poster Title: Is Vitamin D deficiency a Risk Factor for Breast Cancer?

Category: Hematology and Oncology

School: Public Health   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 50

Abstract:

IS VITAMIN D DEFICIENCY A RISK FACTOR FOR BREAST CANCER? R.F.Gonzalez MD, FACS, Certificate Program Student, School of Public Health, University of Colorado Background/Objective: Epidemiologic studies suggest that adequate vitamin D concentrations can exert a beneficial effect reducing breast cancer development. The observed lower risk of breast cancer among women living in the south or regions of high solar radiation was confirmed in a cohort analysis that found that high exposure to sunlight was associated with a 25–65% reduction in breast cancer risk. Despite the supplementation of foods, the majority of vitamin D is derived from casual exposure to sunlight. For most persons, casual sunlight exposure provides 80–90% of the body's circulating stores of vitamin D. In order to confirm the relationship between low levels of Vitamin D with breast cancer, we conducted a case-control study in women who live in an area that receives high levels of UVB irradiation all around the year. Our hypothesis was that circulating 25(OH) D concentrations would be significantly lower in women with a diagnosis of breast cancer than in controls. Methods: A 2:1 case-controlled study of recently diagnosed breast cancer and normal mammogram patients was done in a city located between 21 and 22 degrees north, with an average temperature of 19.2 o C and daily dose of 6 to 7 kWh/square meter of solar energy. The population in 2010 was 1,184,996 inhabitants, and in 2012, 100 new cases of breast cancer were diagnosed and treated. We excluded patients with hyper parathyroidism, malabsortion, skin grafts, thyroid replacement therapy, patients who consumed prescribed or over the counter vitamin D supplements, or had any other malignancy and patients with alteration in serum levels of Calcium, Phosphorus or Magnesium. All patients had an informed consent form and those who accepted were submitted to two separate interviews, one to assess breast cancer risk factors and solar exposure habits and a second one for a nutritional survey of vitamin D intake. Serum levels of Calcium, Phosphorus, Magnesium , 25 OH Vitamin D and Vitamin D Receptor were measured. A bone density scan was performed in all patients. Samples of the tumor tissue were obtained from all cases for review by the same pathologist and for the search of the Vitamin D receptor. All patients had a closing interview in which their results were disclosed to them. Those with abnormalities in Vitamin D or in the bone density study were referred to their primary care physician for treatment. Results: 24 breast cancer patients with an age range of 22 through 79 years, with a median of 50.5 and a mean of 53.6. And 52 controls, 24 to 67 years old, median of 51 and mean of 51.09. Risk factors were similar in both groups. Vitamin D ingestion was deficient in 18 patients and 22 controls and sufficient in 6 patients and 30 controls, OR 2.2. Sun exposure of at least 30 minutes per day was present in 9 patients and 15 controls while 15 patients and 37 controls had less sun exposure or used adequate protection, OR: 1.48. Two

patients and 13 controls had normal Vitamin D levels (30 -60), two patients and 26 controls had low levels (20 to 30) and 18 patients and 12 controls had very low levels (< 20) OR (

Poster Title: BIOMECHANICAL COMPARISON OF TRADITIONAL ANCHORS TO ALL-SUTURE ANCHORS IN A DOUBLE-ROW ROTATOR CUFF REPAIR CADAVER MODEL

Category: Surgery

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2108   Poster Number: 70

Abstract:

BIOMECHANICAL COMPARISON OF TRADITIONAL ANCHORS TO ALL-SUTURE ANCHORS IN A DOUBLE-ROW ROTATOR CUFF REPAIR CADAVER MODEL. A Goschka (MD, SOM), J Hafer, (MD, SOM), T Baldini, K Reynolds, N Aberle, E McCarty, Department of Orthopedics, University of Colorado, Denver, CO.   Objectives: The objective of this study was to assess the strength and failure characteristics of double-row full-thickness supraspinatus repair using a new all-suture anchor, ICONIX2 (Stryker, Mahwah, NJ), versus traditional anchors. Four medial/lateral row anchor combinations were compared in a human cadaveric model (Group A: ICONIX2/ICONIX2; Group B: ICONIX2/Stryker ReelX 3.9mm; Group C: ICONIX2/Stryker ReelX 4.5mm; Group D: Arthrex Bio-CorkScrew FT 4.5mm/Arthrex Bio-SwiveLock 4.75mm (Arthrex Inc., Naples, FL)). No study has yet investigated all-suture anchor biomechanics within the context of a simulated rotator cuff repair.   Methods: Nine human cadaver shoulders were used for each anchor combination. Full-thickness tears were simulated by dissecting the supraspinatus tendon from the greater tuberosity and resecting a distal portion (10mm) of the tendon. After repair, tendons underwent cyclic loading from 10N to 100N at 0.25Hz for 500 cycles, followed by load-to-failure at 1mm/sec. A motion capture system was used to measure the gap formation between the supraspinatus and the humerus at the location of both the anterior and posterior anchors. Load and deflection data was recorded at 25 Hz. Gap formation and construct stiffness were measured at cycles 5, 100, 200, 300, 400, and 500, and for ultimate load. In statistical analysis, one-way ANOVA with Tukey's HSD test in post-hoc analysis was used to assess significance between groups (P≤0.05).   Results: Anchor combination had no statistically significant effect on anterior or posterior gap formation at all cycles (P values between 0.36 and 0.90) (Figure 1), construct stiffness (P values between 0.72 and 0.90), or ultimate load (P=0.06) (Table 1). Anchor pullout was the primary mode of failure for each group.   Conclusions: The new all-suture anchor demonstrated comparable biomechanical performance in multiple double-row anchor combinations to a combination of traditional solid-body anchors. Thus it presents itself as an attractive new option for surgeons looking to further reduce the invasiveness of rotator cuff repairs.   Relevant disclosure for all authors: This study was funded by Stryker Joint Preservation, Mahwah, NJ.

Poster Title: CpG promotes Immunoglobulin A production from human newborns by enhancing B cell responsiveness to T cell help

Category: Immunology and Autoimmune Diseases

School: Graduate   Year: 5th

Poster Location: ED 2 South Room 2306   Poster Number: 15

Abstract:

CPG PROMOTES IMMUNOGLOBULIN A PRODUCTION FROM HUMAN NEWBORNS BY ENHANCING B CELL RESPONSIVENESS TO T CELL HELP. CE Gustafson (Ph.D., G.S), S Miller, D Frank, EN Janoff, Department of Immunology, University of Colorado, Aurora, CO. The absence of immunoglobulin A (IgA) in the intestinal tract renders young infants highly susceptible to enteric infections. Moreover, mucosal vaccines administered to newborns and young infants induce limited IgA responses and require multiple boosters to be effective. Therefore, the identification of newborn-specific factors that can enhance the development of protective IgA is essential.   We found the novel combination of the bacterial DNA analogue CpG combined with soluble (IL-21, IL-4) and cognate (anti-CD40) helper T cell factors (TCF) promoted the production of IgA from B cells of newborns in a direct and CpG dose-dependent manner. Expression of toll-like receptor 9 (TLR9), the receptor for CpG, was expressed by cord blood B cells and upregulated after co-stimulation with CpG and TCF, as was CpG binding. CpG alone increased surface expression of receptors for both T cell stimuli (IL-21 receptor and CD40), whereas CpG and TCF co-stimulation increased IL-21 receptor and CD40 mRNA but not protein expression. Additionally, CpG and TCF co-stimulation increased mRNA expression of the IgA1 heavy chain, as well as factors required for B cell class switch recombination and differentiation.   Taken together, these data suggest that CpG increases newborn's B cell responsiveness to T cell help by altering B cell expression of CD40 and IL-21 receptor and inducing IgA mRNA and protein expression. Thus, CpG may serve as an effective adjuvant to enhance local IgA responses to mucosal vaccines and to induce early protection against enteric infections in very young infants.

Poster Title: BIOMECHANICAL COMPARISON OF TRADITIONAL ANCHORS TO ALL-SUTURE ANCHORS IN A DOUBLE-ROW ROTATOR CUFF REPAIR CADAVER MODEL

Category: Surgery

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2108   Poster Number: 70

Abstract:

BIOMECHANICAL COMPARISON OF TRADITIONAL ANCHORS TO ALL-SUTURE ANCHORS IN A DOUBLE-ROW ROTATOR CUFF REPAIR CADAVER MODEL. A Goschka (MD, SOM), J Hafer, (MD, SOM), T Baldini, K Reynolds, N Aberle, E McCarty, Department of Orthopedics, University of Colorado, Denver, CO.   Objectives: The objective of this study was to assess the strength and failure characteristics of double-row full-thickness supraspinatus repair using a new all-suture anchor, ICONIX2 (Stryker, Mahwah, NJ), versus traditional anchors. Four medial/lateral row anchor combinations were compared in a human cadaveric model (Group A: ICONIX2/ICONIX2; Group B: ICONIX2/Stryker ReelX 3.9mm; Group C: ICONIX2/Stryker ReelX 4.5mm; Group D: Arthrex Bio-CorkScrew FT 4.5mm/Arthrex Bio-SwiveLock 4.75mm (Arthrex Inc., Naples, FL)). No study has yet investigated all-suture anchor biomechanics within the context of a simulated rotator cuff repair.   Methods: Nine human cadaver shoulders were used for each anchor combination. Full-thickness tears were simulated by dissecting the supraspinatus tendon from the greater tuberosity and resecting a distal portion (10mm) of the tendon. After repair, tendons underwent cyclic loading from 10N to 100N at 0.25Hz for 500 cycles, followed by load-to-failure at 1mm/sec. A motion capture system was used to measure the gap formation between the supraspinatus and the humerus at the location of both the anterior and posterior anchors. Load and deflection data was recorded at 25 Hz. Gap formation and construct stiffness were measured at cycles 5, 100, 200, 300, 400, and 500, and for ultimate load. In statistical analysis, one-way ANOVA with Tukey's HSD test in post-hoc analysis was used to assess significance between groups (P≤0.05).   Results: Anchor combination had no statistically significant effect on anterior or posterior gap formation at all cycles (P values between 0.36 and 0.90) (Figure 1), construct stiffness (P values between 0.72 and 0.90), or ultimate load (P=0.06) (Table 1). Anchor pullout was the primary mode of failure for each group.   Conclusions: The new all-suture anchor demonstrated comparable biomechanical performance in multiple double-row anchor combinations to a combination of traditional solid-body anchors. Thus it presents itself as an attractive new option for surgeons looking to further reduce the invasiveness of rotator cuff repairs.   Relevant disclosure for all authors: This study was funded by Stryker Joint Preservation, Mahwah, NJ.

Poster Title: ASSESSMENT OF COMMUNITY HEALTH WORKER TRAINING PROGRAM IN THE PERUVIAN AMAZON DEMONSTRATES EFFECTIVE LEARNING RETENTION: IMPLICATIONS FOR HEALTH CARE EDUCATION IN A RESOURCE-LIMITED SETTING

Category: Education

School: Public Health   Year: 2nd

Poster Location: ED 2 South Room 1307   Poster Number: 12

Abstract:

ASSESSMENT OF COMMUNITY HEALTH WORKER TRAINING PROGRAM IN THE PERUVIAN AMAZON DEMONSTRATES EFFECTIVE LEARNING RETENTION: IMPLICATIONS FOR HEALTH CARE EDUCATION IN A RESOURCE-LIMITED SETTING. KE Hall (MPH, CSPH), MA Miller, MA, VA Fialkowski, ML Cole, JA Boat, JW Bellows, MD, MPH1 & I Shumskiy, Comunidades Unidas Peru, 501.(c)3 not-for-profit organization, Denver, Colorado. 1. Global Health Track Director, University of Colorado School of Medicine   Purpose: UNICEF data suggests under 5 mortality rates (U5MR) rates in rural Peru are nearly double those of urban areas. To reduce U5MR, the World Health Organization developed the Integrated Management of Childhood Illness (IMCI) framework, which utilizes vital signs to classify illness severity in children under five. Using IMCI as a model, Comunidades Unidas Peru (CU Peru) designed and implemented trainings for community health workers (CHWs) in the Peruvian Amazon to correctly measure temperature, heart rate, and respiratory rate. This study evaluated the effectiveness of the training to increase ability to collect and interpret patient vital signs in the rural areas of the Loreto Region in Peru. Method: A vital sign pre- and post-test was administered to CHWs at each training to evaluate improvement over the year and the retention of the vital signs curriculum from year to year. Results: After adjusting for gender, age, and years as a CHW, CHWs that have previously attended CU Peru trainings scored higher on the pre-test than first-time attendees ($p=0.07$); although marginally significant, it implies a trend of curriculum retention. No significant difference was observed in post-test scores between first-time CHW training attendees and those CHWs who had previously attended ($p=0.49$). For those CHWs who had attended training sessions in 2012 and 2013, there was not a significant difference in the post-test scores from 2012 and pre-test scores in 2013 ($p= 0.13$) again indicating a trend in curriculum retention. Conclusion: CHWs who complete the training retain the curriculum from year to year, and performed better at the pre-test than those CHWs who have not previously attended a training. After completing training, first time attendees and repeat attendees did not differ significantly in their post-test scores, indicating that single training provides substantial improvements. Future work will evaluate the effect of training on community health outcomes.

Poster Title: Chronic Physical and Mental Health Conditions Among Homeless Adolescents and Young Adults

Category: Health Care and Public Health

School: Nursing   Year: 2nd

Poster Location: ED 2 South Room 2208   Poster Number: 31

Abstract:

CHRONIC PHYSICAL AND MENTAL HEALTH CONDITIONS AMONG HOMELESS ADOLESCENTS AND YOUNG ADULTS. L Hellerova (BSN), J Francomano and S Harpin, College of Nursing, University of Colorado, Aurora, CO.   The purpose of this study was to examine the characteristics of the homeless adolescent and young adult population living with chronic physical and mental health conditions, as well as to highlight correlates of chronic mental and/or physical health conditions in this population. Research regarding homeless adolescents and young adults suggests that this population has significantly higher rates of, and is at higher risk for developing, chronic physical and/or mental health conditions due to numerous predisposing factors as well as environmental and socioeconomic circumstances. While the data suggests that many in the population have access to healthcare and qualify for health insurance, most of them are not receiving continuous or consistent care, which further deteriorates their potential ability to escape the cycle of homelessness. An anonymous, cross-sectional survey of 1555 homeless youth and young adults ages 12-28 was collected one October evening in 2009 across Minnesota. Volunteer surveyors canvassed participants primarily in shelters and on the streets. Univariate frequencies were used to describe our sample. Crosstabulation tables were used to further describe prevalence of chronic physical and health issues by age strata. In our unweighted sample, the majority of respondents were 18 years or older (91%), female (62%) and educated (71%). 98% of the population reported having a history of being placed in foster care, a group home, halfway house, or transitional home. 293 (19%) of those surveyed reported having a chronic physical health condition, with 73% of those reporting asthma or other respiratory conditions, followed by hypertension, diabetes, and STIs/HIV in order of prevalence. 40% of the sample reported having a mental health condition, nearly one third reporting major depression, followed by bipolar disorder, PTSD and personality disorders as most common diagnoses. Prevalence of chronic physical health conditions was highest among those 18-21 years (22%), while the prevalence of mental health conditions increased steadily from a low of 25% among those under 18 to a high of 44% among those 22-28 years. We present the following correlates of health: education, employment, history of abuse/neglect, out-of-home status, insurance coverage, emergency services use, barriers to health care, and place of health care. Our research helps to confirm previous studies on the physical and mental health status of homeless youth in America. Our findings are limited in they are from a single state at a single point-in-time, and a geographic location (Minnesota) that has a history of well-funded social programs for its vulnerable citizens. Despite high rates of education, employment and health coverage in our sample, these

indicators of health still lag behind those seen in the general population. Healthcare institutions would benefit from training their staff to understand the typology of the homeless youth in an effort to not only provide better treatment when it is sought, but attempt to develop new methods of outreach and preventative care options particularly among those living with chronic physical or mental health conditions.

Poster Title: HUMAN ALDEHYDE DEHYDROGENASE 1B1 POLYMORPHISMS MAY AFFECT THE METABOLISM OF ACETALDEHYDE AND ALL-TRANS RETINALDEHYDE – IN VITRO STUDIES AND COMPUTATIONAL MODELING

Category: Pharmacology and Physiology

School: Graduate   Year: 6th

Poster Location: ED 2 North Room 2301   Poster Number: 81

Abstract:

HUMAN ALDEHYDE DEHYDROGENASE 1B1 POLYMORPHISMS MAY AFFECT THE METABOLISM OF ACETALDEHYDE AND ALL-TRANS RETINALDEHYDE – IN VITRO STUDIES AND COMPUTATIONAL MODELING. Brian C. Jackson (Ph.D, GS), Philip Reigan, David C. Thompson and Vasilis Vasiliou, Department of Pharmaceutical Sciences, University of Colorado, Aurora, CO, Department of Clinical Pharmacy, University of Colorado, Aurora CO 80045 Purpose: To test the metabolism of novel substrates by ALDH1B1 and to predict the effect that human ALDH1B1 polymorphisms will have on these and previously described substrates. Methods: Purified human recombinant ALDH1B1 was used to determine the capacity of ALDH1B1 to metabolize nitroglycerin and all-trans retinaldehyde. Computational-based molecular modeling was used to predict the binding affinities of the substrates acetaldehyde, 4-hydroxynonenal, nitroglycerin, and all-trans retinaldehyde to ALDH1B1 and three human polymorphisms ALDH1B1*2 (A86V), ALDH1B1*3 (L107R), and ALDH1B1*5 (M253V). The binding of the cofactor NAD+ to ALDH1B1 and its polymorphisms was also modeled computationally. These mutant proteins are being expressed in E coli and their kinetic properties are being determined. Results: ALDH1B1 metabolizes and appears to be inhibited by nitroglycerin and has favorable kinetics for metabolism of all-trans retinaldehyde. Differences in calculated docking poses and weak interactions between ligands/cofactor and ALDH enzymes from modeling studies provided a basis for predicting the capacity of each of the variants to metabolize acetaldehyde, nitroglycerin, and all-trans retinaldehyde. Modeling indicated that ALDH1B1*2 and ALDH1B1*5 likely bind NAD+ poorly compared to ALDH1B1 and ALDH2, and all ALDH1B1 mutants had poor binding affinities for nitroglycerin. Conclusions: ALDH1B1 metabolizes the novel substrates nitroglycerin and all-trans-retinaldehyde, and two human polymorphisms (ALDH1B1*2 and ALDH1B1*5) are likely to metabolize substrates poorly, which may affect the roles of ALDH1B1 in stem cells and ethanol metabolism.

