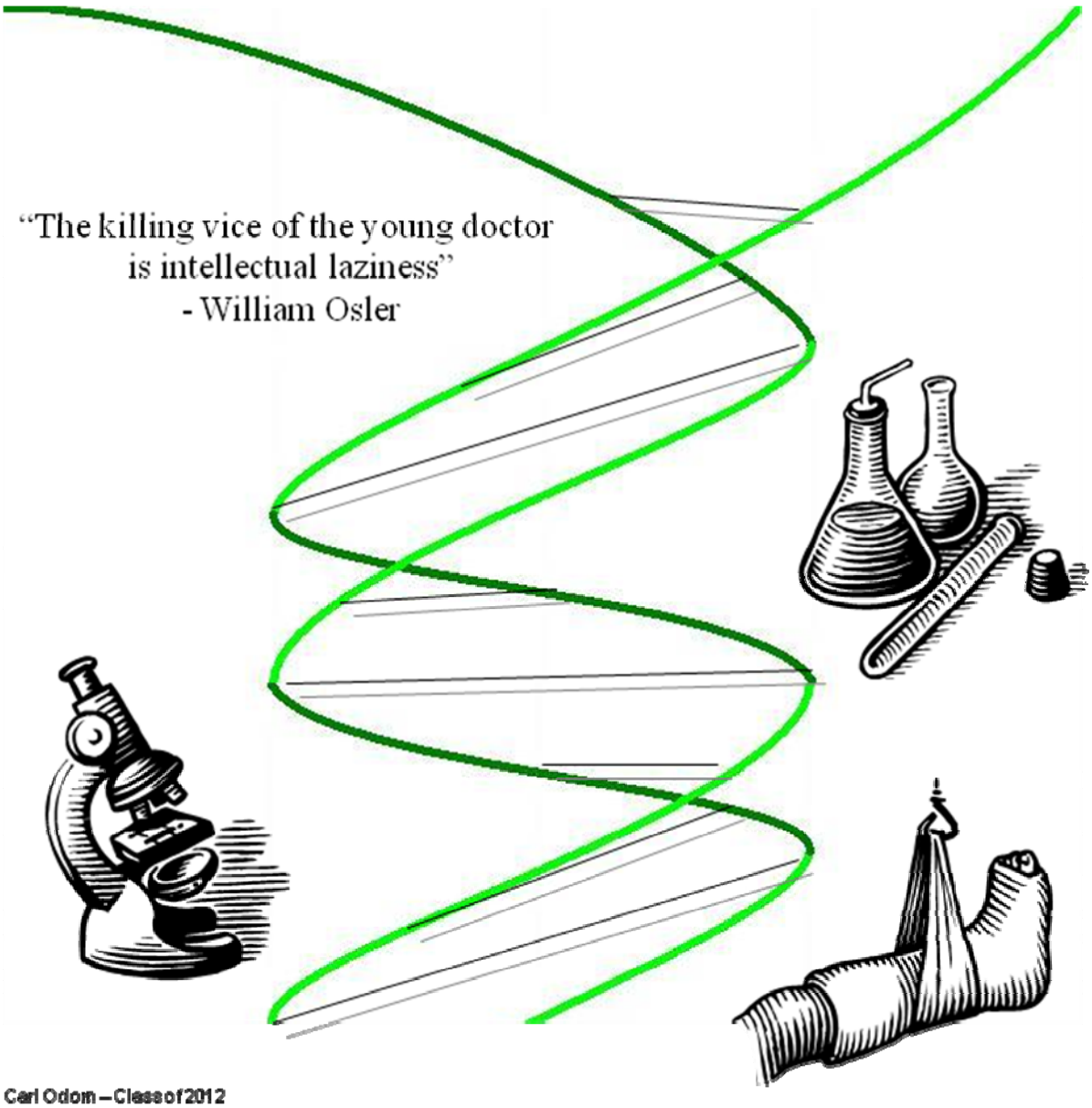
Medical Student Research Day 2009

"The killing vice of the young doctor is intellectual laziness"
- William Osler



Carl Odom – Class of 2012

Forward

Medical Student Research Day provides an opportunity for both medical and MSTP students to present their research to faculty and students. This year 120 abstracts were submitted for presentation at Medical Student Research Day. Carl Odom, Class of 2012, designed the cover of the 2009 Medical Student Research Day abstract book. Funding for Medical Student Research Day is generously provided by the office of Dr. Hughes Evans, Senior Associate Dean for Medical Education.

Acknowledgements

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Dr. Douglas Weigent
Dept. of Physiology & Biophysics

Dr. C Roger White
Dept. of Medicine

Dr. James Willig
Dept. of Medicine

Dr. Bradford Woodworth
Dept. of Surgery

Oral Presentations

Short-term Research

Baran Aksut, MS2
"Transforming growth factor (TGF)-β, endothelin (ET)-1, and angiotensin II (ANGII) downregulate PPARγ gene expression in rat pulmonary artery smooth muscle cells (PASMSs)"
Mentor: Dr. Suzanne Oparil

Harrison Irons, MS2
"A skeleton key to insulin sensitivity and inflammation: osteocalcin effects on cytokine secretion by adipose tissue"
Mentor: Dr. Timothy Garvey

John-Ryan McAnnally, MS2
"Impact of population characteristics and area healthcare resources on mortality variation in the US"
Mentors: Dr. Henry Wang and Dr. Randolph Devereaux

Shari Reeves, MS2
"Cysteine glutamate exchanger upregulation by retinoic-acid"
Mentor: Dr. Brian Sims

Jennifer Stanley, MSTP (year – MS1)
"Syndecan-1 shedding diminishes its nuclear levels: mechanism for stimulation of myeloma tumor growth"
Mentor: Dr. Ralph Sanderson

Bannon Thorpe, MS1
"The effect of screw reinsertion on pull-out strength of screws: are we making trouble?"
Mentor: Dr. Brent Ponce

Stacy Watkins, MSTP (year – graduate 1)
"Biophysical and biomechanical aspects of glioma invasion"
Mentor: Dr. Harald Sontheimer

Oral Presentations

Intermediate-term Research

Michael Alberti, MSTP (year – graduate 2)
"A recombinant adenovirus for targeted gene therapy of inflammation"
Mentor: Dr. David Curiel

Lindsay Brown, MS3
"Understanding the effect of race on the use of emergency department care"
Mentor: Dr. Mary Hawn

Brian Sullivan, MS3
"The utility of computed tomography surveillance for recurrent head and neck squamous cell carcinoma"
Mentor: Dr. Scott Magnuson

Long-term Research

Olusimidele Akinsiku, MSTP (year – graduate 4)
"Functional response of CD8+ cells in the setting of HIV-1 disease"
Mentor: Dr. Paul Goepfert

Stephen Jordan, MSTP (year – graduate 5)
"Identification of a novel malaria vaccine: cross-reactive antibodies in a hypoendemic setting"
Mentor: Dr. Julian Rayner

Chris Yuskaitis, MSTP (year – graduate 3)
"Lithium rescues biochemical and behavioral phenotypes in a mouse model of Fragile X syndrome"
Mentor: Dr. Richard Jope

Poster Presentations

GROUP A

A-1. Travis Lewis, MSTP (year – graduate 4)
"Coxsackie and adenovirus receptor expression dictates neuronal tropism in the mouse substantia nigra"
Mentors: Dr. David Standaert and Dr. David Curiel

A-2. Tiffany Cossey, MS3
"The epigenetics of neonatal neuroprotection"
Mentor: Dr. Brian Sims

A-3. Faraz Sultan, MSTP (year – graduate 2)
"Active DNA demethylation regulates long-term memory"
Mentor: Dr. David Sweatt

A-4. Nguyet Nguyen, MS3
"Characterization of the autophagic lysosomal pathway in traumatic brain injury"
Mentor: Dr. John Shacka

A-5. John Hammond, MSTP (year – graduate 3)
"AMPA receptor trafficking in endosomes in schizophrenia"
Mentor: Dr. Robert McCullumsmith

A-6. Nicholas Reish, MSTP (year – graduate 3)
"Low expression of SynGAP1 as a model of abnormal neocortical development"
Mentor: Dr. Gavin Rumbaugh

A-7. Trey McClugage, MS2
"Mitochondrial dysfunction and multidrug resistance in human gliomas"
Mentor: Dr. Corinne Griguer

A-8. Gina Byekova, MS2
"The role of glioma progenitor cells in clinical responses to oncolytic HSV in patients with GBM"
Mentor: Dr. James Markert

A-9. Lisa Bailey, MS2
"Effects of oxygen tension on CD133 and CD111 expression in glioblastomas"
Mentors: Dr. Yancey Gillespie and Dr. Gregory Friedman