Jacobsen, Kristen

Poster Title: INHIBITION OF MERTK IN TUMOR INFILTRATING LEUKOCYTES DECREASES TUMOR GROWTH IN A MOUSE MODEL OF BREAST CANCER

Category: Immunology and Autoimmune Diseases

School: Graduate

Year: 6th

Poster Location: ED 2 South Room 2306

Poster Number: 17

Abstract:

INHIBITION OF MERTK IN TUMOR INFILTRATING LEUKOCYTES DECREASES TUMOR GROWTH IN A MOUSE MODEL OF BREAST CANCER. KM Jacobsen (Ph.D., GS), RS Cook, AM Wofford, D DeRyckere, J Stanford, E Redente, DM Hunter, X Wang, SV Frye, HS Earp, DK Graham, University of Colorado, Denver, CO. Vanderbilt University, Nashville, TN. National Jewish Health, Denver, CO. University of North Carolina School of Medicine, Chapel Hill, NC. Tumor-associated macrophages (TAMs) and other myeloid-derived cells that infiltrate solid tumors have been shown to support tumor growth, proliferation and metastasis. Increased numbers of TAMs have also been associated with poor prognosis in breast cancer. Previous studies have shown that depletion and re-programming of TAMs are effective methods in reducing tumor growth. Mer receptor tyrosine kinase is expressed on macrophages and is involved in suppressing proinflammatory cytokine production following efferocytosis. Using orthotopic and transgenic mouse models of breast cancer, we observed that Mer inhibition in the tumor microenvironment led to decreased primary tumor growth and metastasis. Lethally irradiated MMTV-PyVmT mice transplanted with Mer-/- bone marrow had a 2-fold reduction in tumor growth and altered cytokine production by tumor infiltrating CD11b+ cells compared to wild-type (WT) bone marrow recipients. Tumor-bearing Mer-/- mice also showed enhanced expression of interleukin (IL)-12 and IL-6, proinflammatory cytokines and reduced expression of immunosuppressive cytokines, including IL-10 compared to tumor-bearing WT mice. The tumor-infiltrating CD8+ lymphocyte population was also increased in Mer-/- mice compared to WT mice. Tumor growth could be restored in Mer-/- mice by CD8+ T cell depletion. To further investigate Mer inhibition in the tumor microenvironment as a viable therapeutic strategy, the efficacy of a novel Mer-selective small molecule tyrosine kinase inhibitor (MerTKi) was evaluated in an orthotopic Mer-negative mammary glad tumor model. After 3 weeks of treatment with MerTKi or vehicle, tumor growth was reduced two-fold in mice treated with MerTKi compared to vehicle only. Taken together, these data suggest that Mer inhibition in tumor infiltrating leukocytes can lead to increased acute inflammatory cytokine production and stimulating CD8+ lymphocyte mediated immune response, validating Mer inhibition in the tumor microenvironment as a promising novel therapeutic target in solid tumors, such as breast cancer.

Poster Title: GELATIN-THROMBIN MATRIX TISSUE SEALANT ALTERS RISK OF PELVIC ABSCESS IN PATIENTS UNDERGOING GYNECOLOGIC SURGERY

Category: Surgery

School: Medicine

Year: 2nd

Poster Location: ED 2 North Room 2112

Poster Number: 71

Abstract:

GELATIN-THROMBIN MATRIX TISSUE SEALANT ALTERS RISK OF PELVIC ABSCESS IN PATIENTS UNDERGOING GYNECOLOGIC SURGERY Jarrett MJ (M.D., SOM), Anderson C, Frank DN, Vázquez-Torres A, Gill R, McCollister BD, Behbakht K University of Colorado School of Medicine Division of Basic Reproductive Sciences and Gynecologic Oncology in the Department of Obstetrics and Gynecology, University of Colorado at Denver and Health Sciences Center, Aurora, Colorado, USA.   PURPOSE: Retrospective review of institutional data indicates intra-operative use of gelatin-thrombin matrix tissue sealant is an independent predictor of pelvic abscess and post-operative infection in hysterectomies. We propose further investigations to test whether this is a property unique to gelatin-thrombin matrix tissue sealants as opposed to other topical hemostatic agents (THAs). METHODS: Culture and molecular techniques will be employed to establish sterility of various THAs. THAs will be innoculated in vitro with a pathogen involved in pelvic abscess to compare colony formation. Finally, THAs will be innoculated in culture with intraoperative swabs taken from the vaginal cuff during hysterectomy procedures to assess for growth of pathogens. Medical and demographic data will be collected from these patients to track clinical outcomes. Total aerobic and anaerobic colony counts and PCR quantification of bacterial 16S rRNA in samples provide outcome measures. Plates which produce >5,000 CFUs will be categorized as "contaminated". Pathogens will be identified using common laboratory techniques. Pelvic abscess is defined as an encapsulated collection of fluid in the pelvis as identified on medical imaging, manual vaginal exam consistent with vaginal cuff infection, and fever (>38C) or leukocytosis (11.1 x 10^9/L). RESULTS: Thirteen samples of various THAs collected displayed no colony formation in culture. PCR quantification of bacterial 16S rRNA has been performed with nine samples of THAs. Two samples of THAs have shown weak reactions indicative of minimal amounts of 16S rRNA, while all other samples are negative for bacterial contamination. CONCLUSIONS: Samples of topical hemostatic agents collected thus far exhibit no colony formation when plated in culture and seven out of nine samples which have undergone PCR quantification of 16S rRNA are negative for bacterial contamination. Two samples with minimal presence of 16S rRNA were negative in culture and could represent environmental contamination.

Poster Title: MOLECULAR DETECTION AND IDENTIFICATION OF STAPHYLOCOCCUS AUREUS IN AIRWAY SAMPLES FROM CHILDREN WITH CYSTIC FIBROSIS

Category: Pulmonary and Critical Care

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2302   Poster Number: 82

Abstract:

MOLECULAR DETECTION AND IDENTIFICATION OF STAPHYLOCOCCUS AUREUS IN AIRWAY SAMPLES FROM CHILDREN WITH CYSTIC FIBROSIS. EJ Johnson (MD, SOM), BD Wagner, FJ Accurso, JK Harris, Department of Pediatrics, Section of Pulmonary Medicine, University of Colorado   Purpose of study: Staphylococcus aureus (Sau) is a common and significant pathogen in cystic fibrosis (CF). Quantitative PCR (qPCR) may provide a rapid, culture-independent approach to diagnosis of Sau airway infections, but a previously evaluated qPCR assay demonstrated poor sensitivity with respect to Sau compared to other airway pathogens. We sought to determine the sensitivity of an alternative qPCR assay that targets amplification of the femA gene to identify Sau directly from airway samples in comparison with qPCR detection by a specific 16s rRNA primer. Methods: DNA extraction was performed with and without enzymatic digestion. Results of the qPCR assay were compared to culture to determine the sensitivity. We examined 87 samples (42 oropharyngeal [OP], 45 expectorated sputum [ES]), 59 of which were culture positive for Sau, and 28 of which were culture negative for Sau. Summary of Results: qPCR detection of Sau was greater in sputum (82.1%, 95% CI 70.3-94.0%) than in oropharyngeal swabs (50.0%, 95% CI 34.9-65.1%) with enzymatic digestion (p=0.02). Samples analyzed without enzymatic digestion had decreased sensitivity for oropharyngeal swabs but not for sputum. Sensitivity in samples with greater than 105 CFU/mL was 100% but 0% for samples with less than 105 CFU/mL. Analysis by staph-specific 16S qPCR had even lower sensitivity consistent with previous studies.Conclusion: We conclude that the femA qPCR assay improves the detection of Sau in sputum compared to the previously reported 16S qPCR assay. However, the sensitivity of the femA qPCR does not approach clinical utility. In addition, molecular identification of Sau in oropharyngeal swabs shows decreased sensitivity compared to sputum.

Poster Title: TYROSINE KINASE INHIBITORS INDUCE TGF-β2 EXPRESSION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA CELL LINES AS A MECHANISM OF ACQUIRED RESISTANCE

Category: Hematology and Oncology

School: Graduate   Year: 5th

Poster Location: ED 2 South Bridge   Poster Number: 52

Abstract:

TYROSINE KINASE INHIBITORS INDUCE TGF-β2 EXPRESSION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA CELL LINES AS A MECHANISM OF ACQUIRED RESISTANCE. EK Kleczko (Ph.D., GS), LR Heasley, ME Marshall, KR Singleton, and LE Heasley. Craniofacial Biology, University of Colorado, Aurora, CO.   The epidermal growth factor receptor (EGFR) is overexpressed in about 90% of head and neck squamous cell carcinoma (HNSCC) tumors, and thus the EGFR-monoclonal antibody cetuximab has been approved to treat HNSCC. Yet the 5-year survival rate for HNSCC is only 40-50%. The efficacy of cetuximab in treating HNSCC may be limited by acquired resistance or the activity of alternative dominant growth factor pathways. Previously, our lab has shown that in addition to EGFR signaling, the fibroblast growth factor receptor (FGFR) pathway participates as an important autocrine signaling pathway in some cetuximab-insensitive HNSCC cell lines, further indicating that inhibiting the EGFR pathway alone will not be effective in treating HNSCC. To identify genes that change in response to EGFR-specific tyrosine kinase inhibitors (TKIs) and to FGFR-specific TKIs that may mediate acquired resistance, we performed an Affymetrix GeneChip screen in which the UMSCC25, Ca9-22, and 584-A2 cell lines were treated for 4 days with 0.3µM AZ8010, an FGFR-TKI, and/or 0.1µM gefitinib, an EGFR-TKI. We found that TGF-β2 mRNA was upregulated following blockade of the dominant receptor pathway. ELISA and qRT-PCR were used to validate this induction of TGF-β2. Treatment with a small molecule inhibitor of TGF-β receptor I (TGFβRI) provided an additive reduction of clonogenic growth when combined with EGFR and/or FGFR TKIs. Silencing TGF-β2 with shRNA led to an additive decrease in clonogenic growth in combination with EGFR and/or FGFR TKIs. Furthermore, we observed an induction of NF-κB activity in the cells following treatment with EGFR and/or FGFR TKIs. This induction was mitigated by the use of a TGF-β2 neutralizing antibody, suggesting that TGF-β2 is signaling through a non-canonical pathway in our model. Additionally, UMSCC25 cells chronically adapted to gefitinib sustained an increase in TGF-β2 expression compared to the control cells. This data suggests that TGF-β2 induction may provide a novel mechanism of acquired resistance to TKIs, and supports the hypothesis that combination therapy will be more effective than monotherapy in treating HNSCC.

Poster Title: Targeted focal cryotherapy (TFT): Single center prospective experience for low grade prostate cancer

Category: Surgery

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2112   Poster Number: 72

Abstract:

TARGETED FOCAL CRYOTHERAPY (TFT): SINGLE CENTER PROSPECTIVE EXPERIENCE FOR LOW GRADE PROSTATE CANCER Kevin Krughoff (MD SOM), JM Phillips, K Eid, C O'Donnell, ED Crawford, AB Barqawi   Patients currently diagnosed with low risk prostate cancer are often over-treated and suffer from complications resulting in detriment to quality-of-life (QOL). Targeted focal therapy (TFT) is a minimally invasive procedure designed to ablate tumor foci while minimizing collateral damage in order to maintain QOL. This is an IRB-approved prospective study conducted to assess the safety and efficacy of TFT using cryotherapy for men aged 40-85 years who were diagnosed with low-risk organ-confined prostate cancer (Gleason ≤ 6 on TRUS biopsy, ≤ 50% tumor burden, PSA < 0.01). The median AUA−SS change was a decrease of 1.5 points ($p < 0.01$). No significant change was observed in the SHIM score ($p = 0.6$). No episodes of urinary incontinence or severe side effects were observed.   TFT in carefully selected patients provides a feasible and practical option for the treatment of low-risk prostate cancer with minimal impact on QOL when compared with other modalities.

Poster Title: NEBULIZED HYPERTONIC SALINE REDUCES PULMONARY INFLAMMATION BY SPECIFIC MECHANISMS: A MODEL TO ATTENUATE ACUTE LUNG INJURY IN MURINE

Category: Surgery

School: Medicine   Year: 4th

Poster Location: ED 2 North Room 2203   Poster Number: 74

Abstract:

NEBULIZED HYPERTONIC SALINE REDUCES PULMONARY INFLAMMATION BY SPECIFIC MECHANISMS: A MODEL TO ATTENUATE ACUTE LUNG INJURY IN MURINE. K. Leasia (M.D., M.S), M. Fragoso, M. Kelher, F. Gamboni, S. Mitra, C. Silliman, A. Suaia, A. Banerjee, E.E. Moore. Department of Surgery, Univeristy of Colorado, Aurora, CO.   Pulmonary inflammation is most commonly caused by bacterial insult, even in the trauma setting. Injury to endothelial-capillary interface by direct application of bacterial endotoxin into the lung results in an increase of pro-inflammatory transcription factors (NF-κB), inflammatory mediators (TNFα, IL-1β,IL-6, IL-8/CINC-1, IFNγ, RANTES, MMP13) and neutrophils. Nebulized hypertonic saline (HTS) is a well-established therapy in several patient populations. Novel use of nebulized HTS has already shown to reduce shock related acute lung injury as it attenuates the pro-inflammatory response, namely MMP13, and promotes the clearance of alveolar fluid in the setting of pulmonary edema. It is unclear by which specific mechanism each of these pro-inflammatory mediators are reduced with the treatment of nebulized HTS. We hypothesize that nebulized HTS reduces the expression of inflammatory medicators in lung injured by lipopolysaccharide by regulating NF-κB.   Sprague-Dawley rats were injected transtracheally with Salmonella enteritidis derived lipopolysaccharide (LPS). LPS incubated rats were then treated with nebulized HTS at predetermined time points for 3 hours. Samples of plasma, bronchoalveolar lavage fluid and lung tissue were obtained for further evaluation of inflammatory mediators.   Results: Pending

Poster Title: MULTIMODALITY IMAGING END-POINT STUDY OF EVEROLIMUS AND GANETESPIB IN TREATMENT OF PANCREATIC CANCER: A PRE-CLINICAL PET/MRI/MRS STUDY

Category: Hematology and Oncology

School: Medicine   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 54

Abstract:

Background: mTOR is strongly linked to cancer cell survival suggesting that inhibiting mTOR with everolimus (RAD001) may inhibit tumor cell growth while promoting cell death. Aim was to determine the efficacy of everolimus in combination with the second generation HSP-90 inhibitor. This study aimed to establish metabolic (FDG-PET and MRS), morphological (DWI), and anatomical (magnetic resonance imaging, MRI) end-points for mTOR and HSP inhibitor response in everolimus-resistant mouse pancreatic adenocarcinoma. Methods: Human Panc-159 tumor xenografts were established in athymic nude mice. Everolimus was administered orally at a daily dose of 5 mg/kg; ganetespib was administered via tail vein injection weekly 100 mg/kg. PET/DWI-MRI imaging was done at baseline, mid-study (Day 8-9), and end of study (Day 21-22). At end of study, mice were sacrificed, and tumors were extracted with perchloric acid for use in 1H-MRS metabolomics. Multivariate analysis was conducted with MetaboAnylast2.0 software. Results: Single treatments showed no significant inhibition of tumor growth or decrease in tumor cellularity. Everolimus single treatment slight decreased ($p = 0.0296$) glucose uptake, while ganetespib alone did not alter glucose uptake. Combination treatment inhibited tumor growth ($p= 0.0018$ by MRI) in addition to decreasing tumor cellularity ($p = 0.0323$) and also decreased glucose uptake ($p = 0.0085$). Multivariate analysis on combined quantitative metabolic and imaging data sets showed group separation between control and combination groups. Variables with highest importance in projection (VIP) in group separation: cellularity (VIP = 3.02), tumor volume (VIP =2.31), phospholipid-associated glycerol (VIP = 1.90), and FDG-SUV (VIP = 1.34). Conclusions: Our study provides the rational of combining everolimus with ganetespib to overcome drug resistance and increase treatment responsiveness in pancreatic cancer. Combination treatment did result in decreased tumor growth, cellularity, phospholipid metabolism and glucose uptake giving potential for these variables to serve as effective biomarkers for therapeutic response once validated in clinical trials. Even though Panc-159 is highly resistant to single everolimus treatment, this combination treatment with an HSP-90 inhibitor provides first evidence of proliferation and metabolic response.

Poster Title: Visualization of Quantitative Data Quality in Electronic Health Records

Category: Health Care and Public Health

School: Public Health   Year: 2nd

Poster Location: ED 2 South Room 2201   Poster Number: 36

Abstract:

VISUALIZATION OF QUANTITATIVE DATA QUALITY IN ELECTRONIC HEALTH RECORDS. MB Leventhal, (BA), Colorado School of Public Health, University of Colorado, Aurora, CO. Electronic health record (EHR) data are increasingly important for public health and clinical research. Yet there is substantial evidence that EHR data may contain significant data quality limitations. Data visualization methods allow users to quickly review large amounts of information. This study used a "fit-for-use" data quality assessment conceptual model (Kahn, 2012) that is comprised of five dimensions – accuracy, objectivity, believability, timeliness and appropriate amount. Three of these dimensions – believability, accuracy and appropriate amount – were used to demonstrate the use of visualization for data quality assessment as applied to a comparative effectiveness research study exploring asthma outcomes. A believability scatterplot of visit dates and related clinical measurement dates revealed unrealistic event sequences, with one measurement date more than a decade before the associated visit date. An appropriate amount plot and timeline showed that fewer than anticipated Asthma Control Test (ACT) scores have been recorded from a smaller than anticipated number of asthma patients. Two of the five clinics with recorded ACT scores had only values in the lowest range, suggesting that those clinics may have only preformed the ACT on patients with severe symptoms. An accuracy bar graph of the number of packs of cigarettes smoked per day revealed potential integer bias, with a majority of values at half a pack or one pack per day, as well as a suspicious outlier observation of eight packs per day. Combining summary analytics with visualizations of EHR data for potential use in research can provide rapid insight into multiple dimensions of data quality.

Levine, Martha

Poster Title: Measuring Nurse Attitudes Towards Childbirth

Category: Child-Maternal Health and Reproductive Sciences

School: Nursing   Year:

Poster Location: ED 2 South Room 1307   Poster Number: 13

Abstract:

Objective: Researchers have found that nursing care can influence patient outcomes during childbirth. The attitudes and beliefs of labor and delivery nurses may affect their care decisions and interventions. To conduct further research on nursing care and patient outcomes, a reliable and valid instrument to measure nurse attitudes and beliefs about childbirth is needed. Design/Setting: The Nurse Attitudes and Beliefs Questionnaire-Revised (NABQ-R) contains 42-items in 5 theoretically derived domains. Each item is scored with a 4-point Likert scale from 1 (strongly disagree) to 4 (strongly agree). A higher score indicates more positive attitudes towards physiologic birth. Participants/ Methods: This online survey study provided an initial psychometric test of the NABQ-R. An e-mail invitation containing a link to a secure electronic survey was sent to all Colorado AWHONN members. The response rate was 21.6% with complete surveys returned from 84 labor and delivery nurses with a mean age of 46.7 years and 18.9 years of perinatal nursing experience. The sample was 98% White with an educational distribution of 17.9% diploma/associate, 42.9% baccalaureate, and 39.3% graduate degrees Results (Data analysis): The NABQ-R scores ranged from 82–156 with a mean of 121.99 + 12.77. Cronbach's α internal consistency reliability estimate was .90. Analysis of variance demonstrated a significant effect of education on NABQ-R scores such that nurses with graduate degrees had significantly more positive attitudes than nurses with baccalaureate (p = .003) or diploma/associate degrees (p = .002). To study construct validity, an exploratory factor analysis (EFA) using principal component analysis and varimax rotation was conducted. Factors with an eigenvalue ≥ 1 were retained and the scree slope suggested a 5-factor solution. Next, a varimax rotation was used with 5 specified factors that accounted for 46.11% of the variance with all items loading on at least one factor. We named the factors: (1) Women's Experience of Birth; (2) Women's Autonomy; (3) Medical Model Conflict; (4) Breech Safety; and (5) Intervention Influence. Conclusion/Implications for nursing practice: We consider this analysis preliminary to a more robust psychometric testing of the NABQ-R with a larger sample. Our results support acceptable initial psychometric properties for the NABQ-R and the EFA results were consistent with existing theory. The development of a theoretically and psychometrically sound instrument to measure nurse attitudes toward physiologic birth will foster additional research to expand our understanding of how nurse attitudes affect the process and outcomes of labor and birth.

Poster Title: DEVELOPMENTAL SCREENING AND AN EARLY CHILDHOOD CARE AND DEVELOPMENT PROGRAM IN SOUTHWEST GUATEMALA

Category: Child-Maternal Health and Reproductive Sciences

School: Medicine   Year: 3rd

Poster Location: ED 2 South Room 1210   Poster Number: 6

Abstract:

DEVELOPMENTAL SCREENING AND AN EARLY CHILDHOOD CARE AND DEVELOPMENT PROGRAM IN SOUTHWEST GUATEMALA. LC Mehner, (MD, SOM), GJ Domek, S Berman, and M Abdel-Maksoud, Center for Global Health, University of Colorado, Aurora, CO Interventions to improve early childhood development and health have the potential to enhance a child's physical growth, socioemotional and cognitive development, as well as the overall economic productivity of a society. The purpose of this research was to conduct a baseline developmental screening assessment of children in a poor region of southwestern Guatemala and to evaluate an early childhood development program specifically designed for this population.   Developmental screening was conducted by Guatemalan community health workers (CHWs) using Spanish age-appropriate versions of the Ages and Stages Questionnaire (ASQ), a screening tool assessing five domains (gross motor, fine motor, communication, personal-social, and problem solving). Demographic and family behavior information was also collected. Early childhood material from the Language Power Program was adapted to create two 30-page flipchart talks to educate mothers on health and development topics relevant to 12–24-month-olds and 24–48-month-olds. A post-survey was given two weeks after the intervention.   Surveys and flipchart talks were completed with 75 mothers of children aged 12-48 months. 36% of mothers were illiterate, while 32% had not received any primary education. 60% of children had a screening delay in at least one ASQ category and 39% had a delay in at least two categories. Fine motor (47%) and problem solving (32%) had the most delays. Specific maternal characteristics (illiteracy, no primary education, and ≥4 pregnancies) were significantly associated with having ≥2 ASQ delays ($p < 0.05$). Children performed best in the communication category (8% with a delay). Certain maternal-child interactive behaviors (plays together with toys and converses when feeding) were significantly associated with fewer communication delays ($p < 0.05$). Post-intervention surveys were completed by 62 mothers, with over 90% saying that after the intervention they increased the amount of time they spent talking, playing, and using a picture book with their child.   Children in southwestern Guatemala were found to have high rates of ASQ-defined developmental delays and could benefit from an intervention that integrates ways to promote early childhood development and health.

Poster Title: HEPATOCYTE GROWTH FACTOR STIMULATES FETAL SHEEP ALVEOLAR TYPE II CELL AND ENDOTHELIAL CELL GROWTH AND IMPROVES LUNG STRUCTURE IN EXPERIMENTAL BRONCHOPULMONARY DYSPLASIA

Category: Pulmonary and Critical Care

School: Medicine   Year: 2nd

Poster Location: ED2 North Room 2302   Poster Number: 85

Abstract:

HEPATOCYTE GROWTH FACTOR STIMULATES FETAL SHEEP ALVEOLAR TYPE II CELL AND ENDOTHELIAL CELL GROWTH AND IMPROVES LUNG STRUCTURE IN EXPERIMENTAL BRONCHOPULMONARY DYSPLASIA. AJ Metoxen (M.D., SOM), GJ Seedorf, and SH Abman, Pediatric Heart and Lung Center, Anschutz Medical Campus, Aurora, CO.   Decreased vascular endothelial growth factor (VEGF) signaling contributes to impaired lung structure in bronchopulmonary dysplasia (BPD). Although VEGF stimulates hepatocyte growth factor (HGF) production, the effects of HGF on the fetal lung are uncertain. To determine the potential role of HGF in BPD, we studied the direct effects of HGF on fetal lung alveolar type 2 cells (AT2C) and endothelial cells (EC), and whether HGF treatment could restore lung growth after VEGF inhibition in vivo. AT2C and EC were harvested from late-gestation fetal sheep lungs and characterized by immunofluorescence and morphotype. Proliferation assays were performed in the presence or absence of HGF (25 ng/mL) over 4 days. Tube formation with or without HGF was studied in EC by standard methods over 18 hours. Newborn rat pups (

Poster Title: HCV Founder Viruses Differentially Induce IFN Gene Responses: Relationship to Cell Type and HCV Genotype

Category: Immunology and Autoimmune Diseases

School: Graduate   Year: 2nd

Poster Location: ED 2 South Room 2304   Poster Number: 26

Abstract:

HEPATITIS C FOUNDER VIRUSES DIFFERENTIALLY INDUCE IFN GENE RESPONSES: RELATIONSHIP TO CELL TYPE AND HEPATITIS C VIRUS GENOTYPE. Angela M Mitchell1, (PhD, GS) Amy EL Stone1, Linling Cheng1, Katelyn Leahy1, Lucy Golden-Mason1, George M Shaw2, Hugo R Rosen1; 1 Department of Medicine: University of Colorado Denver; Aurora, CO. 2 Departments of Medicine and Microbiology, Perelman School of Medicine: University of Pennsylvania; Philadelphia, PA.   Hepatitis C virus (HCV) subverts the HCV-specific interferon (IFN) immune response, while allowing the host to be immune-competent versus other pathogens. There is no vaccine for the virus, and anti-viral therapy is expensive and only effective in a proportion of treated patients. Several genotypes of HCV have been identified, and it is known that the response to traditional HCV therapy differs among genotypes. Consequently, it is of critical importance to understand the differences in the immune response to each of the genotypes. We hypothesize that RNA generated from complete HCV genomes of transmitted/founder (t/f) viruses induces antiviral IFN gene responses in a unique manner among different innate immune cell types.   Full-length genotype 1a, 1b, and 3a t/f hepatitis C virus plasmids were generated after sequencing plasma virion RNA in chronically-infected patients. The plasmids were transformed into and expanded in Stbl2 competent cells. The plasmids were then linearized, digested, and transcribed. The RNA (1µg) was introduced into the cytoplasm of four cell types (Huh 7.5.1 ["cured" hepatocyte cell line], HepG2 [hepatocyte cell line], THP-1 [monocyte cell line], and pDC [plasmacytoid dendritic cell line]). The resulting IFN gene responses were determined via PCR at several time points up to 24 hours.   All cell types responded distinctively to HCV t/f RNA, with Huh 7.5.1 cells responding in a relatively dampened manner compared to other cell types. Additionally, HCV gentoypes differentially induced IFN gene upregulation, with genotype 3a predominantly inducing a greater response. The IFN cascade contains key players in the antiviral immune response to viruses such as HCV. Our data suggests that the IFN response to HCV RNA may vary depending on which genotype a patient is infected with, as well as which cell types are exposed to the viral RNA. Characterization of the immune response to different HCV genotypes will subsequently allow for the development of more effective vaccines and therapeutics.

Poster Title: Routine Health Screening: The Denver National Western Stock Show Experience

Category: Health Care and Public Health

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 2203   Poster Number: 33

Abstract:

ROUTINE HEALTH SCREENING: THE DENVER NATIONAL WESTERN STOCK SHOW EXPERIENCE. BL Morris, (MD, SOM), W LeBlanc, A Ware, B Ingram, J Westfall, Department of Family Medicine, University of Colorado, Denver, CO.   Context: Past research on population-based cardiovascular disease screening has demonstrated an increase in patient awareness of health risk factors.   Objective: To assess baseline health status and access to care in adults living in rural communities across the US Mountain West region.   Setting: These data were collected as part of a prospective cohort study at the National Western Stock Show (NWSS), an annual livestock and agricultural exhibition that attracts ~630,000 people, in Denver, CO. Sponsored by Colorado Area Health Education Centers (AHEC), University of Colorado Anschutz Medical Campus students were trained to perform rapid blood glucose and cholesterol screens prior to performing these procedures on NWSS patients to screen their health status.   Patients: NWSS attendees were eligible to participate in the health screening study. Cholesterol screenings were reserved exclusively for farmers, ranchers and uninsured participants.   Intervention/Instrument: Data were collected and stored using Research Electronic Data Capture (REDCap). Student volunteers electronically captured participant responses to health screening questions and their objective lab results using Apple iPads. Main Outcome Measures: The main outcomes of interest included: patient age, sex, zip code, population density of residence area, weight, height, BMI, blood pressure, blood glucose and non-fasting blood cholesterol. Insurance status, and identification as a farmer or rancher, were self-reported.   Results: Between 2009-2013, 10,216 patients participated in the NWSS screening program. During those 5 years, the level of participation of farmers, ranchers and uninsured patients ranged from 11.4-15.8%, 13.4-15.6%, and 20.3-32.1% of the population screened, respectively. Men consistently participated more than women each year the screening program ran.   Conclusions: The NWSS has the capacity to reach thousands of patients each year. Data gathered reveal that a screening program that is available to reach a wide spectrum of patients may be informative in educating patients about their health risks. Further data analysis will yield more conclusions.

Poster Title: MEMORY CELLS DO NOT REQUIRE SPECIFICITY FOR DONOR-DERIVED ANTIGENS TO DISRUPT TRANSPLANT TOLERANCE

Category: Immunology and Autoimmune Diseases

School: Graduate   Year: 4th

Poster Location: ED 2 South Room 2304   Poster Number: 28

Abstract:

MEMORY CELLS DO NOT REQUIRE SPECIFICITY FOR DONOR-DERIVED ANTIGENS TO DISRUPT TRANSPLANT TOLERANCE. MK Nelsen, (Ph.D., GS), KS Beard, RM Kedl, and RG Gill, Dept. of Immunology, Anschutz Medical Campus, Aurora, CO.   Induction of immune tolerance can prevent graft rejection. Tolerance-promoting agents that target immune cell surface molecules can induce changes in the immune system so that grafts are accepted. Unfortunately, tolerance induction can be blocked by host-derived memory cells, which form after vaccination or pathogen infection. Memory cells reportedly reject grafts because they are pathogen-specific and cross-reactive to donor-derived antigens. In this study, we hypothesized that memory cells can block tolerance without specificity for donor antigens. We predicted that pre-existing memory would be sufficient to break tolerance if it can alter the microenvironment of initial alloantigen presentation.   We exposed mouse recipients to vaccination antigens by immunizing C57BL/6 (H-2Kb) mice with ovalbumin (OVA) and an adjuvant. This immunization generated OVA-specific immune memory. We determined via IFNγ ELISPOT that the OVA immunization did not generate a significant burden of OVA-specific T cells that were cross-reactive for donor-derived BALB (H-2Kd) antigens. We next transplanted OVA-immune mice with BALB allografts. Recipients were treated with one of two common tolerance-promoting therapies: Anti-CD154 alone, or anti-CD154 with donor antigen. We found that OVA-specific memory did not impact therapy-promoted tolerance. We next tested the role of OVA-specific memory in disrupting antigen presentation during tolerance induction. Recipients were given antigen-presenting cells (APCs) that simultaneously expressed donor antigen BALB and the vaccine-associated antigen OVA. Remarkably, transplant tolerance was readily disrupted in all OVA-immune recipients following delivery of this linked antigen. Our studies suggest that naïve T cells were activated following exposure to OVA-memory and linked antigen. Thus, our data indicate that vaccine-induced memory that is not directed against donor-derived antigens can still be a key determinant for disrupting tolerance induction if it interferes with antigen presentation. This reactivity at the level of early antigen exposure -- independent of memory T cells being specific for the actual transplant -- impacted naïve, uncommitted alloreactive T cells and likely promoted their immunity to the transplant.

Poster Title: Foretinib inhibits invasion, a hallmark of malignancy, in glioblastoma multiforme.

Category: Hematology and Oncology

School: Medicine   Year: 5th

Poster Location: ED 2 South Bridge   Poster Number: 56

Abstract:

Malignant glioblastoma (GBM) is a devastating primary malignancy of the brain, with a median patient survival of less than 15 months. One of the primary challenges to effective treatment is the inability to fully resect the primary tumor due to the invasive phenotype of malignant glioma cells. The development and use of targeted therapies that specifically curb the invasive potential of glioma prior to resection may serve to enhance current outcomes and improve patient survival of this devastating disease. TAM (Mer, Axl, and Tyro-3) RTK expression is increased in malignant glioma and correlates with rapid progression of the disease. Preliminary data suggests that TAM RTK expression is increased in induced neurospheres compared to monolayer GBM cells. The RTK inhibitor, foretinib, inhibits c-met, VEGFR2, and c-kit, and notably, all three TAM RTKs at nanomolar concentrations in vitro and is currently being studied in Phase II clinical trials for the treatment of a variety of solid tumors. In this study, the effects of foretinib treatment on the migratory and invasive phenotypes of glioblastoma derived cell lines were assessed using an Xcelligence transwell migration assay, a wound healing assay, as well as by embedding neurospheres derived from glioblastoma cell lines in a three-dimensional collagen matrix. In all three assays, treatment with 100 nM foretinib significantly inhibited invasion and migration of U251, SF188, and A172 cells at 15h and 24h timepoints when compared to DMSO treated controls. shRNA knockdown of Mer in these cell lines also resulted in an abrogated invasion phenotype. Further, siRNA knockdown of Mer resulted in knockdown of the focal adhesion protein FAK, suggesting a novel mechanism by which Mer regulates cell invasion and migration. Together, these findings indicates that administration of foretinib to glioblastoma patients prior to surgical resection may enhance current clinical outcomes by inhibiting the ability of glioblastoma cells to invade into the normal brain tissue.