A-10. George Atkinson, MSTP (year – graduate 5)
"Pin1 regulates STAT3 signaling in glioma"
Mentor: Dr. Tika Benveniste

Poster Presentations

GROUP B

B-1. Bob Hollis, MS2
"Investigating the role of striatal cholinergic neurons in DYT1 dystonia: validation of a mouse model"
Mentor: Dr. David Standaert

B-2. Jennifer Hadley, MSTP (year – MS2)
"Implementing a rat model of acute seizure to study high frequency oscillations"
Mentor: Dr. Rotem Elgavish

B-3. Nikki Brossier, MSTP (year – graduate 4)
"Role of classic ras and r-ras isoforms in the pathogenesis of MPNSTs
Mentor: Dr. Steven Carroll

B-4. Abdurahman Elkhetall, MSTP (year – MS2)
"Normalization of hippocampus quantitative percent pathology map following temporal lobectomy"
Mentor: Dr. Rotem Elgavish

B-5. Heather Allen, MSTP (year – MS2)
"Immune modulation of Parkinson's disease"
Mentor: Dr. David Standaert

B-6. Matt Rutherford, MSTP (year – graduate 2)
"Transcriptional regulation of parvalbumin"
Mentor: Dr. Rita Cowell

B-7. Sinifunanya Nwaobi, MSTP (year – graduate 1)
"Neuroinflammatory role of LRRK2 in Parkinson's disease"
Mentors: Dr. David Standaert and Dr. Andrew West

B-8. Brian Warmus, MSTP (year – MS2)
"Investigating the anatomy underlying behavioral symptoms in frontotemporal dementia"
Mentor: Dr. Erik Roberson

Poster Presentations

GROUP C

C-1. Asher Alberston, MSTP (year – graduate 2)
"Loss of HCN channels may contribute to epilepsy"
Mentor: Dr. John Hablitz

C-2. Vishnu Cuddapah, MSTP (year – graduate 2)
"Chloride channel regulation by CaMKII in human glioma cells"
Mentor: Dr. Harald Sontheimer

C-3. Yawar Qadri, MSTP (year – graduate 5)
"Acid sensing ion channel-1 inhibitors"
Mentor: Dr. Dale Benos

C-4. Avinash Honasoge, MSTP (year – MS2)
"Characterization of CLC-3 knockdown human glioma cells"
Mentor: Dr. Harald Sontheimer

C-5. Elina Levin, MS2
"Mucociliary and ion transport in human airway epithelial cells: effects of a CFTR potentiator"
Mentor: Dr. Steven Rowe

C-6. Daniel Schuster, MS3
"Quercetin increases transepithelial chloride transport in primary murine nasal epithelial cultures"
Mentor: Dr. Bradford Woodworth

C-7. Lauren Stephens, MS2
"Altered bicarbonate-dependent pHi regulation in a cortical collecting duct cell model of ARPKD"
Mentor: Dr. Mark Bevensee

C-8. Chris Azbell, MS2
"Exposure to cigarette smoke condensates reduces calcium-activated chloride channel transport in primary nasal epithelial cultures"
Mentor: Dr. Bradford Woodworth

Poster Presentations

GROUP D

D-1. Paul Ward, MS2

"The effects of cadmium on human bronchial epithelial cells, a novel mechanism for cadmium induced pulmonary dys-function"

Mentor: Dr. Karen Iles

D-2. Jessica Record, MS2

"Detections of rare, surfactant associate gene variants in adults with interstitial lung disease"

Mentor: Dr. Aaron Hamvas (Washington University School of Medicine)

D-3. Erica Johnson, MS2

"Hypochlorous acid (HOCl)-mediated damage to human pulmonary epithelial cells"

Mentors: Dr. Gwendolyn Boyd, Dr. Sadis Matalon, and Dr. Karen Iles

D-4. Justin Jackson, MS2

"Respiratory syncytial virus predisposes lung to injury by chlorine"

Mentor: Dr. Sadis Matalon

D-5. Daniel Israel, MS2

"Hemoptysis and bronchial artery embolization: a review of 96 cases"

Mentors: Dr. Baljendra Kapoor and Dr. Jeffery White

D-6. Zachary Aldewereld, MS2

"Assessment of the effect of medical and surgical closure of PDA on hospital outcomes"

Mentor: Dr. Wally Carlo

Poster Presentations

GROUP E

E-1. Drew Cochran, MS2

"Age and body size are major factors in pacemaker lead longevity in pediatric patients"

Mentor: Dr. Walter Jonson

E-2. Wasef Muzaffar and Kristina Osborn, (Joint First Authors), MS2

"*Predictive value of the extent of fibrosis in the progression of dilated cardiomyopathy"*

Mentor: Dr. Silvio Litovsky

E-3. Allan Seibert, MS3

"Left Ventricular Strain is Reduced in Remote Non-Diseased Segments Following Myocardial Infarction in Patients with Type-2 Diabetes Mellitus."

Mentor: Dr. Louis Dell'Itlalia

E-4. Anand Iyer, MS3

"Uncontrolled hypertension and increased risk for incident heart failure in older adults with hypertension: a propensity-matched prospective population-based study"

Mentor: Dr. Ali Ahmed

E-5. James Gladden, MSTP (year – graduate 3)

"Inhibition of xanthine oxidase preserves left ventricular function in volume overload heart failure"

Mentor: Dr. Louis Dell'Italia

E-6. Adam Edwards, MS3

"Reimplantation is often not indicated following cardiac rhythm management device extraction"

Mentor: Dr. Thomas McElderry

E-7. Stephen Tonks, MS2

"Post-translational modification increases xanthine oxidase activity in volume overload"

Mentor: Dr. Louis Dell'Italia

E-8. Hugh Milteer, MS2

"Low risk of intracerebral hemorrhage with adjunctive IIb/IIIa inhibitors in ad-hoc carotid stenting"

Mentor: Dr. Robert Bourge

E-9. Sirush Vullaganti, MS2

"The combined effect of age and volume overload on cardiac compensation and mitochondrial function"

Mentor: Dr. Louis Dell'Italia

Poster Presentations

GROUP F

F-1. William Ryan Miller, MS2
"Liberation of growth hormone binding protein and its effects on growth hormone signaling"
Mentor: Dr. Stuart Frank

F-2. Nicholas Nolte, MS2
"Increased arginase I protein in nonalcoholic fatty liver disease and implications for nitric oxide bioavailabilty"
Mentor: Dr. Shannon Bailey

F-3. Ryan Corrick, MSTP (year – graduate 3)
"Tissue-specific variation in the development of growth hormone resistance due to injury: skeletal muscle vs. liver"
Mentor: Dr. Joseph Messina

F-4. Brian Dizon, MSTP (year – graduate 5)
"Modulation of autoimmune diabetes development by B lymphocytes specific for N-acetyl-D-glucosamine"
Mentor: Dr. John Kearney

F-5. Sarah Baxley, MSTP (year – graduate 3)
"Mammary gland stem and progenitor cell regulation by TGF beta and Wnt5a"
Mentor: Dr. Rosa Serra

F-6. Victor Lin, MSTP (year – graduate 5)
"TRIP6 Mediates Cell Cycle Progression Through $p27^{KIP1}$ "
Mentor: Dr. Fang-Tsyr Lin

F-7. David Mayhew, MSTP (year – graduate 5)
"The mRNA translation factor eIF2Bε is translated by an internal ribosome entry site (IRES)"
Mentor: Dr. Marcas Bamman

F-8. John Jarboe, MSTP (year – graduate 1)
"Identification of TrkA as a component of the radiation-induced signal transduction pathway"
Mentor: Dr. Christopher Willey

F-9. Tarannum Jaleel, MS2
"Antimicrobial effect of inactive vitamin D on skin"
Mentor: Dr. Richard Gallo

Poster Presentations

GROUP G

G-1. Carl Odom, MS2
"Construction of a conditionally replicating HSV vector that expresses IL-15 as a vaccine adjuvant"
Mentors: Dr. James Markert and Dr. Jackie Parker

G-2. Sherry Yang, MSTP (year – graduate 4)
"A dual-action, armed replicating adenovirus for the treatment of ovarian cancer"
Mentor: Dr. Joanne Douglas

G-3. Lena Gamble, MSTP (year – graduate 5)
"Increased oncolytic ability of a double RGD-modified adenovirus in ovarian cancer"
Mentor: Dr. David Curiel

G-4. Adam Scott, MS2
"A fragment-based approach to discovering novel antifolates"
Mentor: Dr. Debasish Chattopadhyay

G-5. Sandrine Niyongere, MS2
"The role of Slit2 expression in the activation of epithelial-mesenchymal transition in tumor samples"
Mentor: Dr. Hui Xu

G-6. Zach Griffith, MS2
"FNA-based assay predicts therapeutic response to TRA-8 (Death Receptor 5 antibody) treatment"
Mentor: Dr. Piotr Kluesza

G-7. Zachary Dobbin, MSTP (year – MS2)
"Formation of kisspeptins from KiSS1 to determine their role in suppression of cancer metastasis"
Mentor: Dr. Danny Welch

G-8. Haller Jackson, MS2
"Effects of exogenous MEK expression on resistance to tyrosine kinase inhibitors in GIST"
Mentor: Dr. Andrey Frolov

G-9. Jackie Zimmerman, MSTP (year – graduate 1)
"A novel therapeutic approach to breast cancer using amplitude modulated radiofrequencies"
Mentor: Dr. Boris Pasche

Poster Presentations

GROUP H

H-1. MaryKathryn Colburn, MS2
"Therapeutic effect of gastrografin administration in gynecologic oncology patients with bowel dysfunction"
Mentor: Dr. J. Michael Straughn, Jr.