Poster Title: A NOVEL MER TYROSINE KINASE INHIBITOR MEDIATES INCREASED CELL KILLING IN COMBINATION WITH FGFR INHIBITION

Category: Hematology and Oncology

School: Medicine   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 58

Abstract:

A NOVEL MER TYROSINE KINASE INHIBITOR MEDIATES INCREASED CELL KILLING IN COMBINATION WITH FGFR INHIBITION.   TP Newton*, (M.D., SOM), CT Cummings*, GD Kirkpatrick*, TK Hinz*, D DeRyckere*, W Zhang**, X Wang**, S Frye**, HS Earp**, L Heasley*, DK Graham*.   *University of Colorado | Anschutz Medical Campus, Aurora, CO; **University of North Carolina, Chapel Hill, NC Purpose of Study: Although therapies targeting recently identified oncogenic drivers of non-small cell lung cancer (NSCLC) are in clinical use, many patients still lack a targeted therapy option. Therefore, there is continued need for development of new therapeutic strategies. We recently demonstrated oncogenic roles for Mer receptor tyrosine kinase in NSCLC, validating it as a potential therapeutic target. Fibroblast growth factor receptors (FGFR), another class of RTKs that are aberrantly expressed and promote tumorigenesis in NSCLC, have been validated as therapeutic targets in preclinical NSCLC models. Because Mer and FGFR signal primarily through complementary oncogenic pathways (PI3K/AKT and MEK/ERK, respectively), we hypothesized that dual inhibition of FGFR and Mer may provide a therapeutic advantage over inhibition of either kinase alone. In this study we investigated the interaction between a novel Mer-selective small molecule tyrosine kinase inhibitor (TKI) and AZD-4547, an FGFR TKI, in NSCLC cell lines. Methods Used: Colo699 (Mer+, FGFR+) and H226 (Mer+, FGFR+) NSCLC cells were cultured for 14 days in soft agar in the presence of Mer TKI and/or AZD-4547, alone or in combination, and colonies were stained and counted. Changes in the activity of downstream signaling pathways, including PI3K/AKT, MEK/ERK, and STAT proteins were evaluated by immunoblotting. Results and Conclusions: In the soft agar assay, Colo699 and H226 colony formation was inhibited in the presence of Mer TKI and AZD-4547, both as single agents and in combination. Importantly, concurrent treatment with Mer TKI and AZD-4547 resulted in a greater decrease in colony-formation relative to either agent alone. Immunoblotting revealed increased inhibition of pro-survival signaling in cells treated with both inhibitors relative to the single agents. Taken together, these data suggest that combination therapies targeting Mer kinase and FGFR may be effective for treatment of NSCLC and indicate biochemical mechanisms by which the combination therapy may mediate increased anti-tumor activity.

Poster Title: INHIBITING MONOPOLAR SPINDLE 1 KINASE (MPS1/TTK) SUPPRESSES COLONY FORMATION IN MEDULLOBLASTOMA CELLS

Category: Hematology and Oncology

School: Medicine   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 39

Abstract:

INHIBITING MONOPOLAR SPINDLE 1 KINASE (MPS1/TTK) SUPPRESSES COLONY FORMATION IN MEDULLOBLASTOMA CELLS. J Ng (MD, SOM), P Harris, S Venkataraman, I Balakrishnan, R Vibhakar, Department of Pediatrics at Children's Hospital Colorado, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA   Purpose of Study: Medulloblastoma is the most common malignant pediatric brain tumor with less than optimal outcomes. Current therapies include cytotoxic drugs and radiation that target rapidly growing cells. These therapies are associated with significant long-term morbidity including neurocognitive defects and secondary tumors. Therefore, there is a critical need for medulloblastoma therapies that specifically target tumor cell populations.   The Vibhakar laboratory has recently identified several kinases involved in the G2/M cell cycle checkpoint to influence medulloblastoma cell viability. Among these is the Mps1 kinase. Mps1 is involved in chromosomal segregation during mitosis and overexpression of Mps1 is associated with aneuploidy. Studies have shown that inhibiting Mps1 induces abnormal chromosome segregation and apoptosis in breast cancer and osteosarcoma. Despite the abnormal overexpression of Mps1 in some medulloblastomas, the effect of Mps1 inhibition on medulloblastoma tumor cell growth has yet to be evaluated.   Methods Used: Expression of MPS1 mRNA and protein in medulloblastoma tumor lines was evaluated using qRT-PCR and Western blot. To investigate the therapeutic efficacy of inhibiting Mps1, we used a clinically relevant inhibitor of Mps1 (NMS-P715). We performed cell proliferation and colony focus assays using well-characterized medulloblastoma cell lines.   Summary of Results: Expression of MPS1 DNA and mRNA was elevated in all medulloblastoma samples and tumor lines as compared to normal cerebellum. Inhibition of Mps1 decreased amount of active Mps1 and significantly decreased the colony-forming ability of medulloblastoma cells.   Conclusions: These analyses suggest that targeting Mps1 via small molecule inhibitors may be a valuable approach in medulloblastoma therapy.

Poster Title: Role of CD4+ CD40+ T-Cells in Predicting Type 1 Diabetes Onset

Category: Immunology and Autoimmune Diseases

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 2305   Poster Number: 21

Abstract:

THE ROLE OF CD4+ CD40+ T-CELLS IN PREDICTING TYPE 1 DIABETES ONSET. D. Nguyen (MD, SOM), G. Vaitaitis, J. Carter, D. Waid, D. Wagner, Webb-Waring Center and Department of Medicine, University of Colorado, Denver CO   Purpose of study: The goal of this research is to probe further into the CD4+CD40+ T cell (Th40) profiles in pre- type 1 diabetic patients (pre-T1D) in order to produce a comprehensive blood test that includes HLA haplotype and risk-predicting autoantibodies to accurately predict T1D onset. Th40 cells have been identified as a potential biomarker for inflammatory auto-immune disease in both a Type 1 diabetes mouse model and in patients with T1D. Patients labeled as pre-diabetic have normal blood glucose levels but have HLA-DR3 or HLA-DR4 risk genes along with the presence of one or more of four risk-predicting autoantibodies (IAA, ZnT8, GAD, IA2). Methods Used: T1D, pre-T1D, new onset T1D, and control patients recruited from TrialNet patients at the Barbara Davis Center, Denver CO and Wisconsin Blood Center, Milwaukee, WI. Peripheral blood is collected by brachial venal puncture and passed through Ficoll with the lymphocyte layer collected. Percentage Th40+ cells out of Th4+ cells is determined by staining and flow cytometry. Summary of Results: New onset diabetics (n=28) had statistically similar Th40 levels to existing T1D patients (n=238). Pre-T1D patients (n=32) have Th40 cell levels ranging from that found in non-diabetic controls (22.1±8.4%) to that found in long term T1D patients (45.5 ±5.4%), and can be stratified into a Th40 low, medium, and high risk groups. Some patients defined as high risk according to autoantibody level had low Th40 levels, while some of those at low risk according to autoantibody level had high Th40 levels. Conclusion: With this data, we will create a database that potentially can reliably predict T1D development and outcomes. We hypothesize that high Th40 levels correspond to increased risk of developing T1D, poorer prognosis, and more complications. A T1D database will be established to correlate risk of developing T1D with clinical variables such as Th40 levels, HbA1c, c-peptide levels, complications, insulin use, HLA, autoantibody type, cytokines, and Treg levels, potentially providing better risk assessment capabilities.

Poster Title: EXPRESSION PATTERNS OF NBEAL2 IN HUMAN TISSUES AND A MEGAKARYOCYTIC CELL LINE.

Category: Hematology and Oncology

School: Graduate   Year: 3rd

Poster Location: ED 2 South Bridge   Poster Number: 41

Abstract:

EXPRESSION PATTERNS OF NBEAL2 IN HUMAN TISSUES AND A MEGAKARYOCYTIC CELL LINE. L Noetzli, (PhD, GS), N Smith, G Brodsky, S Di Pietro, and J Di Paola, Human Medical Genetics and Genomics Program, University of Colorado Denver, Aurora, CO   Gray platelet syndrome (GPS) is a rare bleeding disorder characterized by low platelet count, large platelets, and deficient alpha granules in platelets and megakaryocytes (platelet producing bone marrow cells). The genetic cause of GPS was recently investigated by our lab, and deleterious mutations were found in the gene Neurobeachin-like 2 NBEAL2. NBEAL2 is a member of a family of proteins that contain a BEACH domain which has been associated with vesicular trafficking and receptor signaling. Vesicular trafficking defects are probable in GPS due to the fact that the alpha granules (platelet secretory vesicles) are deficient and improperly packaged. Very little is known about NBEAL2 other than its involvement with GPS.   Purpose: The purpose of this study is to determine the relative expression of NBEAL2 in a human cDNA library and the approximate subcellular localization of NBEAL2 in megakaryocytes. Methods: qPCR was used to measure the relative transcript abundance of NBEAL2 in a human cDNA library. A novel antibody against NBEAL2 was used to study the cellular localization of NBEAL2 by cellular fractionation and immunofluorescence in a megakaryocyte cell line (Dami) and primary mouse megakaryocytes.   Results: qPCR showed highest NBEAL2 expression in CD33+ (myeloid lineage) cells, which was 54.3 fold higher than the tissue with lowest expression (skeletal muscle).   Cellular fractionation showed NBEAL2 in fraction 1 of megakaryocytes, which corresponds to the small vesicle fraction. Immunofluorescence of NBEAL2 in megakaryocytes showed punctate staining, which also suggests a vesicular localization.   Conclusion: NBEAL2 expression was highest in a myeloid lineage cell which is expected due to the platelet phenotype of GPS. Alternatively, NBEAL2 expression was low in the brain despite the homology to the Neurobeachin (NBEA) brain specific protein. Cellular fractionation and immunofluorescence results suggest that NBEAL2 is associated with small cytoplasmic vesicles. This finding is consistent with the vesicular trafficking function of BEACH domain containing proteins. Characterizing the cellular localization of NBEAL2 will improve our understanding of GPS and alpha granule biogenesis.

Poster Title: FACTORS GOVERNING B CELL ACQUISITION OF AUTOANTIGEN & FUNCTION IN TYPE 1 DIABETES

Category: Immunology and Autoimmune Diseases

School: Graduate   Year: 4th

Poster Location: ED 2 South Room 2305   Poster Number: 23

Abstract:

FACTORS GOVERNING B CELL ACQUISITION OF AUTOANTIGEN & FUNCTION IN TYPE 1 DIABETES. TA Packard, (Ph.D., GS), RM Hinman, A Getahun, RS Lindsay, RS Friedman, JW Thomas, and JC Cambier. Department of Immunology, University of Colorado, Denver, CO. Type I diabetes (T1D) is an autoimmune disease of increasing incidence worldwide, presumably arising from complex interactions of heritable and environmental factors. Though T cells are thought to be the primary effector cells driving disease development, studies have shown that B cells are necessary for diabetes in a mouse model (NOD). B cell repertoire bias towards insulin-binding B cells (IBCs) in VH125 transgenic mice allows for diabetes development, whereas NOD mice with the non-insulin binding VH281 are protected. Despite utility of anti-islet antibodies as a biomarker for disease, these autoantibodies have been shown to be dispensable in disease pathology. Thus, B cells are thought to contribute to disease via antigen presentation. This study seeks to address the role of IBCs in T1D pathology, and tolerance mechanisms in the non-diabetic animal. Results: Using B cells bearing B cell antigen-receptors (BCR) of high- and low-affinity for insulin (Transgenic-Retrogenic IBCs, TR-IBCs), we demonstrate that BCR affinity affects insulin acquisition in disease susceptible hosts. We find that in vivo most TR-IBCs, including those bearing high-affinity BCR, are not associated with significant amounts of antigen. However, a small proportion of high-affinity TR-IBCs have detectable levels of receptor-associated insulin in NOD hosts. The frequency of these high-affinity TR-IBCs and their level of insulin acquisition are increased in the pancreas and pancreatic lymph node (PLN) in NOD mice, as compared to other organs--or non-susceptible B6 mice. Using an in vitro model of tolerance induction, we find that NOD B cells may quickly regain function following exposure to autoantigen. Conclusions: These findings are significant in demonstrating that B cells bearing high-affinity insulin-binding BCR bind ambient antigen in vivo under conditions of impending development of diabetes. Insulin-bound cells are enriched in the pancreas and PLN of NOD mice, consistent with higher levels of both soluble and crystalline insulin at these sites associated with islet damage. These findings support a model in which most IBCs in B6 mice are antigen-ignorant. The pancreatic environment of the NOD host allows for the acquisition of insulin by high-affinity IBCs. Together, we propose that insulin-binding B cells in a NOD host are more exposed to insulin and are less tolerant to autoantigen exposure.

Palacios-Helgeson, Leslie

Poster Title: The Pneumatic Cell Collector: a novel and effective instrument for tumor enrichment in solid tumor mutational studies

Category: Hematology and Oncology

School: Medicine   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 60

Abstract:

TUMOR CELL ENRICHMENT USING A PNEUMATIC CELL COLLECTOR. LK Palacios-Helgeson, (MD, SOM), Q Ren, WA Franklin, Department of Pathology, University of Colorado, Denver, CO.   Background: Human tumors contain both malignant cells and contaminating normal cells. It is often necessary to enrich for tumor cells to avoid complicating molecular analysis. In collaboration with Mechanical Engineering Dept. (Team 18) at UC Boulder, our lab developed a manual tumor cell enrichment protocol utilizing a dissecting microscope and pneumatic cell collector (PCC). With the PCC, we obtain highly concentrated tumor cell component from paraffin sections. We used PCC-enriched patient lung tumor samples for genetic analysis and compared results to data previously obtained by other pre-analytical methods. Purpose: To validate PCC use hypothesizing that DNA extracted is sufficient in quantity and quality for clinical molecular testing and mutation status remains unchanged from results by other pre-analytical methods. Methods: Lung cancer resection cases with known KRAS or EGFR mutations were blindly microdissected. Sections are formalin-fixed paraffin embedded tissue mounted on glass slides and hematoxylin stained. Sections are covered with viscous supension medium, glycerol, that traps dislodged cells loosened during microdissection. A Pasteur pipette drawn to a point with a Sutter pipette puller is connected to the PCC. Under the scope, cells are manually dislodged with the tip and, suspended in glycerol, aspirated under PCC-controlled vacuum and discharged into an appropriate tube for extraction. DNA is extracted from enriched tumor cells with QIAamp DSP DNA FFPE Tissue Kit and quantity and quality assessed by Nanodrop spectrophotometer. Mutation status was re-analyzed by Sanger sequencing. Original results of cases are compared to those obtained by PCC pre-analytical enrichment method. Results: Of (10) cases of EGFR mutations and (12) of KRAS mutations, all 22 reconfirmed. DNA yield: 300ng to 6mg per microdissection, sufficient for clinical molecular testing. DNA 260/280 values were around 2.0, sufficient quality for molecular analysis. Lastly, mutant signals robust in comparison to previous analysis. Conclusions: Though enrichment of tumor cells from a mixed cell population in tissue sections is a challenge in somatic mutation analyses, the PCC reliably facilitates tumor cell enrichment with satisfactory DNA quality and quantity for accurate downstream mutation analysis.

Pasha, Hamza

Poster Title: THE INTERACTIVE ROLE OF AGOUTI-RELATED PEPTIDE AND LIPOPROTEIN LIPASE IN THE BRAIN ON LIPID METABOLISM

Category: Metabolism and Endocrinology

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2102   Poster Number: 63

Abstract:

THE INTERACTIVE ROLE OF AGRP AND LPL IN THE BRAIN ON LIPID METABOLISM. HM Pasha, AE Libby, H Wang, and RH Eckel, Department of Medicine, University of Colorado, Denver, CO.   Purpose of Study: Obesity, a major epidemic in our society, is a condition of excess fat mass that results from the dysregulation of energy homeostasis. Substantial evidence implicates the central nervous system (CNS) in playing an important role in regulation of energy balance. Agouti-related protein (AgRP)-producing neurons are importantly related to the regulation of food intake, energy expenditure, and body weight. Lipoprotein Lipase (LPL) is a lipid processing enzyme that is present in the CNS. In a genetically-modified mouse lacking neuron specific LPL (NEXLPL-/-), there was a marked increased in AgRP expression before the development of obesity. The development of obesity was associated with an increase in food intake and a decrease in energy expenditure. To explore the mechanism by which LPL deficiency could be modulating AgRP expression, we used siRNA technology to knockdown LPL mRNA in N44 mouse hypothalamic cells.   Methods: N44 mouse hypothalamic cell lines were newly characterized and served as an in vitro model for neuronal lipid signaling. These hypothalamic cells accumulate lipids droplets as measured by AdipoRed stain. For the siRNA transfection experiment, the N44 cells were cultured and then transfected with a complex containing LPL siRNA and lipofectamine. RNA was isolated from transfected and control N44 cells with the Qiagen RNA Isolation Kit. The Real-Time PCR protocol was a two step process: RNA was reverse transcribed to single stranded complementary DNA with Thermo Scientific cDNA Synthesis Kit and the DNA was amplified with GoTaq Polymerase. The samples were run on a Veriti 96 well Thermocycler and then were loaded onto a 3% Agarose gel with Ethidium Bromide stain for imaging. In addition to LPL mRNA expression, LPL activity was measured by using radiolabeled triglyceride to determine the enzymatic activity of LPL.   Results: The LPL siRNA transfection resulted in a 83% decrease in LPL mRNA expression when compared to control, P

Poster Title: Association Between Health Insurance Type and Primary Care-Treatable Emergency Department Visits in the United States

Category: Health Care and Public Health

School: Medicine   Year: 3rd

Poster Location: ED 2 South Room 2201   Poster Number: 35

Abstract:

ASSOCIATION BETWEEN HEALTH INSURANCE TYPE AND PRIMARY CARE-TREATABLE EMERGENCY DEPARTMENT VISITS IN THE UNITED STATES. P Pukurdpol, MPH, MD candidate in Medical School; JL Wiler, MD, MBA; RY Hsia, MD, MSc, AA Ginde, MD, MPH. Department of Emergency Medicine, University of Colorado School of Medicine; Aurora, CO. Objectives: To determine the association of health insurance type and arrival time, as indicators of limited availability of primary care, with Primary Care Treatable (PCT) classification of emergency department (ED) visits in the United States. Methods: We analyzed 241,167 ED visits from the 1997 to 2009 National Hospital Ambulatory Medical Care Surveys. The primary outcome was the probability of the primary ED diagnosis being PCT, as defined by the New York University ED algorithm. The primary predictors were health insurance type and arrival time. We used multivariable linear regression to determine associations after adjusting for demographic variables. Results: Medicaid visits had a 1.7% [95%CI, 1.2-2.2] and uninsured visits a 2.4% [95%CI, 1.9-3.0] higher probability of PCT classification, compared to privately insured visits. Medicare visits had a 1.4% [95%CI, 0.7-2.0] lower probability of PCT classification. However, the PCT probability of Medicare visits increased at a rate of 5.2% per decade [95%CI, 3.8-6.5], double that of Medicaid visits (2.5% per decade [95%CI, 1.3-3.7]). The PCT probability of privately insured visits remained stable (+0.5% per decade, 95%CI, -0.7 to 1.6). Compared to business hours, weekend visits had a 1.5% (95%CI, 1.0-2.0) higher PCT probability, while night visits had a lower PCT probability (-2.7% [95%CI, -3.3 to -2.2]). Conclusions: Medicaid, uninsured, and weekend ED visits were independently associated with a higher probability of being PCT, which implicates limited access to primary care as a possible cause. While Medicare insurance was associated with a lower PCT probability, this association increased at a faster rate than for other insurance types.

Poster Title: Speckle Tracking Echocardiography to Screen for Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Category: Cardiovascular

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 1210   Poster Number: 5

Abstract:

SPECKLE TRACKING ECHOCARDIOGRAPHY TO SCREEN FOR PULMONARY HYPERTENSION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE. JL Rice (M.D., SOM), A Stream, J Dorosz, T Bull, Department of Medicine, University of Colorado, Denver, CO Pulmonary hypertension (PH) is a common complication of chronic obstructive pulmonary disease (COPD) and is associated with increased morbidity and mortality. Echocardiographic measures as currently employed have poor predictive value for the diagnosis of PH in COPD. Lung hyperinflation makes it difficult to get adequate imaging windows for measurement of the tricuspid regurgitation gradient, which is highly dependent on proper image acquisition angle and is the primary means of estimating pulmonary artery pressure (PAP) by echocardiography. Right ventricular (RV) strain obtained by speckle tracking echocardiography (STE) is a measure of myocardial deformation which correlates with RV function, PAP, and survival in subjects with PAH. We hypothesized that RV strain estimates would be feasible and readily obtained than estimated Right Ventricular Systolic Pressure (RVSP) by tricuspid regurgitation velocity in subjects with severe COPD, and that RV strain would correlate with invasive hemodynamic measurements. Retrospective analysis of RV strain values using standard apical views from 54 subjects with severe COPD with echocardiogram performed within 48 hours of pulmonary artery catheterization were included in the analysis. Tricuspid Regurgitation was identified in 17 (31%), while RV strain was obtained for 44 (81%). Absolute values of RV strain correlated inversely with pulmonary vascular resistance (PVR) (r2 0.17, p 0.02). Subjects with a PVR>3 Wood Units (WU) were compared to those with PVR ≤ 3 WU. Median RV free wall strain for subjects with PVR ≤ 3 WU was -23% (range -29 to -15) versus -20% for those with PVR >3 WU (range -23 to -12), p 0.05. A receiver operating characteristic curve demonstrated an RV free wall strain of -24% to be 92% sensitive and 42% specific for identifying PVR>3 WU (AUC 0.74). Conclusion: Using STE, RV strain estimates are feasible in the majority of subjects with severe COPD. Absolute values of RV strain vary inversely with PVR and may improve screening for PH in subjects with COPD. Our results suggest that the limitations imposed upon routine echocardiographic screening techniques by severe COPD are significantly reduced or eliminated using STE without requiring additional studies or echocardiographic views.

Poster Title: Application of SNP Microarrays to the Genome-Wide Analysis of Chromosomal Instability in Premalignant Airway Lesions

Category: Pulmonary and Critical Care

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2302   Poster Number: 84

Abstract:

APPLICATION OF SNP MICROARRAYS TO THE GENOME-WIDE ANALYSIS OF CHROMOSOMAL INSTABILITY IN PREMALIGNANT AIRWAY LESIONS. JL Rice (M.D., SOM), I Nakachi, WA Franklin, YE Miller, MW Geraci, SPORE in Lung Cancer, Department of Medicine, University of Colorado, Denver, CO   Chromosomal instability is central to carcinogenesis. In lung squamous cell carcinogenesis, the histopathologic changes in bronchial epithelia that precede cancer development been well documented, and several studies have supported the concept that somatic chromosomal alterations (SCAs) are prognostic biomarkers than premalignant histology alone. However, the detection of SCAs in premalignant lesions using high-resolution microarrays remains challenging because clinical sample heterogeneity dilutes the aberrant cell information. To overcome this hurdle, we first described and validated an algorithm for sensitive SCA detection, termed delta-theta (θ). This concise algorithm is derived from the difference in allelic balance between paired tumor and normal samples determined from single nucleotide polymorphism microarrays (SNP arrays), controlling for natural copy number variations by directly reflecting somatic events. In a simulated titration series of cancer and normal cell mixtures, delta-θ allows for the detection of SCAs even with a large proportion of normal cells (up to 90%).We verified the sensitivity of delta-θ by analyzing heterogeneous tissue with known tumor content, then applied this analytic strategy to heterogeneous clinical specimens including whole biopsies and brushings compared to the patient's blood. SCAs were successfully detected across the whole genome in all invasive cancer cases (6/6) carcinoma in situ (3/3), and moderate to severe dysplasia (3/11). Fluorescence in situ hybridization (FISH) and CN-qPCR assays were performed to validate SCAs identified using SNP microarray and delta-θ. In the lesions studied, we observed not only previously well-described SCAs but also unique abnormalities, and widespread airway sampling demonstrated that field cancerization reflected by SCAs at multiple sites was detectable. To our knowledge, this is the first study to use a SNP array-based approach to successfully identify SCAs in preinvasive bronchial lesions across the entire genome using whole bronchial biopsies and brushings. We believe this is an important novel method that expands our ability to assess genomic instability in the airway epithelia as a biomarker of lung cancer risk.

Poster Title: The Introduction of Effective Sunscreen and Changes in Melanoma Incidence in the United States: 1975-2010

Category: Health Care and Public Health

School: Public Health   Year: 2nd

Poster Location: ED 2 South Room 2201   Poster Number: 37

Abstract:

INTRODUCTION OF EFFECTIVE SUNSCREEN AND CHANGES IN MELANOMA INCIDENCE IN THE UNITED STATES:1975-2000. CA Ricklefs, (MPH, CSPH), LA Crane, Department of Community and Behavioral Health, Colorado School of Public Health, Aurora, CO.   With their introduction in 1984, sunscreens with an SPF of 15+ have become a major approach to melanoma prevention. This study examined whether the introduction of high SPF sunscreens is associated with a reduction in melanoma for birth cohorts born after 1984.   Using Surveillance, Epidemiology, and End Results (SEER) program data, age-specific melanoma incidence rates were calculated for each 5-year birth cohort (1890-2010) for every diagnosis year (1975-2010). Graphs, adjusted odds ratio estimates up to age 20, and 95% Wald confidence intervals were calculated using logistic regression and compared across three birth cohorts (1975-1979, 1980-1984, and 1985-1989) that represent exposure before, during, and after the introduction of effective sunscreens.   For both males and females in birth cohorts starting in 1890, melanoma incidence increased in each subsequent birth cohort; males had three times higher incidence than females later in life. Comparisons for females born in 1980-1984 vs. 1975-1979 (aOR=1.476, 95% Wald CI: 1.171-1.861) showed a significant increase in incidence with a non-significant difference between 1980-1984 and 1985-1989. Males born in 1985-1989 showed a significant increase compared to 1975-1979 (aOR=1.411, 95% Wald CI: 1.060-1.878) with a non-significant difference for those born in 1980-1984.   Although melanoma incidence rates continue to increase in subsequent birth cohorts after the introduction of sunscreen, rates for females may be leveling off. Sun protection methods in addition to sunscreen are warranted. Future studies should continue to follow trends for these birth cohorts as they age and examine the potential effects of broadband sunscreens introduced in the 2000's.

Rodriguez, Santiago

Poster Title: Exploring the Applicability of Apoptotic Cells for Tissue Regeneration

Category: Materials and Basic Processes

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2203   Poster Number: 73

Abstract:

The current state-of-the-art treatment for massive burn trauma uses cultured epithelium from a non-affected area of skin of the patient to develop large epithelial sheets - a lengthy process that can take 2-3 weeks to prepare. If this delay could be drastically reduced and tissue regeneration significantly improved, patient recovery would benefit considerably. A recently published study showed that apoptotic cells around a wound activate the "Phoenix Rising" pathway that induces nearby stem cells to proliferate thereby promoting wound healing and tissue regeneration. This breakthrough has led us to explore the hypothesis that apoptotic cells may improve human graft regeneration in vivo. If allogeneic fibroblasts and keratinocytes could be used as the source of the apoptotic cells, these cells could then be expanded within approximately one week, instead 2-3 weeks required for current culture methods. In addition, should we prove this hypothesis, it may be possible to identify and purify the factors released by these apoptotic cells and employ them in the clinic to improve skin regeneration in burn patients. In our experiment, a piece of skin was surgically removed from an immunodeficient mouse and a grafting chamber was placed directly on the muscle fascia. The grafting chamber serves as a physical barrier to invading mouse skin during human graft formation, keeps material out of the wounds, and maintains humidity. Our control grafts only include viable human skin cells. Subsequent grafts include apoptotic cells, achieved by treatment with apoptosis inducing drugs such as Mitomycin C, Staurosporine, and DBeQ. Efficiency of skin graft regeneration will be assessed and compared to those of the control group that are grafted without apoptotic cells. In addition we will compare the effect of inducing apoptosis by different pathways with different drugs. We have not yet acquired all of our results, but we have concluded that Caspase 3 appears to be a vital component of apoptosis-mediated stem cell proliferation and tissue regeneration. Mitomycin C, a Caspase 3 independent apoptosis inducer, did not appear to induce tissue regeneration. However, before eliminating Mitomycin C as a candidate, we must experiment with different cellular conditions such as using different numbers of keratinocytes and different numbers of apoptotically-induced cells.

Poster Title: INVESTIGATING THE ENDOGENOUS ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR IN ANOIKIS RESISTANCE

Category: Hematology and Oncology

School: Graduate   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 43

Abstract:

INVESTIGATING THE ENDOGENOUS ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR IN ANOIKIS RESISTANCE. Thomas Rogers (B.S), Nicholas D'Amato (Ph.D), Jennifer Richer (Ph.D). Department of Pathology, University of Colorado-Anschutz Medical Campus   Background: Anoikis is a specialized form of programmed cell death induced in response to detachment from the extracellular matrix. Anoikis resistance is thought to be a critical trait of metastatic cancer cells, enabling them to leave the primary tumor and travel through the vasculature or lymphatics in transit to a metastatic site. This is particularly important for the highly metastatic, aggressive triple-negative breast cancers (TNBC). Global profiling via microarray analysis identified a number of up-regulated genes differentially expressed by BT549 (TNBC) cells grown in suspended versus adherent conditions in vitro, the highest of which derive from the kynurenine pathway. Interestingly, a key metabolite of this pathway, L-Kynurenine (L-Kyn) has been implicated to activate the aryl hydrocarbon receptor (AhR), another up-regulated gene in suspension. Hypothesis: Endogenous activation of the aryl hydrocarbon receptor, mediated by the up-regulation of the tryptophan metabolism pathway, confers anoikis resistance specifically in triple-negative breast cancer cell lines Methods: We initially assessed transcript and protein levels of TDO2, KYNU and AhR through real time qPCR and Western Blot. Next, using an AhR reporter plasmid, we measured luciferase activity in suspension compared to adherent condition. Upon confirmation of increased AhR reporter activity in suspension, small molecule inhibitors for TDO2 and AhR were used to target AhR reporter activity, AhR transcriptional readout, and anoikis resistance in TNBC. Results: AhR and TDO2 increase at both the transcript and protein level in suspension in TNBC. AhR reporter activity increases in suspension in both luminal and TNBC, but higher in TNBC AhR reporter activity decreased by AhR inhibitor and TDO2 in TNBC TDO2 inhibitor reduces transcription of AhR target gene and increases cell death in suspension L-Kyn increases AhR reporter activity

Poster Title: Care Coordination Rounds

Category: Humanities and Bioethics

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 2301   Poster Number: 30

Abstract:

CARE COORDINATION ROUNDS R De Andrade Pereira, (MD UC-SOM), M Rovira, (MD UC-SOM) S Groves, D Medrano, M Muszelik, M Ross, J Sweigart MD, D Tad-Y MD, R Peirce MD, Division of General Internal Medicine, University of Colorado, Aurora, CO.   Well-designed multidisciplinary rounds (MDRs) have been shown to decrease stroke mortality. Thus, hospitals hoping to become Centers of Excellence have been charged by JAHCO (Joint Commission: Accreditation, Health Care and Certification) to implement disease-specific MDRs. However, at the University of Colorado Hospital, a JAHCO Stroke Center of Excellence, the current state stroke MDRs, based on frontline staff feedback, are one that interferes with interprofessional communication and patient-care coordination, which results in an increased patient length of stay. In an effort to decrease the length of stay of ischemic stroke patients, a redesign of the current MDRs gave rise to the Care Coordination Rounds (CCRs). This redesign hopes to enable efficient quality conversation between all neurology teams involved by way of an improved [CCR] platform for the exchange of patient information. In doing so, end goals of the new CCRs are three-fold: Decrease the length of stay of ischemic stroke patients, decrease the amount of work experienced by each neurology personnel, and to produce an overall increase in patient satisfaction and education. Future goals for the project aim to achieve CCRs that function off both face-to-face rounding combined with a facilitation tool for both ease of information access and the ability for Stroke Team Members to be "present in absentia". The Stroke Team Care Coordination Rounds are currently in the first phases of implementation at UCH. Initial feedback has shown promising reviews from staff and patients alike.

Poster Title: ALDH16A1 INTERACTING WITH HPRT1 IN THE PURINE SALVAGE PATHWAY

Category: Immunology and Autoimmune Diseases

School: Graduate   Year: 3rd

Poster Location: ED 2 South Room 2306   Poster Number: 16

Abstract:

M Sandoval (Ph.D., Toxicology), B Jackson, Y Chen, R Johnson, and V Vasiliou. Department of Pharmaceutical Sciences, University of Colorado School of Pharmacy, Aurora, CO.   Gout, a common form of inflammatory arthritis, is strongly associated with elevated uric acid concentrations in the blood (hyperuricemia). A recent study identified a rare single nucleotide polymorphism in the aldehyde dehydrogenase 16A1 (ALDH16A1) gene, ALDH16A1*2, shows a strong association with hyperuricemia and gout (Stefansson, 2011). ALDH16A1 is a novel and unique member of the ALDH superfamily in relation to its protein structure and has been identified as a binding partner of multiple proteins. Hypoxanthine-phosphoribosyltransferase (HPRT1) is a potentially important binding target for ALDH16A1 in the context of gout pathophysiology because it plays a key role in the purine salvage pathway and reduced/absence of its activity are known to cause hyperuricemia and gout. The purpose of this study is to determine if ALDH16A1 plays a role in hyperuricemia and gout by modulating HPRT1 in the purine salvage pathway. Methods: Molecular modeling was performed to determine if ALDH16A1 is catalytically inactive and the binding ability with HPRT1. Transfection and immunoprecipitation were performed to assess the ex vivo interaction between ALDH16A1 and HPRT1. Uric acid generation in transfected cells overexpressing ALDH16A1 was determined to assess the possible role of ALDH16A1 in the purine salvage pathway. Results: Molecular modeling predicts human ALDH16A1 protein would lack catalytic activity due to the absence of the catalytically important cysteine residue (Cys-302) as well as a loss of substrate binding and cofactor binding (NAD+) pockets. Molecular modeling as well as ex vivo interaction studies implies that ALDH16A1, but not ALDH16A1*2, may interact with HPRT1. The decrease in uric acid generation in ALDH16A1 overexpressing cell lines implies a possible role of ALDH16A1 in the purine metabolism pathway. Conclusion: These results lead to the intriguing possibility that association between ALDH16A1 and HPRT1 may be required for optimal HPRT1 activity; disruption of this interaction may contribute to the hyperuricemia seen in ALDH16A1*2 carriers.