H-2. Ryan Burton, MS3
"Prognostic indicators of treatment success in biliary dyskinesia"
Mentor: Dr. Mary Hawn

H-3. Lindsay Brown and Ryan Burton, MS3 (joint first authors)
"Multiple preoperative endoscopic interventions are associated with worse outcomes after laparoscopic Heller myotomy for achalasia"
Mentor: Dr. Mary Hawn

H-4. Virginia Planz, MS2
"Common bile duct dilatation in post-cholecystectomy patients"
Mentors: Dr. Mark Lockhart and Dr. Lincoln Berland

H-5. Nicole Falls, MS3
"Patient preference may explain regional variation in mastectomy rates"
Mentor: Dr. Helen Krontiras

H-6. Evan Thomas, MSTP (year – graduate 1)
"Comparison of single and multi-arc single-isocenter volumetric arc radiosurgery to traditional gamma K"
Mentor: Dr. John Fiveash

H-7. Anrab Mitra, MS2
"Correlation of SD-OCT imaging and histological staining in pathology identification in ARMD eyes"
Mentor: Dr. Christine Curcio

Poster Presentations

GROUP I

I-1. Hikel Boohaker, MS3

"Factors associated with meniscus and cartilage lesions in primary and revision ACL reconstructions: an evaluation of 3069 patients"

Mentor: Dr. Brent Ponce

I-2. Alex Feng, MS2

"Absence of common carotid artery: a case study"

Mentor: Dr. Baljendra Kapoor

I-3. Alex Feng, MS2

"Bow Hunter's Syndrome: a case study"

Mentor: Dr. Baljendra Kapoor

I-4. Brandon Pardi, MS2

"Use of foam acetabular components for periacetabular bone loss with primary total hip arthroplasty"

Mentor: Dr. Henry Siegel

I-5. John Rodriquez-Feo, III MS2

"Development of an infected, open fracture model with MRSA and Acinetobacter in a rat"

Mentor: Dr. Rena Stewart

I-6. Natalie Roebuck, MS2

"*Timing of cleft palate surgery and speech outcome"*

Mentor: Dr. Nathaniel Robin

I-7. Adam Weber, MS2

"Injurious effect of the curveball: a 10-year longitudinal study"

Mentor: Dr. Glenn Fleisig

Poster Presentations

GROUP J

J-1. Sarah Whitley, MSTP (year – graduate 5)
"Regulation of Il-17 transcription in CD4+ T cells"
Mentor: Dr. Casey Weaver

J-2. Mark Stoddard, MSTP (year – MS2)
"Tracking intraperitoneal IL-10 producing regulatory B cells in vivo"
Mentor: Dr. John Kearney

J-3. Daniel Schreeder, MSTP (year – graduate 5)
"Biological characterization of Fc receptor-like 6 (FCRL6) – an inhibitory receptor of the MHC class II"
Mentor: Dr. Randall Davis

J-4. Katie Poholek, MSTP (year – MS2)
"The role of Twist1 in the regulation of inflammation during colitis"
Mentor: Dr. Laurie Harrington

J-5. Carson Moseley, MS1
"TNF/iNOS-producing dendritic cells – the necessary evil of lethal influenza virus infection"
Mentor: Dr. Robert Webster and Dr. Peter Doherty

J-6. Suzanne McCluskey, MS2
"Development of novel high avidity fusion proteins"
Mentors: Dr. Max Cooper and Dr. Goetz Ehrhardt

J-7. Kayci Huff, MSTP (year – graduate 3)
"Mucosal TGF-βΛl-6 axis regulates effector T cell function
Mentor: Dr. Phillip Smith

J-8. Emily Blosser, MSTP (year – graduate 1)
"The role of Th17 cells and commensal flora in gut mucosal defense"
Mentor: Dr. David Randolph

J-9. Scott Love, MS3
"Comparison of maternal and child hepatitis B antibodies at 18-48 months postpartum"
Mentors: Dr. John Arnold and Dr. David Kimberlin

Poster Presentations

GROUP K

K-1. Mike Lopker, Jr, MSTP (year – graduate 1)
"Identification, molecular cloning and characterization of mucosally transmitted SIVsmE660"
Mentor: Dr. George Shaw

K-2. David Gaston, MSTP (year – graduate 2)
"Prior immunity to HSV-1 limits gag-specific immune responses elicited by a HSV-1 vaccine vector"
Mentor: Dr. Jacqueline Parker

K-3. Juan Calix, MSTP (year – graduate 2)
"Disruption of the O-acetyltransferase, *wcj*E_{11A} is the genetic basis of a new pneumococcal serotype"
Mentor: Dr. Moon Nahm

K-4. Jena Blumenthal, MS2
"Tropism and genetic variation at UL131 of various strains of human cytomegalovirus"
Mentor: Dr. Shannon Ross

K-5. Kinley Beck, MS2
"Real-time PCR for the detection of methicillin-resistant Staphylococcus aureus bacteremia"
Mentors: Dr. John Baddley and Dr. Mukesh Patel

K-6. Lisa Akhtar, MSTP (year – graduate 4)
"SOC3 inhibits antiviral IFN-β signaling to enhance HIV-1 replication in macrophages: implications for HIV associated dementia"
Mentor: Dr. Tika Benveniste

K-7. Aimee Merino, MSTP (year – graduate 3)
"KIR gene polymorphisms in HIV-1 infection"
Mentor: Dr. Richard Kaslow

K-8. Nick Parrish, MSTP (year – graduate 1)
"A rev1-vpu polymorphism in HIV impairs envelope glycoprotein expression and pseudovirion infectivity"
Mentor: Dr. Beatrice Hahn

K-9. Ryan Wells, MSTP (year – graduate 3)
"MmpS4 and MmpS5 are OMPs of Mycobacterim tuberculosis required for growth under low iron"
Mentor: Dr Michael Niederweis

Poster Presentations

GROUP L

L-1. Jim Ellison, MS2
"National health insurance: Alabama family physicians' attitudes"
Mentor: Dr. John Wheat

L-2. Sara Singhal, MS2
"The impact of palliative care consultations on end-of-life decisions in pediatric cancer patients"
Mentor: Dr. Justin Baker

L-3. Gavin Wilks, MS2
"Variables affecting readiness of Alabama family physicians to retire"
Mentor: Dr. John Wheat

L-4. Harry Saag, MS2
"Children's Hospital of Alabama and the case mix index"
Mentor: Dr. Crayton Fargason

L-5. Alexis Mason, MS2
"Argomedicine for the deep south"
Mentors: Dr. John Wheat and Dr. James Leeper

L-6. Katy Charlton, MS2
"Handoffs, morning to night shift checkouts: are we following national recommendations?"
Mentor: Dr. Carlos Estrada

L-7. Rozalyn Love, MS3
"Medical student knowledge, experiences, and attitudes about midwifery"
Mentors: Dr. Kimberly Hoover and Dr. Kerri Bevis

L-8. Rozalyn Love, MS3
"Pregnancy outcomes in single active-duty military women"
Mentor: Dr. Alice Goepfert

Poster Presentations

GROUP M

M-1. Ellie Pattanaik, MS2
"Use of exclusion diets on children with autism spectrum disorders (ASD)"
Mentor: Dr. Miriam Peralta

M-2. Michael Kozak, MS2
"Computer-administered assessment of mental health and substance abuse disorders in an HIV clinic"
Mentor: Dr. Michael Mugavero

M-3. Mathias Allen, MS2
"Estimates of pediatric severe sepsis in U.S. emergency departments"
Mentor: Dr. Henry Wang

M-4. Alan Cease, MS2
"Analysis of child passenger safety in patients of a pediatric emergency department"
Mentor: Dr. Kathy Monroe

M-5. MeKeisha Pickens, MS2
"WALKFIT: the efficacy of moderate intensity exercise in the promotion of weight loss and prevention"
Mentor: Dr. Nefertiti Durant

M-6. Tyler Tate, MS2
"Temporal changes in obesity in an HIV clinic"
Mentor: Dr. Michael Mugavero

M-7. Mary Orr, MS2
"Factors associated with missed outpatient HIV visits: first steps in developing a clinical prediction routine"
Mentor: Dr. Herrick Siegel

M-8. Whitney McNeil, MS2
"Survey of homeless service agents: homeless access to health care"
Mentor: Dr. Stefan Kertesz

Akhtar, Lisa Nowoslawski (Lisa)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Etty (Tika) Benveniste, PhD
Title	SOCS3 Inhibits Antiviral IFN- β Signaling to Enhance HIV-1 Replication in Macrophages: Implications for HIV Associated Dementia

Abstract

Human immunodeficiency virus (HIV)-1 invades the central nervous system (CNS) early following systemic infection, but typically does not lead to the cognitive impairments characteristic of HIV Associated Dementia (HAD) until late in disease progression. Initially, viral replication within the brain is effectively suppressed. Interferon (IFN)-β is thought to play a dominant role in this suppression by inhibiting HIV-1 replication in macrophages, the most important source of productive HIV-1 infection in the brain. However, the mechanism by which HIV-1 eventually overcomes IFN-β's antiviral effect is unknown. Here, we show that the HIV-1 protein transactivator of transcription (Tat) induces the expression of Suppressor Of Cytokine Signaling (SOCS) 3, a potent inhibitor of type I IFN signaling, in macrophages. Consequently, we demonstrate that HIV-1 Tat treated macrophages have a diminished response to IFN-β, which is rescued in macrophages deficient for SOCS3 expression. *In vitro*, the inhibitory effect of IFN-β on HIV-1 replication is overcome upon SOCS3 expression, while *in vivo* analysis of simian immunodeficiency virus (SIV)-infected macaque brain indicates that increased SOCS3 expression correlates with recurrence of viral replication and onset of CNS disease. These studies indicate that SOCS3 expression, induced by stimuli present in the HIV-1-infected brain such as Tat, inhibits antiviral IFN-β signaling and enhances HIV-1 replication in macrophages. This functional consequence of increased SOCS3 expression *in vitro*, supported by a correlation with onset of CNS disease *in vivo*, further suggests a role for SOCS3 expression in promoting progression toward HAD.

Akinsiku, Olusimidele Tolulope (Olusimidele)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Paul A. Goepfert
Title	Functional Response of CD8+ T cells in the Setting of HIV-1 Disease

Abstract

A number of factors affect the efficacy and development of $CD8^+$ T cell responses, including signals received during stimulation, ability to secrete soluble anti-viral factors, and dynamics of viral peptide presentation. While it is apparent that $CD8^+$ cytotoxic T lymphocyte (CTL) responses are an important part of host defense during HIV-1 infection, it is unclear which components of the response are critical for long-lasting protection. The detection of HIV-1-specific $CD8^+$ T cells that maintain proliferative capacity is a strong correlate of decreased viral load in the infected host. Additional studies have reported that the proliferation of HIV-1-specific CTLs correlates with production of interleukin-2 (IL-2). We predicted that maintenance of an IL-2 response identifies a population of effector $CD8^+$ T cells with enhanced ability to produce anti-viral soluble factors and restrict HIV-1 replication as observed by flow cytometry and *in vitro* functional assays. Virus-specific CTL responses were analyzed in subjects chronically infected with HIV-1 and off antiretroviral therapy (ART). Interferon-gamma (IFN-γ) and IL-2 ELISpot assays were used to identify antigen-specific responses. Peptides yielding positive responses were used to expand epitope-specific CTL lines. CTL lines were analyzed for polyfunctionality (degranulation, cytokine production, release of cytoloytic enzymes) and virus neutralization capacity.HIV-1 specific responses were commonly detected; however, IL-2 production was only observed in CTL lines derived from patients with non-progressive disease. When functional avidity was assessed, IL-2 producing CTLs were not obviously responding to a lower peptide concentration when compared to CTLs producing IFN-γ. Using the *i*VSA, we can identify differences in the antiviral function of HIV-1 specific CTL lines. Thus far, the CTL line displaying the most efficient virus suppression is positive for IL-2 function. IL-2 production may be an important marker of CTLs able to mediate enhanced control of HIV-1 replication and studies are on-going to understand the underlying mechanisms.

Aksut, Baran

Project Length	Short
Prior Research Experience	Yes
FundingSource	NIH T35 Short Term Training Grant
Advisor	Suzanne Oparil
Title	Transforming Growth Factor (TGF)-β, Endothelin (ET)-1, and Angiotensin II (ANGII) Downregulate PPARγ Gene Expression in Rat Pulmonary Artery Smooth Muscle Cells (PASMCs).

Abstract

Introduction: Activation of peroxisome proliferator-activated receptor-γ (PPARγ) in lung has been shown to decrease pulmonary vascular remodeling/fibrosis associated with hypoxic pulmonary hypertension. Previous studies have demonstrated that TGF-β plays an important role in hypoxia-induced vascular remodeling/fibrosis in lung. The current study tested the hypotheses that endogenous PPARγ gene expression is downregulated in lung exposed to chronic hypoxia and in PASMCs treated with TGF-β, ET-1, or ANGII. Methods: In the in vivo study, young adult male Sprague-Dawley rats were exposed to air (n=6) or 10% O_2 (n=6) for 2 weeks in a hypoxic chamber. Lungs were then harvested for Western blotting analysis for assessment of PPARγ expression. In the in vitro study, isolated rat PASMCs were used to examine the effects of TGF-β, ET-1, or ANGII on PPARγ mRNA and protein expression. Quiescent PASMCs (3-4 passages) were treated with TGF-β1 (2 ng/ml), ET-1 (200 nM), or ANGII (200 nM) for 24 hrs. Cellular mRNA and protein were extracted and subjected to quantitative Real-time RT-PCR and Western blot analyses. Results: 2-wk hypoxic exposure significantly decreased PPARγ protein levels in rat lungs (>75% reduction in hypoxic lungs, $p< 0.01$). In PASMCs, PPARγ protein and mRNA levels were significantly decreased with TGF-β (mRNA: 23% reduction; protein: 53% reduction), ET-1 (mRNA: 28% reduction; protein 53% reduction), or ANGII (mRNA 26% reduction; protein: 52% reduction) treatment. Conclusion: These results indicate that TGF-β, ET-1, and ANGII inhibit expression of PPARγ, a putative endogenous anti-fibrogenic factor, in PASMCs. These observations, coupled with the finding that chronic hypoxic exposure decreases PPARγ in lung, suggests that TGF-β, ET-1 or ANGII-induced downregulation of PPARγ in PASMCs represents a novel mechanism of hypoxia-induced pulmonary vascular remodeling/fibrosis. The interaction between these growth factors and PPARγ signaling pathways may play an important role in modulating the pro-fibrogenic response of lung to hypoxic exposure.

Alberti, Michael O (Michael)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. David Curiel
Title	A Recombinant Adenovirus for Targeted Gene Therapy of Inflammation.

Abstract

Neutrophilic infiltration is essential for host defense. However, excessive recruitment and perturbed clearance of activated neutrophils is a hallmark of many diseases, as the products these cells utilize for protection also mediate fibrosis and tissue damage. Although neutrophil depletion studies have transiently improved inflammatory disease models, sustained depletion carries an increased risk of infection and is limited by the rapid rate in which neutrophils are repopulated from the bone marrow reserve. Since neutrophils are the primary mediators of inflammation, we hypothesized that Adenovirus (Ad) vectors could be targeted to neutrophils and these cells could serve as vehicles to deliver therapeutic genes to inflamed tissues. Given that neutrophils lack the coxsackievirus adenovirus receptor (CAR) and are thus resistant to Ad infection, we proposed to genetically modify the Ad fiber protein to redirect Ad tropism towards these cells. To do so, a bacteriophage library was panned against murine bone marrow leukocytes to identify a neutrophil-binding peptide (NBP). The consensus sequence identified was genetically incorporated into a recombinant fiber that lacks the native CAR-binding domain, knob. Ad reporter gene expression vectors containing the recombinant fiber were rescued and shown to maintain neutrophil binding specificity. Upon intravenous delivery, the altered tropism realized a lung targeting index five orders of magnitude greater than that obtained with Ad vectors containing the wild type fiber. Lung targeting was specific, as transgene expression was barely detected in other organs, with the lowest levels detected in liver. Flow cytometric analyses of the cell types bound and transduced suggest that the NBP virus is first sequestered on the surface of neutrophils and is subsequently “handed off” to lung endothelial cells as the neutrophils roll along the lung microvasculature. These studies are an important first-step in validating systemic Ad targeting as an approach for gene therapy of inflammatory disorders.