Poster Title: Combining canonical B-catenin pathway inhibition with EGFR inhibitors in non-small cell lung cancer

Category: Hematology and Oncology

School: Graduate   Year: 3rd

Poster Location: ED 2 South Bridge   Poster Number: 45

Abstract:

COMBINING CANONICAL WNT PATHWAY INHIBITION WITH EGFR INHIBITORS IN NON-SMALL CELL LUNG CANCER. HA Scarborough (Ph.D., GS) M Casas-Selves, BA Helfrich, PA Bunn and JV DeGregori   Purpose of Study: Recent advances in treatment strategy in non-small cell lung cancer (NSCLC) have involved its division into molecular subsets according to specific driver mutations, which occur in genes that encode for signaling proteins necessary for proliferation and survival. Targeted therapies inhibiting specific receptor tyrosine kinases have shown clinical promise but rarely produce complete responses and are not curative, suggesting the existence of escape mechanisms promoting cell survival. Methods and Results: Using a genome-wide shRNA screen, we identified that the canonical Wnt pathway contributes to the maintenance of NSCLC cells during inhibition of the epidermal growth factor receptor (EGFR). We have demonstrated that inhibition of tankyrase and other components of the Wnt pathway significantly increased the efficacy of EGFR inhibitors and that the ability of drugs targeting tankyrase and other pathway components to synergistically eliminate NSCLC cells is dependent on inhibition of β-catenin-dependent transcription. Additionally, we have applied these strategies to orthotopic mouse models and have shown that treatment with a combination of a tankyrase inhibitor and an EGFR inhibitor results in decreased tumor burden and a significant improvement in survival when compared to treatment with an EGFR inhibitor alone. Future directions: In order to more comprehensively query Wnt pathway dependencies in NSCLC, we have constructed a custom shRNA library containing key nodes in multiple Wnt-regulated pathways (canonical and non-canonical) and have performed a functional genomics screen across a comprehensive array of NSCLC lines. In total, the goal of these studies is the development of combination therapies targeting EGFR and Wnt pathways that lead to more durable remissions for NSCLC.

Poster Title: Invasive Coronary Procedure Use and Outcomes among Patients with Post-Traumatic Stress Disorder: Insights from the VA CART Program

Category: Cardiovascular

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 1203   Poster Number: 2

Abstract:

INVASIVE CORONARY PROCEDURE USE AND OUTCOMES AMONG PATIENTS WITH POST-TRAUMATIC STRESS DISORDER: INSIGHTS FROM THE VA CART PROGRAM. JH Schilling (M.D., SOM), SM Bradley, MA Stanislawski, DB Bekelman, LL Monteith, BE Cohen, SC Hunt, D Milek, TM Maddox, PM Ho, S Shore, PD Varosy, and JS Rumsfeld, Colorado Cardiovascular Outcomes Research, Denver, CO.   Post-traumatic stress disorder (PTSD) is associated with increased risk of developing and dying from coronary artery disease (CAD). However, patterns of use of invasive coronary procedures and post-procedural outcomes in patients with PTSD are unknown. Among all Veterans Affairs (VA) patients who underwent coronary angiography from October 2007 to September 2010, we compared patient characteristics and clinical presentation by presence of PTSD. Among patients with obstructive CAD identified on angiography, we assessed risk-adjusted one-year rates of all-cause mortality, myocardial infarction (MI), and revascularization. We then assessed the impact of concurrent depression or anxiety, alcohol or substance use disorders, and frequency of outpatient follow-up on post-procedural outcomes. Overall, 116,488 patients underwent angiography, of which 14,917 (12.8%) had PTSD. Compared to those without PTSD, patients with PTSD were younger, had higher rates of cardiovascular risk factors and were more likely to have had a prior MI. Patients with PTSD were more likely to present for elective indications of stable angina or atypical chest pain and less likely to have obstructive CAD identified at angiography. Among the 71,477 patients with obstructive CAD, PTSD was not associated with unadjusted one-year rates of MI or revascularization, but was associated with lower unadjusted one-year all-cause mortality. This association remained after adjustment for cardiovascular risk, non-psychiatric comorbidity, depression, anxiety, alcohol or substance use disorders, and frequency of outpatient follow-up. Among Veterans undergoing coronary angiography in the VA health care system, those with PTSD were more likely to present with elective indications and less likely to have obstructive CAD. Among patients with obstructive CAD at angiography, PTSD was not associated with adverse one-year outcomes of MI, revascularization, or all-cause mortality.

Poster Title: WEST NILE VIRUS ALTERS THE ACTIVITY AND EXPRESSION OF CAP-DEPENDENT TRANSLATION INITATION COMPONENTS DOWNSTREAM OF MTORC1

Category: Microbiology and Infectious Diseases

School: Graduate   Year: 3rd

Poster Location: ED 2 North Room 2106   Poster Number: 66

Abstract:

WEST NILE VIRUS ALTERS THE ACTIVITY AND EXPRESSION OF CAP-DEPENDENT TRANSLATION INITATION COMPONENTS DOWNSTREAM OF MTORC1. K.D. Shives (Ph.D., GS) JD Beckham. Department of Microbiology, University of Colorado Anschutz Medical Campus, Aurora, CO.   Since its introduction in New York City in 1999, West Nile virus (WNV) has spread to all 48 contiguous United States and is now the leading cause of epidemic encephalitis in North America. As member of the family Flaviviridae, WNV is part of a group of clinically-important human pathogens including Dengue virus, Yellow Fever virus, St. Louis encephalitis virus, and Japanese encephalitis virus. As this family of (+) sense ssRNA viruses has a very limited coding capacity (average of 10 distinct protein products produced), Flaviviruses are obligated to co-opt a significant amount of cellular factors in order to translate their genomes effectively. Currently, the manner in which Flaviviruses translate their genomes in the host cell is incompletely understood and elucidation of the molecular mechanisms that support WNV genome translation will provide broad understanding for the basic mechanisms required to translate viral RNA. Our previous work has shown that WNV activates the evolutionarily-conserved mammalian target of rapamycin (mTOR) pathway during infection. MTOR is a serine/threonine kinase that acts as a central cellular censor of nutrient status and exercises control of vital anabolic and catabolic cellular responses such as protein synthesis and autophagy, respectively. Our work utilizing an inducible knock-out system of the major mTOR co-factors Raptor (mTORC1) or Rictor (mTORC2) has shown that the mTORC1 is activated in support of WNV growth and viral protein synthesis. We now show that eukaryotic initiation factor 4B (eIF4B), p70 ribosomal protein S6 kinase (p70S6K) and ribosomal protein S6 (rpS6) are activated following WNV-induced mTOR activation. We also show that WNV infection enhances expression of total rpS6, but total eIF4B levels decrease over the course of infection. Our studies show that WNV manipulates cap-dependent translation machinery downstream of mTORC1 in support of viral gene expression. Ongoing studies will determine the roles of specific translation initiation events that determine the outcome of viral RNA competitions for host translation machinery.

Poster Title: Utilization of guideline-concordant therapies as a function of patient risk in myocardial infarction post-discharge

Category: Cardiovascular

School: Graduate   Year: 2nd

Poster Location: ED 2 South Room 1303   Poster Number: 7

Abstract:

UTILIZATION OF GUIDELINE-CONCORDANT THERAPIES AS A FUNCTION OF PATIENT RISK IN MYOCARDIAL INFARCTION POST-DISCHARGE S Shore (MSC, GS); Y Li; PG Jones; TM Maddox; SM Bradley; J Spertus; PM Ho   Background: Prior studies have demonstrated that high-risk acute myocardial infarction (AMI) patients are less likely to receive guideline-concordant medications during hospitalization (risk-treatment paradox). However, it is unknown if this paradox persists following hospital discharge. We assessed if persistence to medications post-discharge varies by patient risk-status. Methods: Data were analyzed from combined PREMIER and TRIUMPH registries: prospective, 31-center U.S. registries of AMI patients from 2003-2008. Persistence to medications was assessed through interviews at 1, 6 and 12 months post-discharge among those discharged on appropriate therapies. Outcomes assessed included persistent use of individual and all guideline concordant medications post-discharge, which included aspirin, beta-blockers, statins and angiotensin antagonists. Association between risk-status and medication persistence post-discharge was assessed using repeated measures analysis.   Results: We included 6,434 AMI patients discharged home, classified into low (n=2,824), moderate (n=2,014) or high-risk categories (n=1,596) based on GRACE risk score. High-risk status was associated with lower likelihood of receiving all appropriate therapies at discharge compared to low-risk patients (RR 0.88; 95% CI 0.84-0.92). After multivariable adjustment and compared to low-risk patients, there was an association between high-risk patients discharged on all appropriate medications and lower persistence to all medications in the year following discharge (RR 0.88; 95% CI 0.83-0.92). The association between high-risk patients and low persistence remained for each individual medication classes. From 2003-2008, persistence to therapy in the year after discharge improved marginally among high-risk patients (RR 1.04; 95% CI 1.03-1.05 per 6-monthly increase in time interval). Conclusion: Risk-treatment paradox persists beyond discharge following AMI with marginal improvement in persistence to medications over time. Improved efforts are needed to bolster medication persistence post discharge in high-risk patients.

Poster Title: Patterns of adherence to dabigatran and its association with outcomes

Category: Cardiovascular

School: Graduate   Year: 2nd

Poster Location: ED 2 South Room 1209   Poster Number: 4

Abstract:

PATTERNS OF ADHERENCE TO DABIGATRAN AND ITS ASSOCIATION WITH OUTCOMES S Shore (MSc, GS), E Carey, M Turakhia, C Jackevicius, F Cunningham, L Pilote, SM Bradley, TM Maddox, J Rumsfeld, P Varosy, PM Ho.   Background: Dabigatran is a novel oral anti-coagulant (NOAC) that reduces risk of stroke in patients with non-valvular atrial fibrillation (NVAF). It does not require routine monitoring with laboratory testing which may have an adverse impact on adherence. We examined adherence to dabigatran in the first year after initiation and assessed the association between dabigatran non-adherence and outcomes. Methods: We studied a national cohort of 5,376 patients with NVAF, initiated on dabigatran between October-2010 and September-2012 at all Veterans Affairs hospitals. Adherence to dabigatran calculated as proportion of days covered (PDC; number of days supplied divided by observation period). Then, we assessed the association between adherence and adverse outcomes (composite of stroke and all-cause mortality) using Cox Proportional Hazards regression with adherence as a time-varying covariate and adjusting for demographic and clinical variables. Results: Mean age of the study cohort was 71 years, 98% were males and mean CHADS2 score was 2.4+1.2. Median PDC was 94% (IQR 76%-100%; mean PDC 84%+22%) over a median follow-up of 244 days (IQR 140-351). A total of 1,494 (28%) patients had a PDC

Poster Title: ALDEHYDE DEHYDROGENASE 1B1 IS REQUIRED FOR COLON TUMORIGENESIS BY MODULATING WNT-SIGNALING AND METABOLIZING RETINALDEHYDE

Category: Hematology and Oncology

School: Pharmacy   Year: 5th

Poster Location: ED 2 South Bridge   Poster Number: 47

Abstract:

ALDEHYDE DEHYDROGENASE1B1 IS REQUIRED FOR COLON TUMORIGENESIS BY MODULATING WNT-SIGNALING AND METABOLIZING RETINALDEHYDE Singh S1 (Ph. D., SOP), Arcaroli J 3, Chen Y1, Jackson BC1, Messersmith W3, Orlicky D 4, Thompson DC2, Vasiliou V.1 1Department of Pharmaceutical Sciences and 2Department of Clinical Pharmacy University of Colorado Anschutz Medical Campus, Aurora, CO 80045 3Division of Medical Oncology and 4Department of Pathology University of Colorado School of Medicine, Aurora, CO 80045   Aldehyde dehydrogenase 1B1 (ALDH1B1) is a mitochondrial enzyme that shows 65% and 72% amino acid homology with ALDH1A1 and ALDH2, respectively. In human normal colon, ALDH1B1 is expressed only at the crypt base, along with stem cells. It is highly expressed in all cancerous cells of human colonic adenocarcinomas. This pattern of expression corresponds closely to that observed for Wnt signaling activity in normal and cancerous colon. In the present study, we show that shRNA mediated knockdown of ALDH1B1 reduced the number and size of spheroids formed by human colon cancer cells in a three-dimensional matrigel culture. In addition, ALDH1B1 knockdown depletes the putative highly carcinogenic ALDHbright colon cancer cells and significantly decreased xenograft tumor formation in athymic (nu+/nu+) mice. Gene expression studies on the Wnt-signaling pathway revealed upregulation of Axin2 (a negative regulator of the Wnt pathway) and downregulation of beta-catenin (a critical protein in the canonical Wnt-signaling pathway) and Wnt dependent transcription of cMyc in ALDH1B1-depleted colon cancer cells. We have also found that ALDH1B1 metabolizes all trans-retinaldehyde efficiently with Km of 25 µM to generate retinoic acid which has been reported to increase expression of pro-survival genes and tumor growth by activating PPAR　□□□□　in colon ance functional role in colon cancer tumorigenesis by modulating the Wnt signaling pathway and participating in retinoic acid formation.

Poster Title: ARTHRITOGENIC ALPHAVIRUS INFECTION INDUCES IMMUNOSUPPRESSIVE MACROPHAGES TO ESCAPE THE ANTI-VIRAL T CELL RESPONSE

Category: Microbiology and Infectious Diseases

School: Graduate   Year: 6th

Poster Location: ED 2 North Room 2106   Poster Number: 68

Abstract:

Ross River virus (RRV) and chikungunya virus (CHIKV), are mosquito-transmitted alphaviruses that cause a debilitating musculoskeletal inflammatory disease, which often persists for months to years. Evidence from humans and animal models indicate that RRV/CHIKV RNA and antigen remain detectable in tissues for weeks to months after infection, which is associated with protracted disease signs. Thus, understanding immunological mechanisms that control the clearance of arthritogenic alphaviruses is essential for the development of new therapeutic strategies. We found that arginase 1 (Arg1), a gene associated with wound repair and immunosuppressive activity in macrophages, was dramatically induced in the musculoskeletal inflammatory lesions and tissue-infiltrating macrophages of RRV- and CHIKV-infected mice. Mice specifically deleted for Arg1 in myeloid cells (LysMcre;Arg1F/F) had reduced viral loads and improved tissue pathology at late, but not early, times post-RRV infection. Depletion of both CD4+ and CD8+ T cells increased viral loads in LysMcre;Arg1F/F mice to levels detected in WT mice, suggesting that myeloid cell Arg1 inhibits clearance of RRV by suppressing anti-viral T cells. Utilizing a recombinant RRV, we detected virus-specific CD8+ T cells in lymphoid and inflamed muscle tissues of infected WT and LysMcre;Arg1F/F mice. Interestingly, virus-specific CD8+ T cells isolated from inflamed muscle tissue of LysMcre;Arg1F/F but not WT mice stained for the T cell activation marker CD44, suggesting that the musculoskeletal tissue environment alters the T cell activation phenotype in an Arg1-dependent manner. In addition to expressing Arg1, macrophages isolated from RRV-infected mice also express inducible nitric oxide synthase (iNOS; Nos2), a phenotype associated with production of potently immunosuppressive reactive nitrogen species such as peroxynitrite (PNT). We detected PNT activity in musculoskeletal tissues of RRV- and CHIKV-infected mice, which was reduced in LysMcre;Arg1F/F mice. Consistent with these data, clearance of RRV is improved in Nos2-/- mice. These findings suggest that Arg1- and iNOS-mediated PNT production suppresses anti-viral T cell activity and diminishes host control of RRV infection. Our studies provide new insights into the immunological mechanisms that control the clearance of arthritogenic alphaviruses and the role of myeloid cells in inflammation and immunity.