Albertson, Asher Jefferson (Asher)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. John Hablitz
Title	Loss of HCN Channels May Contribute to Epilepsy.

Abstract

Epilepsy is a life altering condition affecting approximately 2.7 million people worldwide. Many patients with epilepsy experience seizures resistant to anticonvulsant medication. This illustrates that, despite vigorous research, little is known regarding the underlying cellular mechanisms of epilepsy. We have hypothesized that misregulation of hyperpolarization activated non-selective cation (HCN) channels may be one possible pathology underlying epileptic hyperexcitability. These channels paradoxically open at hyperpolarized membrane potentials causing an inward current (I_h) which depolarizes the membrane. HCN channels are expressed primarily within the dendrites of pyramidal neurons where they modulate electrical signals from distal inputs by altering the input resistance and resting membrane potentials. Blockade of HCN channels has previously been shown to increase the intrinsic excitability of neurons, increase post-synaptic summation, and depolarize the resting membrane potential. Furthermore, in several models of induced epilepsy, HCN channel expression is reduced. We have examined the effect of HCN channel blockade on the spatiotemporal spread of activity across large sections of the neocortical network using voltage sensitive dyes. Blocking HCN channels caused the duration of electrical activity in normal cortex to increase. Interestingly, enhancement of HCN channel function with the drug lamotrigine, significantly down regulated the spread of activity. Many brain malformations are associated with epilepsy. We further examined the spatiotemporal spread of activity in a model malformation epilepsy featuring a cortical lesion. We found that neocortical activity spread significantly farther in regions near the malformation. Furthermore, the effect of HCN channel blockade was significantly diminished. These results suggest that loss of HCN channels may play an important role in generating the abnormal neural activity seen in epilepsy.

Aldewereld, Zachary Taylor (Zachary)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Wally Carlo
Title	Assessment of the effect of medical and surgical closure of PDA on hospital outcomes

Abstract

A symptomatic patent ductus arteriosus (PDA) has been associated with several morbidities in premature infants including bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and intraventricular hemorrhage (IVH). However, studies investigating early closure of PDAs have only found benefit with regard to IVH. In spite of the lack of evidence showing long-term benefit of early closure of a symptomatic PDA, it is standard practice to treat a symptomatic PDA with a cyclooxygenase (COX) inhibitor or surgical ligation if COX inhibitors fail or are contraindicated. At UAB, a lower index of suspicion has lead to fewer diagnoses of PDA and therefore less treatment. In order to assess the effect this has on outcomes for the patient, results from UAB were compared to results from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). This multicenter, randomized controlled trial included two treatment groups: one that received prophylactic indomethacin, a COX inhibitor, and one that received placebo. Diagnosis and treatment of PDA was similar in both groups. A database in the UAB Department of Neonatology and retrospective chart reviews were used to collect the data for UAB patients. A chi-square analysis was used to compare results from UAB to each of the two groups. The significant findings are as follows. UAB diagnosed significantly more PDAs than the treatment group ($P \approx 0$) and significantly fewer than the placebo group ($P \approx 0$). The need for supplemental oxygen at 36 weeks postmenstrual age was significantly reduced for infants at UAB ($P \approx 0$ for both). Severe IVH was higher in infants at UAB ($P \approx 0$ compared to treatment group, $P=0.03$ compared to placebo group). Death was similar to the treatment group ($P=0.12$) but higher than the placebo group ($P=0.01$). All other outcomes compared were similar. These results suggest that aggressive treatment of the PDA may not be the best course.

Allen, Heather Elizabeth (Heather)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	David Standaert
Title	Immune Modulation of Parkinson's Disease

Abstract

It has recently been proposed that the immune system is involved in the initiation, regulation and propagation of dopaminergic neuronal death in Parkinson's disease. Two studies in an established alpha-synuclein overexpression mouse model of Parkinson's investigated differences in the expression of Nurr1, an anti-inflammatory transcription factor, and the amount of CD4+ cell invasion into the substantia nigra. A third clinical study in human Parkinson's patients is currently investigating the functional differences in T cells during progressing Parkinson's.

Male C57BL/6 mice were injected stereotactically with adeno-associated virus combined with GFP, a negative control, and alpha-synuclein, the Parkinson's model.

Expression of Nurr1. Two weeks post-injection, wild-type mice were sacrificed, and the substantia nigra was dissected. LPS, a positive control, was injected into the right substantia nigra to a separate group of mice. Total RNA was isolated and reverse transcribed into cDNA. Quantitative PCR was performed to determine expression of Nurr1. Nurr1 expression was unchanged in wild type and FcγR knockout mice. An NFκB inhibitor also did not change Nurr1 expression.

CD4+ cell invasion. Six months post-injection, wild-type and FcγR knockout mice were sacrificed and perfused; the brains were dissected and sectioned. Sections were stained with DAB/nickel to GFP or alpha-synuclein/CD4 respectively. CD4+ lymphocytes in the substantia nigra were counted using stereology. Results are inconclusive.

T cell characterization in human Parkinson's patients. Control participants and Parkinson's patients who have < 10 year history of the disease are questioned about their health, environmental risks, and activities of daily living. They participate in a physical exam designed to assess disease progression; then, participants donate 50mL of blood. The cells are separated, and FACS analysis is completed. This is a preliminary study in collaboration with the Gendelman lab at the University of Nebraska, and there are no results yet.

Allen, Mathias Wallace (Mathias)

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Henry Wang, MD
Title	Estimates of Pediatric Severe Sepsis in U.S. Emergency Departments

Abstract

In the United States severe sepsis causes a significant amount of mortality and morbidity in the pediatric population every year, with the majority of these patients initially presenting to the emergency department. Unfortunately, there is little epidemiological data available for pediatric patients presenting to emergency departments with suspected severe sepsis. Our study attempted to estimate the number and distribution of cases of suspected severe sepsis presenting to emergency departments in the United States. We analyzed data from 2001-2006 National Hospital Ambulatory Medical Care Survey to include all patients <=18 years of age. Pediatric patients were suspected of having severe sepsis if evidence of infection with accompanying organ dysfunction was present. Infection was defined as having an ICD-9 (*International Classification of Diseases, 9th Revision*) code identifying infection or a triage temperature less than 96.8° F or greater than 100.4° F. Organ dysfunction was defined as having an ICD-9 code identifying organ dysfunction or a systolic blood pressure <= 5^{th} percentile of normal for each pediatric age group. There were an estimated 176.4 million pediatric ED visits from 2001-2006, of those 59.8 million presented with evidence of infection, and about 580,000 cases of suspected severe sepsis. Pediatric suspected severe sepsis cases account for approximately 97,000 ED visits per year and 0.33% of all pediatric ED visits. The data also shows that patients <=1 year of age make up the largest number of cases of suspected pediatric severe sepsis with about 42,000 ED visits annually. The annual number of cases of suspected pediatric severe sepsis presenting to United States emergency departments appears to be more prevalent than previous studies have suggested.

Atkinson, George

Project Length	Long
Prior Research Experience	Yes
FundingSource	NIH Medical Scientist Training Program Grant
Advisor	Dr. Etty (Tika) Benveniste
Title	Pin1 Regulates STAT3 Signaling in Glioma

Abstract

Glioblastoma (GBM) is the most frequent and malignant primary brain tumor in adults. While new therapeutic regimens have marginally improved overall patient lifespans, the lethality and aggressive nature of GBM warrants further investigation into its underlying biology. The mammalian Signal Transducers and Activators of Transcription (STAT) family of proteins, particularly STAT3, is aberrantly activated in GBMs. A protein that may play a regulatory role in the STAT3 pathway is peptidyl-prolyl isomerase (PPIase) Pin1. Pin1 protein levels are elevated in a variety of tumors, and, in many cases, the expression of this protein varies directly with tumor grade. It has also been demonstrated previously that Pin1 directly interacts with STAT3. We hypothesize that the elevated level of Pin1 in GBM increases the active STAT3 content in the nuclei of GBM cells, causing increases in STAT3 signaling and corresponding increases in the expression of STAT3 regulated genes.

Azbell, Christopher Haywood (Chris)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Bradford Woodworth
Title	Exposure to cigarette smoke condensate reduces calcium-activated chloride channel transport in prima

Abstract

Background: Decreased mucociliary clearance (MCC) plays an important role in the pathophysiology of chronic rhinosinusitis (CRS). Tobacco-related effects on MCC include decreased hydration of the airway surface liquid (ASL) via inhibition of chloride (C^{l-}) secretion and decreased ciliary function. Cystic fibrosis transmembrane conductance regulator (CFTR) channels are the predominant C^{l-} transport channel within respiratory epithelial cells. Activation of secondary C^{l-} transport pathways through calcium-activated chloride channels (CaCC) has been postulated as a potential mechanism to rescue CFTR-mediated transport. However, it is unclear whether CaCC's are affected by tobacco exposure.

Objective: To determine the effect of cigarette smoke condensate on CaCC mediated chloride secretion in sinonasal epithelia.

Methods: We exposed well-characterized primary murine nasal septal epithelial (MNSE) and human sinonasal epithelial (HSNE) cultures to cigarette smoke condensate (CSC) in Ussing chambers and compared results to control cultures. We investigated the stimulation and inhibition of C^{l-} secretion using pharmacologic manipulation. We isolated CaCC mediated short-circuit current (ΔISC) through stimulation of P2Y purinergic receptors with either UTP, ATP-γ-S, or ATP and selective inhibition of CFTR pathways.

Results: Change in CaCC mediated current, which represents transepithelial Ca-mediated C^{l-} secretion, was significantly decreased in CSC exposed MNSE (32.8 +/- 4.6 ΔISC /cm^2) compared to controls (47.5 +/- 2.3 ΔISC /cm^2). HSNE response was (16.1 +/- 0.6 ΔISC /cm^2) in CSC exposed cells compared to controls (22.7 +/- 0.0 ΔISC /cm^2).

Conclusions: CSC affects multiple pathways of C^{l-} transport, including CaCC mediated currents and, thus, MCC. Ways to effectively mitigate the effects of tobacco smoke on sinonasal epithelium through stimulation of C^{l-} transport should aid individuals with CRS and frequent tobacco smoke exposure.

Bailey, Lisa Rae (Lisa)

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	G. Yancey Gillespie, Gregory Friedman
Title	Effects of Oxygen Tension on CD133 and CD111 Expression in Glioblastomas

Abstract

Background: *Glioblastoma Multiforme* (GBM) tumors are universally fatal brain tumors whose therapeutic resistance has been attributed to a small subpopulation of radiation- and chemotherapy-resistant cells termed glioma progenitor cells (GPC) that give rise to and maintain the neoplastic clone. We hypothesize that the GPC phenotype is largely driven by hypoxia.

Objective: We sought to determine GBM expression level of CD133, a putative GPC marker, and CD111, an adhesion molecule that serves as an entry receptor for herpes simplex virus (HSV) which is a novel, targeted GBM therapy, in tissue culture under normoxic and hypoxic environments.

Methods: Two established cell lines, D54 and U251, and two xenografts, X12 and D456, were grown in normoxia and at 5% O_2, the oxygen concentration tumors normally experience *in vivo*. Cells were then counted and analyzed by FACS analysis after treatment with fluorochrome labeled antibodies to CD133 and CD111 at scheduled time points over 14 days.

Results: All cell lines had a higher growth rate in normoxia versus hypoxia during the observation period. Interestingly, CD133 expression was higher after 14 days in hypoxia as compared to normoxia in U251 (34% vs 15%) and in D456 (40% vs 15%) but no difference was seen in D54 and X12 cells. CD111 expression increased in both xenografts under hypoxia (53% to 94% in D456 and 8% to 33% in X12) but no increase was seen in the established cell lines.

Conclusions: GBM cell lines and xenografts appear to grow less well initially when moved from normoxia to hypoxia. This may be due to cells adjusting from an oxidative phosphorylation phenotype to a glycolytic one. Expression of CD133 can increase in hypoxia but this does not appear to be universal for all GBMs. Increased CD111 expression under hypoxia may improve HSV infectivity and result in a better therapeutic effect.

Baxley, Sarah Emily (Sarah)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Rosa Serra
Title	Mammary gland stem and progenitor cell regulation by TGFbeta and Wnt5a

Abstract

Transforming growth factor beta (Tgfβ) is critical for proper mammary gland development and has been shown to positively regulate Wnt5a, a non-canonical Wnt. Wnt5a is necessary for Tgfβ-mediated suppression of ductal development in mice. Wnt5a$^{-/-}$ mammary tissue exhibits accelerated development compared to wildtype tissue and loss decreased tumor latency and increased tumor growth rate. Given that loss of Wnt5a expression has been associated with poor prognosis in breast cancer patients, investigating the mechanism of Wnt5a-mediated growth inhibition in the mammary gland will help us understand the consequences of its loss in breast cancer.

Wnt signaling can be divided into two broad categories: canonical and non-canonical. Canonical Wnt signaling involves the stabilization and nuclear translocation of β-catenin. Activation of β-catenin leads to cell proliferation, growth, and stem cell maintenance. Non-canonical Wnts act independently of β-catenin and can inhibit canonical Wnt signals. We hypothesize that Wnt5a and TGFβ may be regulating mammary gland growth through suppression of the mammary stem cell population, perhaps via inhibition of canonical Wnt signals.

The current study aims to elucidate the role of Wnt5a and TGFβ in regulation of the mammary gland stem and/or progenitor cell populations. Previous data demonstrated that Wnt5a$^{-/-}$ tumors display increased β-catenin and markers associated with more undifferentiated epithelial cells such as cytokeratin 6. Here, we show that loss of TGFβ or Wnt5a signaling increases in the progenitor marker Sca-1/Ly6a in mammary gland tissue. Additionally, we demonstrate increases in *in vitro* stem cell numbers with a loss of Wnt5a via mammosphere assay, a suspension culture to propagate mammary gland stem cells. Addition of TGFβ to mammosphere assays decreases the number of mammospheres. Further studies are aimed at investigating the role of Wnt5a in stem cell regulation during pregnancy and lactation and also in breast cancer development.

Beck, Kinley Danae (Kinley)

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	John Baddley and Mukesh Patel
Title	Real-time PCR for the Detection of Methicillin-Resistant Staphylococcus aureus Bacteremia

Abstract

Background: The clinical advantages of rapid diagnostic tests to identify methicillin-resistant *Staphylococcus aureus* (MRSA) versus traditional culture techniques have not been well established. We designed an ongoing study to determine if a real-time PCR test to identify MRSA bacteremia leads to improvements in clinical care compared to culture techniques.

Methods: We conducted a retrospective cohort study of patients at the Birmingham Veterans Medical Center. Patients with blood cultures (BCx) positive for gram-positive cocci in clusters were included; electronic records were reviewed for demographics, comorbidities, hospital stay data, culture results, and antibiotic therapy. Descriptive statistics identified common characteristics and treatment strategies.

Results: Fifty-six patients were identified; mean age 62.4 years, 98% male, and 53.4% African-American. Common comorbidities included hypertension (80.4%), DM type 2 (46.4%), chronic renal insufficiency (44.6%), COPD (30.2%), dialysis (26.8%), malignancy (19.6%), and liver disease (19.6%). Mean Charlson comorbidity index was 5, and $\geq$ 6 in 41%. Mean/median length of stay was 12.8/7 days. BCx results were 13 (23.3%) methicillin-susceptible *S. aureus* (MSSA), 21 (37.5%) MRSA, 21 (37.5%) coagulase-negative staphylococci (CNS), and 1 (1.8%) other species. Mean/median time to positive BCx was 1.08 days/0.87 days. Mean/median time from BCx growth final organism identification was 2.27d/2.03 d. Mean/median time from culture to final organism ID was 3.31/2.98 days. Initial antimicrobial therapy was vancomycin in 55 (98%) patients.

Conclusions: Earlier identification of bloodstream pathogens would have allowed more appropriate decisions regarding antimicrobial therapy earlier in the course of care in the majority of patients in this study – nafcillin for MSSA and no antibiotics for many of the CNS. A comparison of this cohort to patients in whom a real-time PCR test is used to rapidly identify staphylococcal species is ongoing.

Blosser, Emily Greenwood (Emily)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	David Randolph, MD, PhD
Title	The Role of Th17 Cells and Commensal Flora in Gut Mucosal Defense

Abstract

Bacterial sepsis is a leading cause of death in premature infants. Studies have shown that Gram-positive bacteria, such as coagulase-negative Staphylococci, cause 70% of infections occurring in premature infants; however, Gram-negative bacterial infections are more likely to cause sepsis and death. Cesarean section delivery and frequent antibiotic use disrupt natural bacterial colonization patterns in the preterm intestine. When the gut is inevitably exposed to pathogenic bacteria, the dearth of normal gut flora allows for pathogen overgrowth. This together with immature epithelial barrier and immune functions puts preterm infants at high risk of bacterial translocation across the epithelium with resulting sepsis.