Poster Title: DISCERING PROTEIN KINASE C δ'S TUMOR PROMOTING ROLE IN K-RAS ADDICTED LUNG CANCER

Category: Hematology and Oncology

School: Graduate   Year: 7th

Poster Location: ED 2 South Bridge   Poster Number: 49

Abstract:

DISCERING PROTEIN KINASE C δ'S TUMOR PROMOTING ROLE IN K-RAS ADDICTED LUNG CANCER. JM Symonds (Ph.D. candidate, Graduate Program in Cancer Biology), AM Ohm, and ME Reyland. Department of Craniofacial Biology and the Graduate Program in Cancer Biology, University of Colorado Denver, Aurora, CO.   Oncogenic activation of K-ras occurs in 25% of Non-Small Cell Lung Cancers (NCSLC), however strategies to target K-ras have been ineffective due to limited knowledge of its downstream effectors. Our work has shown that Protein Kinase C δ (PKCδ) is a tumor promoter in NSCLC cells that are addicted to K-ras. In this context, PKCδ is a positive regulator of the Mitogen Activated Protein Kinase (MAPK) pathway and tumorigenesis. To explore targets of PKCδ in the context of oncogenic K-ras, we analyzed mRNA levels by microarray to identify genes regulated in K-ras addicted NSCLC with PKCδ loss. This study revealed over 3000 genes are regulated by PKCδ, independent of K-ras oncogene addiction, with 210 genes regulated by PKCδ only in K-ras addicted NSCLC cells. Pathway analysis showed that genes from both groups are enriched in extracellular matrix (ECM)-receptor interactions. We validated a subset of these genes by quantitative Polymerase Chain Reaction (qPCR). Strikingly, the mRNA levels for ten integrins were decreased with PKCδ loss in both K-ras addicted and non-addicted cells. Integrins are receptors for ECM. Two integrins, αV and β3, were found to be regulated by PKCδ only in K-ras addicted cells, and depletion of PKCδ reduced integrin αVβ3 expression at the cell surface in these cells. Integrin αVβ3 is over-expressed in tumor cells and is associated with higher incidence of metastasis. Integrin αVβ3 also behaves as a pro-survival factor in both attached and suspension cultures, enhancing tumor cells' metastatic potential. K-ras addicted NSCLC cell lines are dependent on PKCδ to regulate their survival in suspension conditions, an approximation of metastatic ability. Preliminary data suggests that restoration of PKCδ in NSCLC cell lines rescues integrin αVβ3 mRNA expression and cell survival following suspension culture. Taken together, our findings indicate that PKCδ is acting as a tumor promoter in K-ras addicted NSCLC by regulating expression of integrin αVβ3, and inhibiting PKCδ could be an attractive therapeutic target. These results further underscore how K-ras oncogene addiction signaling should be explored to develop more effective treatments for NSCLC.

Poster Title: REPURPOSING ANTIANGIOGENESIS DRUGS TO PREVENT HYPOXIC CEREBRAL INJURY

Category: Neuroscience and Brain and Behavior – Adult

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2307   Poster Number: 87

Abstract:

REPURPOSING ANTIANGIOGENESIS DRUGS TO PREVENT HYPOXIC CEREBRAL INJURY. S Tarshis (MD, CUSoM), D Irwin, CUSoM.   Purpose of Study: Understanding the destruction processes of an oxygen starved brain can provide insight to unknown brain function under metabolic stress, hypoxic vascular injury in the blood brain barrier, and potential treatments for a wide range of diseases especially those including high ICP. A great mechanism for studying the hypoxic brain is high altitude, with its worst outcome (HACE) serving as our model. HACE is a deadly and unpredictable brain disease for which there is still no effective prevention. A new prophylactic treatment for high altitude cerebral edema (HHACE) needs to be developed, without the inefficacy of acetazolamide and the dangerous side effects of dexamethazone. Rather than treating the resulting symptom (drastic cerebral edema) with a nonspecific anti-inflammatory, HACE should be prevented by blocking the disease pathway farther upstream its vascular edema pathway. I hope to repurpose an already existing anti-angiogenic drug to prevent the onset of HACE. This approach will also better reveal the mechanisms of HACE onset, a pathway still not well understood. Already existing anti-angiogenic drugs, currently used for tumor growth delay and wet macular degeneration should be tested for efficacy in HACE prevention. Although these drugs are meant for angiogenesis inhibition, some will most likely prevent vascular permeability as well, since vascular leakiness must precede angiogenesis for new vessel formation to be possible. These chemicals are selective, meaning fewer unwanted side-effects or toxicity, and reversible, suggesting safer effects. Most importantly, all these potential drugs are cell permeable; the chemicals can pass directly through the endothelial cells, astrocytic endfeet, and tight junctions that comprise the blood brain barrier. This means that they can be administered intravenously or, after some modification, orally, and no injection directly into the brain (unrealistic for future transition to human patients) will be necessary. Methods Used: We exposed 25 rats to hypoxic conditions treated with antiangiogenesis drugs or antioxidants (to test if another pathway, reactive oxygen species, were instead the main cause of HACE) and 5 to control conditions. Their brains were analyzed for leak and inflammation using the Evans Blue protocol. Summary of Results and Conclusion: (pending statistical analysis)

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

Category: Pharmacology and Physiology

School: Pharmacy   Year: 4th

Poster Location: ED 2 North Room 2302   Poster Number: 83

Abstract:

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

Tompkins, Amanda

Poster Title: Erosive Capacity of Five Commercial Bleaching Products on Human Enamel

Category: Materials and Basic Processes

School: Dentistry   Year: 1st

Poster Location: ED 2 North Room 2206   Poster Number: 75

Abstract:

EROSIVE CAPACITY OF FIVE COMMERCIAL BLEACHING PRODUCTS ON HUMAN ENAMEL AM Tompkins (DDS, SODM), SS Coleman, and CM Carey, Department of Craniofacial Biology, School of Dental Medicine, Aurora, CO. The majority of commercial tooth bleaching products on the market contain varying concentrations of hydrogen peroxide or carbamide peroxide as active ingredients.   Others contain chemicals such as sodium chlorite in place of these peroxide derivatives. The popularity of tooth whitening continues to increase; therefore, the potential deleterious effects including possible enamel erosion should be investigated.   Objective: Determine the erosive capacity of five commercial bleaching products on human tooth enamel.   Methods: Thinned (110µm) tooth slices with attached transmission microscope grids were mounted into epoxy between coverslips. Digital microphotographs of samples were taken prior to and following bleach exposure. Nine sample groups (n=6 for each group) were utilized: Philips Zoom Nite White (ZNW), Dr. Collin's All White (AW), Crest Vivid White Whitestrips (CWS), Natural White 5-Minute White (NW), Opalescence Boost (OB), and citric acid standards at CA1.0%, CA0.25%, CA0.07% and CA0.0%. Samples were treated following manufacturers' instructions or 1 hour for CA standards. Enamel erosion was determined from the comparison of pre and post digital microphotographs using Image-J (resolution=±2µm/pixel).   Results: No significant erosion was observed among the different bleaching products (ANOVA, $p > 0.05$). Significant erosion was observed in 0.25% and 1.0% CA standards (p

Poster Title: Community-Based, Targeted CPR Education to Improve Survival from Out-of-Hospital Cardiac Arrest in High-Risk Neighborhoods

Category: Health Care and Public Health

School: Medicine   Year: 2nd

Poster Location: ED 2 South Room 2207   Poster Number: 32

Abstract:

COMMUNITY-BASED, TARGETED CPR EDUCATION. T Califf (MD, SOM), T Tran (MD, SOM), C Sasson, M Tran, M Carmona, and A Nassel, Department of Emergency Medicine, University of Colorado, Aurora, CO.   Background: High-risk neighborhoods, defined as having a low prevalence of bystander CPR and high incidence of out-of-hospital cardiac arrest (OHCA), may be targets for community-based interventions. The HANDDS Program is a novel intervention to increase awareness of OHCA symptoms and provision of hands-only CPR in these neighborhoods.   Objective: To conduct a pilot, community-based hands-only CPR trial for residents of high-risk neighborhoods in Denver.   Methods: Design: Prospective community-based clinical trial. Setting: Targeted high-risk neighborhoods in Denver, CO metropolitan area. Population: Convenience sample of 344 residents were recruited during the 12-week study period. Intervention: Participants completed a demographic survey and pre-test to assess baseline knowledge of CPR. Subjects then completed a group hands-only CPR training lasting 1 hour using the CPR Anytime kit, which included an educational DVD and hands-on skills training with an inflatable mannequin. After the intervention, participants were asked to complete the same 5-question survey to assess their retention of knowledge. They were also asked to use these kits to train other community members over a 2-6 week period. A $10 incentive was given for participation in the study. Two-sample t-tests were conducted to assess for differences in hands-only CPR knowledge pre- and post-CPR training.   Results: Demographics are given in Table 1 for 344 participants. Participants were Asian (50.0%) and black (35.6%), female (68.0%), had completed high school (26.8%), and had an annual income of less than $30,000 (37.1%). After the intervention, the mean number of questions about CPR answered correctly increased (Table 2). Most participants (84.6%) felt comfortable performing hands-only CPR after the intervention. One hundred forty-nine (43.4%) participants returned trainee data at the end of the study, with an additional 812 people trained.   Conclusion: With 344 CPR Anytime Kits, we trained 1156 members of high-risk neighborhoods in hands-only CPR (average of 3.36 people/kit). Participants demonstrated increased knowledge of CPR and enthusiasm to train others. A targeted, community-based CPR intervention is a feasible way to increase bystander CPR training in high-risk neighborhoods.

Poster Title: BASAL GANGLIA CHANGES IN PRIMARY FOCAL DYSTONIA CORRELATE WITH INCREASED DEPRESSION AND ANXIETY SYMPTOMS

Category: Neuroscience and Brain and Behavior – Adult

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2307   Poster Number: 88

Abstract:

BASAL GANGLIA CHANGES IN PRIMARY FOCAL DYSTONIA CORRELATE WITH INCREASED DEPRESSION AND ANXIETY SYMPTOMS. Rebecca Tran (MD candidate in SOM), Erika Shelton, Brian Berman (MD, MS). Department of Neurology, University of Colorado School of Medicine, Aurora, CO.   Primary focal dystonia (PFD) is a chronic neurological disorder with abnormal and sustained muscle contractions. PFD is associated with increased risk of anxiety and depression, but the pathophysiology of these non-motor symptoms is unknown. In this study we compared functional connectivity (FC) maps of PFD patients to healthy controls (HC) to examine differences in basal ganglia (BG) circuits involved in motor and non-motor functioning. We then tested for relationships between FC changes and clinical assessments of symptoms.   Methods: FC maps of 12 PFD patients and 19 HC were assessed with resting state functional MRI scans. Motor and limbic symptoms were assessed with different scales (e.g., the Beck Depression Inventory for depression). We applied seed-based analysis to examine FC of four BG networks using the dorsal caudal putamen, ventral rostral putamen, inferior ventral striatum, and dorsal caudate, which serve as nodes in motor, motivation, behavior, and cognitive circuits, respectively. Using a two-sample t-test we identified clusters in which PFD patients had significant differences in FC compared to HC. We then correlated FC within these clusters in PFD patients with clinical measures.   Results: Compared to HC, PFD patients demonstrated FC changes in all four BG circuits with altered connectivity found to involve the thalamus, insula, and cerebellum. In PFD patients, changes in FC of the motor BG circuit were correlated with motor symptoms ($r = +0.69$, p

Poster Title: CANCER CELL EXOSOME PROTEOMIC REVEAL TRANSCRIPTIONAL REGULATORY PROTEIN WITH THE POTENTIAL TO MEDIATE MALIGNANT DISEASE PROGRESSION

Category: Hematology and Oncology

School: Medicine   Year: 3rd

Poster Location: ED 2 South Bridge   Poster Number: 51

Abstract:

CANCER CELL EXOSOME PROTEOMIC REVEAL TRANSCRIPTIONAL REGULATORY PROTEIN WITH THE POTENTIAL TO MEDIATE MALIGNANT DISEASE PROGRESSION Timothy Ung (MD, SOM)1,2, Helen Madsen2 , Justin Hellwinkel2 , Alex Lencioni, 2 Michael W Graner PhD 2 1. University of Colorado School of Medicine, 2. Department of Neurosurgery, University of Colorado School of Medicine   Background: Exosomes are virus-sized, membrane enclosed vesicles with origins in the cellular endosomal system, but are released extracellularly. As a population, these tiny vesicles carry relatively enormous amounts of information in their protein, lipid, and nucleic acid content, and the vesicles can have profound impacts on recipient cells.   Methods: To further evaluate the presence and significance of transcriptional regulatory proteins within exosomes we: 1] Reviewed previous laboratory data derived from primary medulloblastoma cell lines and D17 Canine Osteosacroma cell lines and 2] Search through ExoCarta for all previously discovered exosomal proteins. Data gathered was filtered for presence of transcription regulatory proteins and interactomes were constructed for further evaluation of cell line derived proteins.   Results: There exist numerous proteins that may have potential roles in transcriptional and translational regulation. Search to all of the proteins in the ExoCarta database; using gene ontogeny approaches, indicates that many of these factors are implicated in many of the processes involved in cancer initiation and progression, including modulations of the immune response. This information suggests to us that some of the effects of exosomes on recipient cells may be due to the delivery of protein factors that can directly and fundamentally change the transcriptional landscape of the cells, and in a tumor setting, this is likely to tilt the advantage towards the cancer.

Poster Title: NTRK1 GENE FUSIONS ARE A NOVEL ONCOGENE TARGET IN LUNG CANCER

Category: Hematology and Oncology

School: Graduate   Year: 3rd

Poster Location: ED 2 South Bridge   Poster Number: 53

Abstract:

A. Vaishnavi (1) (Ph.D., GS), M. Capelletti (2), A. T. Le (1), S. Kako (1), M. Butaney (2), S. Mahale (1), D. L. Aisner (1), J. Haas (3), S. W. Andrews (3), D. Lipson (4), P. Stephens (4), M. Varella-Garcia (1), V. A. Miller (4), P. A. Jänne (2), and R. C. Doebele (1.) 1 University of Colorado Cancer Center 2 Dana Farber Cancer Institute 3 Array BioPharma 4 Foundation Medicine, Inc. NTRK1 GENE FUSIONS ARE A NOVEL ONCOGENE TARGET IN LUNG CANCER   The identification and therapeutic targeting of oncogenic drivers in lung adenocarcinoma has led to substantial clinical improvements for patients with EGFR mutations or ALK fusions. Nevertheless, many lung cancer patients do not yet have an identified oncogenic driver and the discovery of new actionable oncogenic drivers is an active area of investigation. Our lab has recently identified NTRK1 gene fusions as a new actionable driver in lung cancer (Vaishnavi et al., Nature Medicine, 2013.)   Gene rearrangements involving the kinase domain of NTRK1, the gene that encodes the high-affinity nerve growth factor receptor, TrkA, were initially identified by next-generation sequencing (NGS), and confirmed using fluorescent in situ hybridization (FISH). This preliminary screen estimates NTRK1 gene fusions occur in 3.3% of lung adenocarcinomas. Cloning and expression of MPRIP- and CD74-NTRK1 in NIH-3T3 and Ba/F3 cells demonstrates constitutive activation of the TrkA kinase domain and cell transformation. Treatment of cells expressing NTRK1 fusions with several candidate pan-Trk inhibitors (ARRY-772, -523, and -470) as well as the multikinase inhibitors CEP-701 and crizotinib demonstrate decreased phosphorylation of both the fusion oncoproteins, and critical downstream signaling pathways, as well as inhibition of cell proliferation. Treatment of the index patient harboring the MPRIP-NTRK1 fusion with crizotinib led to minor transient tumor shrinkage. In summary, we identified a novel class of oncogenes, NTRK1 fusions, in lung adenocarcinomas that can be detected by NGS or FISH. Additional studies to determine the frequency and biological characteristics of NTRK1 fusions in lung cancer are ongoing. Our findings suggest prospective clinical trials of Trk inhibitors in NTRK1 fusion positive patients may be warranted.

Poster Title: ANTI-INFLAMMATORY ROLE OF IFN-γ AND THE IL-10 RECEPTOR IN THE RESTITUTION OF BARRIER FUNCTION AND RESOLUTION OF INFLAMMATORY BOWEL DISEASE.

Category: Immunology and Autoimmune Diseases

School: Medicine   Year: 2nd

Poster Location: Ed 2 South Room 2306   Poster Number: 19

Abstract:

AUTHORS: T.W. Vickery, (MD Candidate, SOM), K.E. Wilson, E.L. Campbell, C.J. Kelly, A.J. Bayless, B. Saeedi, S.P. Colgan, and D.J. Kominsky.   ANTI-INFLAMMATORY ROLE OF IFN-γ AND THE IL-10 RECEPTOR IN THE RESTITUTION OF BARRIER FUNCTION AND RESOLUTION OF INFLAMMATORY BOWEL DISEASE. PURPOSE: Investigate the mechanism of IFN-γ induced IL-10 receptor (IL-10R) expression on barrier restitution and return to homeostasis in models of inflammatory bowel disease (IBD). METHODS: IL-10R was identified as a target in IFN-γ treated intestinal epithelial cells (IEC) using microarray analysis. Lentiviral particles were used to knockdown the IL-10R in human epithelial cells (T84) in vitro. The effects of IL-10R expression were characterized using qPCR, western blot, and confocal microscopy. The role of IL-10R expression on epithelial junctional proteins was examined using trans-epithelial resistance (TER) and FITC-dextran flux assays. Finally, IL-10R expression was investigated in vivo using a murine IBD model, conditional IL-10 knockout mice, and human IBD patient samples. RESULTS: In vitro studies revealed that IFN-γ selectively induced the expression of IL-10R1 on the apical surface of IEC in a time dependent manner. Activation of the IL-10R functionally induced canonical IL-10 target gene expression in IEC concomitant with enhanced barrier restitution. Additionally, knockdown of IL-10R1 in intestinal epithelial cells results in impaired barrier function. Colonic tissue isolated from murine colitis revealed that levels of IL-10R and intracellular SOCS3 were increased in the epithelium and coincided with increased tissue IFN-g and IL-10 cytokines. IL-10R null mice demonstrated significantly worse disease as measured by colon length, barrier function, and pro-inflammatory cytokines (TNFα, IL-1β, and IL-6). Immunofluorescent staining revealed apical expression of the IL-10R in colitic mouse tissue. Furthermore, treatment of mice with rIFN-γ induced apical expression of IL-10R1 in the colonic epithelium. Finally, diseased human tissue demonstrated increased IL-10R1 transcript with apical IEC localization. CONCLUSIONS: These results suggest a critical anti-inflammatory role for IFN-γ induced expression of the IL-10R in the restitution of barrier function following intestinal epithelial inflammatory insult.

Poster Title: Functions of Early B cell Factor 1 (EBF1) in human leukemia and transcriptional repression.

Category: Hematology and Oncology

School: Graduate   Year: 4th

Poster Location: ED 2 South Bridge   Poster Number: 55

Abstract:

FUNCTIONS OF EARLY B CELL FACTOR 1 IN HUMAN LEUKEMIA AND TRANSCRIPTIONAL REPRESSION. SJ Welsh, (Ph.D., GS)a and J Hagmana,b. aMolecular Biology, University of Colorado School of Medicine. bIntegrated Department of Immunology, National Jewish Health.   The transcription factor Early B Cell Factor 1 (EBF1) is required for normal B cell development. Expressed throughout B cell lymphopoiesis, EBF1 regulates over 500 genes. EBF1 drives B cell identity by turning on genes necessary for B lineage specification but also by repressing genes from non-B cell lineages. EBF1 activates genes required for B cell signaling, metabolism, cellular adhesion, and migration. How EBF1 represses genes during normal development is far less understood. Opposite this normal development, a recent intra-chromosomal deletion that results in a novel gene fusion between EBF1 and the tyrosine kinase domain of Platelet Derived Growth Factor Receptor Beta (PDGFRβ) was identified in a sub-population of high-risk pediatric B cell acute lymphoblastic leukemia patients. We hypothesize that fusion of EBF1 to the active receptor tyrosine kinase (RTK) domain results in oncogenesis and inhibits EBF1's ability to control normal B cell lymphopoiesis. Furthermore, inactivation of the attached RTK by inhibitors (TKI) restores partial EBF1 function to EBF1:PDGFRβ. Consequently, a reservoir of B cells harboring EBF1:PDGFRβ may be generated and cause relapse in patients treated with TKI. Overall, the purpose of my study is to better understand EBF1 function. To do this, I am investigating two unique, but overlapping, EBF1 regulatory processes: (1) the functional consequences of the leukemic EBF1:PDGFRβ relative to EBF1, and (2) the molecular mechanisms of EBF1-mediated gene repression during normal lymphopoiesis. I am utilizing biochemical, cell-based, next-gen sequencing, and bioinformatic approaches to study EBF1 in both normal and leukemic B-cell contexts. Our lab has previously demonstrated that EBF1 represses non-B cell specific genes during normal development, and we are working to elucidate the mechanisms. With regards to leukemia, we have shown that use of common drug therapies like imatinib (Gleevec) on cells harboring the EBF1:PDGFRβ fusion protein unmasks EBF1 function with possible unforeseen consequences. Our studies will continue to elucidate the molecular mechanisms of EBF1 function and provide insights into leukemia onset, progression, remission and response to current targeted therapies.

Poster Title: Targeting Tyrosine Phosphorylation of PKCδ For Radio-Protection of the Salivary Gland

Category: Hematology and Oncology

School: Graduate   Year: 7th

Poster Location: ED 2 South Bridge   Poster Number: 57

Abstract:

TARGETING TYROSINE PHOSPHORYLATION OF PROTEIN KINASE Cδ ⬚FOR RADIO PROTECTION OF THE SALIVARY GLAND. S Wie, (Ph.D., GS), T Adwan, J Degregori, SM Anderson, ME, Reyland, Department of Craniofacial Biology, University of Colorado Anschutz Medical Campus, Aurora, CO.   Radiation therapy for head and neck cancer can result in extensive damage to normal adjacent tissues such as the salivary gland and oral mucosa. We have shown that tyrosine phosphorylation at Y64 and Y155 activates protein kinase Cδ (PKCδ) in response to apoptotic stimuli by facilitating it's nuclear import. Here we explore tyrosine phosphorylation of PKCδ as a therapeutic target for protection of radiation sensitive healthy tissues. We identify the damage inducible kinase, c-Abl, as the PKCδ Y155 kinase, and c-Src as the Y64 kinase.   Phosphorylation at these sites is co-operative, with phosphorylation of PKCδ at Y155 facilitating phosphorylation at Y64, thus assuring that the pro-apoptotic function of PKCδ is activated only in the context of cellular damage. Depletion of c-Abl or c-Src with shRNA decreased irradiation and etoposide induced apoptosis, suggesting that inhibitors of these kinases may be useful therapeutically. To test this we used Dasatinib, a broad-spectrum tyrosine kinase inhibitor. Pretreatment with Dasatinib blocked phosphorylation of PKCδ at both Y64 and Y155, while expression of a "gate-keeper" mutant of c-Abl or c-Src that is active in the presence of the inhibitor, restored Y155 and Y64 phosphorylation, respectively. Imatinib, a c-Abl selective inhibitor, also specifically inhibited Y155 phosphorylation. Both Dasatinib and Imatinib blocked binding of PKCδ to importin-α and nuclear import, and suppressed etoposide and radiation induced apoptosis in vitro. In vivo, pre-treatment of mice with Dasatinib blocked radiation-induced apoptosis in the salivary gland by > 60%. These data suggest that tyrosine kinase inhibitors may be useful prophylactically for protection of non-tumor tissues in patients undergoing radiotherapy of the head and neck.

Poster Title: Improving Surgical Outcomes by Optimizing Pre-Operative Nutritional Support: A Quality Improvement Project

Category: Surgery

School: Medicine   Year: 2nd

Poster Location: ED 2 North Room 2206   Poster Number: 76

Abstract:

IMPROVING SURGICAL OUTCOMES BY OPTIMIZING PRE-OPERATIVE NUTRITIONAL SUPPORT: A QUALITY IMPROVEMENT PROJECT JD Williams, (M.D., SOM) and P. Wischmeyer, Department of Anesthesiology, University of Colorado Denver, Aurora, Colorado This quality improvement project aims to improve nutritional screening and support (NSS) in GI surgical patients at University of Colorado Hospital in order to improve the primary clinical outcomes of post-operative infection rate and length-of-hospital-stay (LOS). Leading clinical nutrition societies give strong recommendations to pre-operative nutritional optimization and the use of immunonutrition (IN) diets for patients undergoing major surgery. However, published survey data indicate that less than 20% of surgeons perform pre-operative nutritional screening, only 23% utilize any pre-operative nutrition intervention, and less than 1% of surgical patients receive IN diets.   Methods and goals of this project are: 1) Quantify current baseline clinical outcomes and NSS via chart reviews 2) Assess current clinical practices and barriers to optimal NSS via stakeholder interviews 3) Develop a system-level improvement initiative that includes a patient-centric screening tool 4) Implement the improvement initiative, run serial Plan-Do-Study-Act cycles and track outcomes   Pending full results, we will assess charts for the adequacy of NSS, post-operative infection rate and LOS via objective scoring scales and duplicate review. Preliminary analysis of clinician surveys identifies the lack of a standard NSS tool as a leading barrier to the adoption of better NSS and IN utilization and also reveals a general consensus regarding the importance of NSS. Development of a NSS screening tool will be deployed and we will utilize statistical process control (SPC) methodology and generate SPC run charts to track changes to infection rate and LOS.   In sum, this project aims to fill a large gap in the translation of medical knowledge, in the form of guideline recommendations, into actual practice. Development of a patient-centric NSS protocol is an important first step in developing a replicable model for all pre-operative GI surgical clinics.

Poster Title: Antibody and Immune Therapy in Glioblastoma

Category: Hematology and Oncology

School: Medicine   Year: 2nd

Poster Location: ED 2 South Bridge   Poster Number: 59

Abstract:

ANTIBODY AND IMMUNE THERAPY IN GLIOBLASTOMA. KE Wyns, (MD, SOM), AM Griesinger, AM Donson, and NK Foreman, Department of Pediatric Oncology, University of Colorado, Aurora, CO.   Purpose: Glioblastoma multiforme (GBM) is a grade IV malignant astrocytic tumor classically associated with elevated levels of EGFR expression. When dimerized, EGFR initiates phosphorylation cascades that, in turn, create a pro-oncogenic environment for GBM development and metastasis. In conjunction with elevated EGFR levels, the innate and adaptive immune systems hold critical roles in advancing a pro-oncogenic environment.   Experimental Design: Given that Cetuximab works directly to inhibit EGFR, microarray and western studies were performed to assess the EGFR status of stock GBM lines. From this data, four cell lines were selected for co-culture cytotoxicity assays. Cytotoxicity assays were developed to test combination drug therapies with Cetuximab, GM-CSF and the following cytokines: IL-12, IL-2, and IL-10. LDH, Annexin V Affinity and BrdU/7AAD assays were run for each treatment condition to assess cell death, apoptotic activity and mitotic activity. The same treatment regimen was applied to GBM organotypic slice model to ascertain the direct therapeutic effect in explants of CNS tissue.   Results: From our LDH co-culture assays, immune stimulating cytokines (i.e. IL-2) were found to promote GBM cell lysis, whereas the pro-oncogenic cytokines (i.e. IL-10) were observed to protect GBM cells from antibody-dependent cell-mediated cytotoxicity. BrdU/7AAD assays also showed that immune-stimulating treatments resulted in lower GBM mitotic activity as well as G0/G1 cell cycle arrest; this finding indicates low cell viability in treated GBM populations. Furthermore, Annexin studies revealed apoptotic cell death in GBM populations treated with combination immune therapy. Organotypic slice culture corroborated the adherent cell culture findings; combination therapies stimulated immune cell mitosis and growth, while simultaneously causing a decrease in tumor cell growth. Conclusions: As is evidenced by our studies, combined myeloid stimulation with Cetuximab treatment results in increased GBM cell death as well as G0/G1 cell cycle arrest. Our preliminary data suggests that immune-stimulating therapies should be considered for further studies in tumor infiltrating leukocyte (TIL) models and in vivo studies.

Poster Title: QUINONE-INDUCED PROTEIN HANDLING CHANGES: IMPLICATIONS FOR MAJOR PROTEIN HANDLING SYSTEMS IN QUINONE MEDIATED TOXICITY

Category: Materials and Basic Processes

School: Graduate

Year: 5th

Poster Location: ED 2 South Room 1307

Poster Number: 14

Abstract:

QUINONE-INDUCED PROTEIN HANDLING CHANGES: IMPLICATIONS FOR MAJOR PROTEIN HANDLING SYSTEMS IN QUINONE MEDIATED TOXICITY. R Xiong, (Ph.D., GS), D Siegel, D Ross, Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, Anschutz Medical Campus, University of Colorado, Aurora, CO Para-quinones such as 1,4-benzoquinone (BQ) and menadione (MD) and ortho-quinones including the oxidation products of catecholamines, are derived from the oxidation of xenobiotics as well as endogenous molecules. Both BQ and MD have been shown to perturb protein-handling systems and we have demonstrated that the dopamine-derived quinone aminochrome (AC) could inhibit proteasomal activity. Since the potential hazardous effects of quinones on protein handling systems, including the 20/26S proteasome, the ER stress/unfolded protein response (UPR), autophagy, heat shock proteins (Hsps) and aggresome formation have not been investigated in detail, we conducted this study to systematically examine quinone-induced protein handling changes. In addition, the potential importance of NAD(P)H: quinone oxidoreductase 1 (NQO1) in modulating protein handling changes and toxicity was investigated using stable transfection to generate an isogenic NQO1-overexpressing neural cell line. Our data showed that both BQ and AC could inhibit proteasomal activity and activate the ER stress response in rat dopaminergic N27 cells as indicated by increased phosphorylation of eIF2α. While menadione had no significant effect on any protein handling systems, AC was able to stimulate autophagic flux and induce formation of aggresomes as determined by increased LC3 I/II turnover and the formation of ubiquitin positive inclusion bodies. By modulating quinone-induced ER stress responses, NQO1 protected against BQ toxicity but potentiated AC and MD toxicity. This suggests that NQO1 mediated reduction to unstable hydroquinones and subsequent redox cycling was important for the activation of the ER stress response and toxicity of AC and MD in N27 cells. In summary, our data demonstrates that quinone-specific changes in protein handling are evident in N27 cells and the induction of the ER stress response is associated with quinone-mediated toxicity.

Zak, Joseph

Poster Title: CONTROL OF GABA RELEASE AND GLOMERULAR OUTPUT BY METABOTROPIC GLUTAMATE RECEPTORS IN THE OLFACTORY BULB

Category: Neuroscience and Brain and Behavior – Adult

School: Graduate   Year: 4th

Poster Location: ED 2 North Room 2308   Poster Number: 89

Abstract:

Olfactory contrast enhancement is often proposed to arise through inhibitory GABAergic mechanisms that filter odor signals based on their strength. Here we examined a novel mechanism that could underlie such signal filtering within olfactory bulb glomeruli that depends on the commonly-observed ability of metabotropic glutamate receptors (mGluRs) to down-regulate GABA release (e.g., see Hayashi et al., 1993). Because mGluRs are likely to be primarily activated by extrasynaptic glutamate, their activation should occur when a glomerulus receives strong inputs from olfactory sensory neurons (OSNs); hence disinhibition and passage of excitatory signals should preferentially occur with strong inputs. Importantly, it has also been established that extrasynaptic glutamatergic signaling is robust within glomeruli. To test the role of mGluRs in glomerular signal processing, we performed patch-clamp recordings in rat olfactory bulb slices, first asking what effect mGluR activation has on inhibition from GABAergic periglomerular (PG) cells onto tufted cells, a critical regulator of activation of output mitral cells. We found that local puff-application of the group II mGluR-specific agonist DCG-IV (5 μM) on a glomerulus significantly reduced GABA release from PG cells onto tufted cells evoked by OSN stimulation ($47\pm15\%$ decrease in inhibitory current, $n = 5$; $p = 0.035$), while also increasing the number of evoked spikes in tufted cells ($66\pm20\%$ increase, $n = 6$; $p = 0.023$). At the same time, an antagonist for group II mGluRs (LY341495, 1 μM) enhanced GABA release from PG cells ($25\pm5\%$ increase in inhibitory current, $n = 6$; $p = 0.005$). Thus, activation of mGluRs in glomeruli can disinhibit tufted cells through modulation of GABA release, and moreover, these receptors can be activated by native glutamate transients. In terms of the mitral cell response, we found complex, biphasic effects of mGluR activation. Puff-application of the agonist DCG-IV hyperpolarized mitral cells (1.1 ± 0.2 mV, $n = 9$) and reduced their spiking in response to OSN stimulation ($71\pm12\%$ decrease in spike number, $n = 7$; $p = 0.0015$), different from the enhanced excitation seen in tufted cells, but there was depolarization and increased spiking above control levels upon immediate removal of DCG-IV ($60\pm24\%$ increase in spike number, $n = 7$; $p = 0.046$). The enhanced excitation of mitral cells following the mGluR-mediated hyperpolarization could be due to hyperpolarization-activated cation channels. Our results suggest that mechanisms exist to support an mGluR-dependent glomerular signal filter, although the temporal dynamics of the filter could differ between the output tufted cells and mitral cells.

Poster Title: Regulation of Natural Killer T Cell Development by Schnurri3

Category: Immunology and Autoimmune Diseases

School: Medicine   Year:

Poster Location: ED 2 South Room 2306   Poster Number: 18

Abstract:

REGULATION OF NATURAL KILLER T CELL DEVELOPMENT BY SCHNURRI3. J. Zhang (MD/PhD MS, GS) and L. Gapin, The Integrated Department of Immunology at the University of Colorado School of Medicine and National Jewish Health, Denver, CO.   The main goal of this study is to elucidate the mechanisms by which the zinc finger protein, Schnurri3 (also Hivep3, KRC, ZAS3, RC), regulates natural killer T (NKT) cell development. Natural killer T cells are unique glycolipid recognizing T cells that participate in disease processes such as ischemic reperfusion, diabetes, and tumor progression. They belong to a group of agonistly selected cells: a population of $\alpha\beta$ T cells, which display activated, innate-like characteristics. In contrast to conventional cells, which are selected on MHC expressed on thymic epithelial stromal cells, NKT cells are selected on CD1-expressing double-positive cortical thymocytes. During development, NKT cells sequentially express surface markers that correspond to its progressive development in the thymus. When activated, NKT cells rapidly secrete high levels of interferon gamma (IFN-γ) and interleukin-4 (IL-4). We have found that NKT cells are dependent on the large zinc finger protein, Schnurri3, for normal development in the thymus as well as proper function in the periphery. While development of conventional T cells are normal in Schnurri3 deficient mouse, NKT cells are decreased in number at every single stage of development. Furthermore, although Schnurri3 deficient mice are enriched for the immature CD44+NK1.1- stage, known to be biased for secretion of IL-4, we observed that Schnurri3 deficient NKT cells secrete less IFN-γ and IL-4. Also, preliminary bone marrow chimeras indicate that Schnurri3 exerts its effect in a cell intrinsic manner. Taken together, these results demonstrate that the unique pathway involved in NKT cell development is marked by a critical role in Schnurri3 and that this disruption causes substantial effects on NKT cell development in the thymus.