Th17 cells, a subset of T cells recently identified, are believed to be important in mucosal immunity in the gut. These cells produce interleukins (IL) -17 and -22 that fortify the epithelial barrier. Humans deficient in Th17 responses suffer repeated bacterial infections, and mice deficient in IL-17 and IL-22 show increased susceptibility to bacterial pneumonia.

We hypothesize that the susceptibility of pre-term infants to bacterial sepsis may be caused by a relative deficiency in Th17 function at birth and that colonization with normal flora may promote Th17 development. To examine the relationships between Th17 cells, commensal flora, and pathogenic bacteria, we plan to do the following: First, we will use genetically engineered IL-17 reporter mice to examine the natural history of Th17 development in neonatal mice. Second, we will determine the role of normal gut flora in Th17 development. Third, we will determine the role of Th17 cells in a mouse model of Klebsiella sepsis. Fourth and finally, we will determine the role of normal gut flora in preventing sepsis.

Blumenthal, Jena

Project Length	Short
Prior Research Experience	Yes
FundingSource	NIH T35 short term training grant
Advisor	Shannon A Ross
Title	Tropism and genetic variation at UL131 of various strains of Human Cytomegalovirus

Abstract

Objective: Different strains of Human Cytomegalovirus (HCMV) have been adapted for use in the lab over many years and passages in fibroblasts. The aim of these experiments is to see how well lab adapted strains vs. clinical isolates grow in different cell types, particularly fibroblasts and epithelial cells. The UL131 gene of the lab adapted strains was tested to see if they matched the published genes because this locus is known to be of importance for viral tropism.
Methods: Viral stocks were grown and concentrated. Different cell types were grown in 24 well plates and inoculated with 4 viral strains and a mock. The cells were harvested at 12, 24, and 48 hours and the original viral concentrates and the cell lysates were run on real time PCR to obtain the viral load and efficiency of infection. UL131 was run on qualitative PCR and sequenced for comparison.
Results: The lab adapted strains grew better in fibroblasts than in the epithelial cells in general with AD169 growing the best of any of the viruses overall. The efficiency of the AD169 in the fibroblasts being 58x greater at 48 hours than in the epithelial cells. The TR virus also grew better in the epithelial cells and had the greatest difference of 206x at the 48 hour time point, up from 13x greater and 2x greater at 12 and 24 hours respectively. The two clinical isolates A and B both had different growth patterns than the lab adapted strains. A and B both grew better in the epithelial cell line. Generally, there was about 3x better growth on the epithelial cells. The UL131 locus was another focus of the study and was sequenced here. The AD169 variant used in this study matches the AD169 UK variant UL131 exactly. The TR strain used in this study matches the Merlin variant perfectly in nucleotides as well as matches the Merlin and Towne strains' predicted amino acid sequences. The clinical isolates were not sequenced for this study.
Conclusion: The fact that AD169 grew most efficiently in fibroblast cells is not surprising due to the fact that it has been selecting for them for so long with its extensive use in the laboratory. The surprise here was the growth of AD169 in epithelial cells. The American Type Culture Collection variant that was believed to be the strain that was used is known to have a nonsense mutation and truncation of the UL131 gene, but the variant we used actually matched the UK variant which is known to grow to a small extent in epithelial cells. Another interesting point was that both of the clinical isolates grew better at all points in epithelial than in fibroblasts thus mimicking human infection better than their laboratory counterparts.

Boohaker, Hikel

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	None
Advisor	Dr. Brent Ponce
Title	Factors Associated with Meniscus and Cartilage Lesions in Primary and Revision ACL Reconstructions: An Evaluation of 3069 Patients

Abstract

Purpose: The purpose of this study was to evaluate factors associated with meniscal and chondral lesions in primary and revision anterior cruciate ligament reconstructions from a single institution.

Methods: A retrospective analysis was performed on revision ACL reconstructions at a single institution between 9/01 - 12/08. Items assessed included: age, gender, sport, activity level, chronicity of the tear, and additional ligamentous injury. These variables were assessed for association with meniscal and chondral injuries. The findings were compared to a cohort of primary ACL reconstructions from the same study period.

Results: Two hundred ninety-four revision ACL reconstructions were identified. The comparative cohort consisted of 2775 primary ACL reconstructions. In the revision group, rates of meniscal injury (43.8% Vs. 51.9%, $p<0.001$) were significantly lower. Rates of chondral injury were greater in the revision group (39.5% Vs. 24.0%, $p<0.001$). Patients in the revision group tended to present later (53.7% were chronic) than in the primary reconstruction group (32.2%) ($p<0.001$). Rates of chondral injury increased with chronicity and were higher in the revision setting ($p<0.05$). Of the variables assessed, time from injury to surgery, increased age, and male gender were associated with increased rates of chondral lesion. These differences were seen in the primary and revision groups and between the two groups.

Conclusion: Patients with revision ACL reconstruction tend to present later and have less meniscal injuries while having higher rates of chondral injuries than patients undergoing primary ACL reconstruction.

Clinical Relevance: Global knee damage increases with time delay prior to surgical stabilization and in revision settings.

Brossier, Nicole Marie (Nikki)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Steven Carroll
Title	Role of Classic Ras and R-Ras isoforms in the pathogenesis of MPNSTs

Abstract

Neurofibromin negatively regulates classic Ras (H, N, and K-Ras) and R-Ras (R-Ras, R-Ras2, and M-Ras) proteins. Neurofibromin loss in malignant peripheral nerve sheath tumors (MPNSTs) thus leads to Ras hyperactivation, suggesting that the Ras proteins required for MPNST pathogenesis would be appropriate therapeutic targets. To identify the classic Ras and/or R-Ras proteins mediating MPNST proliferation and migration, we examined the expression and action of these molecules in MPNST cells. H-Ras, N-Ras, and R-Ras2 were uniformly present in 8 MPNST cell lines, while K-Ras and R-Ras expression were variable. MPNST cells also expressed specific guanine nucleotide exchange factors capable of activating both classic Ras and R-Ras proteins. Mitogenesis of the NF1- associated ST88-14 and T265 cell lines was inhibited by both dominant negative H-Ras (a mutant Ras isoform known to inhibit the activation of the classic Ras proteins) and dominant negative R-Ras (a mutant Ras isoform which similarly inhibits activation of R-Ras subfamily members). These two mutants also decreased migration and soft agar colony formation in the ST88-14 line. However, ablation of N-Ras and K-Ras had no affect on either mitogenesis or migration in the ST88-14 cell line. We conclude that both classic Ras and R-Ras subfamily members likely contribute to MPNST pathogenesis, and that functional overlap of Ras proteins may make it necessary to broadly inhibit both of these subfamilies in order to correct the Ras hyperactivation defect occurring secondary to NF1 loss. Supported by R01 NS048353 and F30 NS063626-01.

Brown, Lindsay Elizabeth (Lindsay)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Mary Hawn, MD
Title	Understanding the effect of race on the use of Emergency Department care

Abstract

Objective: African-Americans are more likely than Caucasians to access health care through the emergency department (ED); however, the reasons behind this pattern are unclear. We investigate the effect of race, age, perceived health, insurance and socioeconomic status on the preference of ED use.

Methods: This is a prospective survey of low acuity patients seen in the ED during June and July of 2009. After informed consent, patients were administered a 30-question survey that captured demographics, health care utilization, and baseline health status. The primary outcome of interest was utilization of the ED, defined by frequency of ED visits in the last six months and patient-reported routine place of health care. Secondary outcomes of interest included barriers to primary care and patient perception of health.

Results: 301 patients completed the survey of whom 56% were African-American and 45% were uninsured. There were no significant differences among racial groups with respect to age (p=0.067), health insurance (p=0.639), or employment rate (p=0.95). Overall, 38% of patients reported more than 2 visits to the ED in the past six months. African-Americans were more likely to report more than 2 visits to the ED (41% vs. 34%) and a preference for the ED for their usual place of care (24% vs. 13%, p≤0.0001). No significant differences between racial groups were found for access to primary care. On logistic regression modeling, it was found that race (p=0.02), insurance status (p=<0.0001) and number of ED visits (p=0.0031) were independent determinants for usual place of health care.

Conclusions: African-Americans are more likely than Caucasians to designate the ED as their routine place of health care. The racial disparity does not appear to result from differences in health insurance, access to primary care, or patient perception of health. This study recognizes the need for continuity of care in African-American and uninsured populations.

Brown, Lindsay Elizabeth and Burton, Ryan (Joint First Authors)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Mary Hawn, MD
Title	Mutiple preoperative endoscopic interventions are associated with worse outcomes after laparoscopic Heller myotomy for achalasia

Abstract

Background: The effect of preoperative pneumatic dilation or botulinum toxin injection on outcomes after laparoscopic Heller myotomy (LHM) for achalasia is unclear. We compared outcomes in patients with and without multiple preoperative endoscopic interventions.

Methods: This cohort study categorized achalasia patients undergoing first-time LHM by the number of preoperative endoscopic interventions: zero or one intervention versus two or more interventions. Outcomes of interest included surgical failure (defined as the need for re-intervention), gastrointestinal symptoms, and health-related quality of life. Logistic regression modeling was performed to determine the independent effect of multiple preoperative endoscopic interventions on the likelihood of surgical failure.

Results: One hundred thirty-four patients were included; 88 (66%) had 0-1 preoperative intervention and 46 (34%) had multiple (>1) interventions. The incidence of surgical failure was 7% in the 0-1 intervention group and 28% in the >1 intervention group ($p<0.01$). Greater improvements in gastrointestinal symptoms and health-related quality of life were seen in the 0-1 intervention group. On logistic regression modeling, the likelihood of surgical failure was significantly higher in the >1 intervention group (OR=5.1, 95% CI 1.6-15.8, p=0.005).

Conclusions: Multiple endoscopic treatments are associated with poorer outcomes and should be limited to achalasia patients who fail surgical therapy.

Burton, Ryan Curtis (Ryan)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	
Advisor	Dr. Mary Hawn
Title	Prognostic Indicators of Treatment Success in Biliary Dyskinesia

Abstract

Background: Biliary dyskinesia is defined by right upper quadrant pain with abnormal gallbladder function (GBEF≤35%) in the absence of gallstones. The main diagnostic test is the hepatobiliary iminodiacetic acid scan with cholecystokinin provocation (CCK-HIDA), which provides gallbladder ejection fraction (GBEF). The purpose of our study was to investigate patients with a CCK-HIDA scan to determine predictors of symptom resolution among patients treated with cholecystectomy or other medical treatments.

Methods: Records of patients with gastrointestinal symptoms who underwent a CCK-HIDA scan from January 2004 through December 2008 were reviewed. Outcomes were obtained by chart review. Patient demographics, symptoms, comorbidities, evaluating tests, treatment type, pathology, and treatment response were recorded.

Results: Three hundred thirty-two patients underwent CCK-HIDA scan, with 293 meeting inclusion criteria. Seventy-nine (27%) met biliary dyskinesia criteria (Group 1), while 214 (73%) had gallstones or GBEF>35%, excluding them from a diagnosis of biliary dyskinesia (Group 2). Of 246 patients with follow up, 76 (31%) underwent cholecystectomy—41 (54%) in Group 1 and 35 (46%) in Group 2. Complete symptom resolution (total N=127, 60%) in Group 1 was 65.6% (21/32) with cholecystectomy versus 34.4% (11/32) without cholecystectomy ($p<0.001$). In Group 2, complete symptom resolution with cholecystectomy was seen in 48.4%(16/33) with stones and 51.5%(17/33) without stones ($p=0.0002$). Among biliary dyskinesia patients, 44.5% (33/74) were diagnosed with gastroesophageal reflux disease (GERD), 62.3% (48/77) had previous abdominal surgeries, and 6.2% (12/74) had diabetes mellitus (DM).

Conclusion: High levels of symptom resolution were seen amongst all patients with gallbladder disease, regardless of treatment. Patients with biliary dyskinesia had more improvement with cholecystectomy, while patients outside of this diagnosis fared better with medical treatment. GERD and previous abdominal surgery were associated with biliary diskinesia (not statistically significant). Further study is needed through a randomized controlled trial in order to better assess and treat biliary dyskinesia.

Byekova, Yevgeniya A (Gina)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. James M. Markert
Title	The Role of Glioma Progenitor Cells in Clinical Responses to Oncolytic HSV in Patients with GBM

Abstract

The use of oncolytic viral vectors such as human Herpes Simplex Virus (oHSV) is a novel approach to treat glioblastoma multiforme. A marked variation in patients' responsiveness to this therapy has been observed in clinical trials. The basis of this variability is currently unknown. Glioma progenitor cells (GPCs) expressing CD133 have been implicated in gliomagenesis, tumor recurrence, and resistance to radiation/chemotherapy. We hypothesize that GPCs are also relatively resistant to oHSV therapy and patients whose gliomas have lower fractions of GPCs will have a better response to viral therapy. To determine if CD133 represents a reliable marker for neural stem cells, we performed immunofluorescent (IF) double staining of formalin-fixed, paraffin-embedded (FFPE) postnatal murine brains for CD133 and another neural stem cell marker, nestin. To assess relative fractions of GPCs in human gliomas, we performed immunofluorescent labeling of FFPE human glioma xenografts using anti-CD133 antibodies followed by computerized quantitation of immunofluorescence. We observed a marked co-localization of CD133 and nestin demonstrating that CD133 could be used as a reliable biomarker for neural stem cells. We also demonstrated that relative fractions of GPCs were variable among the different xenografts. Interestingly, GBM1046 derived from the long-term survivor of the oHSV therapy trial exhibited one of the lowest levels of GPCs. This study marks a first step in the characterization of individual marker expression profiles in GBMs that might enable 1) stratification of patients and outcome prediction in oHSV therapy, and 2) testing of new viruses specifically targeted to GPCs.

Calix, Juan Jose (Juan)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Moon H Nahm
Title	Disruption of the O-acetyltransferase, *wcjE$_{11A}$* is the Genetic Basis of a New Pneumococcal Serotype

Abstract

Serotype 11A is among the top five isolated pneumococcal serotypes from carriage and disease-causing strains. Using monoclonal antibodies, two antigenically distinct subtypes can be identified among 11A clinical isolates. This study shows that 11Aα, the more commonly occurring subtype, and 11Aβ are genetically and serologically distinguishable strains. Investigating differences in the sequence of their *cps* loci revealed that the genes responsible for capsule synthesis are identical in 11Aα and 11Aβ except for a disrupted *wcjE$_{11A}$* gene, a putative O-acetyltransferase, in 11Aβ. Further investigation with seven different 11Aβ strains revealed variable disruption of the *wcjE$_{11A}$* gene by either an insertion of a transposable element, an internal deletion, a point mutation or nucleotide duplication. *In vitro* disruption of *wcjE$_{11A}$* in an 11Aα strain resulted in the 11Aβ phenotype. These findings are in concordance with recent biochemical evidence showing that the major difference between the subtypes' capsules is the presence of an O-acetylated 1-phosphoglycerol. Both subtypes are equally fit during *in vitro* growth, and seroconversion between the subtypes was undetectedunder normal laboratory conditions, indicating that the 11Aβ phenotype is unlikely to have emerged due to laboratory passage. This study illustrates a new means for serotype emergence in which multiple mechanisms of gene disruption can give rise to serologically distinct strains *in vivo*. We propose designating the 11Aα capsule subtype as the 11A serotype and 11Aβ as 11E, a new serotype.

Cease, Alan Tyler (Alan)

Project Length	Short
Prior Research Experience	No
Funding Source	
Advisor	Kathy Monroe, M.D.
Title	Analysis of Child Passenger Safety in Patients of a Pediatric Emergency Department

Abstract

Purpose: To determine the number of children properly restrained during transit to a pediatric Emergency Department (ED) for care. As well as to ascertain parental knowledge of Alabama laws and American Academy of Pediatric (AAP) guidelines and where they obtain this information.

Methods: Taking place in ED patient exam rooms, a convenience sample of Alabama parents who have children $\leq$ 13 years of age was surveyed over a five week period. Appropriate use of child passenger safety (CPS) restraints was determined using Alabama law and AAP recommendations. Use of Car Seat Checks provided by Children's Hospital and Safe Kids, knowledge of Alabama laws and CPS guidelines, and the source of the information used by parents were ascertained.

Results: Among 525 patients identified, 520 (99.0%) participated. Appropriate use per Alabama law and AAP guidelines was 72.3% and 60.6%, respectively. 5.0% were unrestrained. Booster seats were the most commonly misused restraint (8.3% used correctly). Car seats were reportedly used correctly 81.9% of the time. Parents who had used the Car Seat Checks program had significantly higher correct booster seat and car seat use (91.2% and 94.6%, respectively). Unfortunately, only 31.2% of patients had knowledge of the Car Seat Checks program and only 40.6% knew the current law. Most often parents stated that the hospital where their child was born was the primary (and sometimes only) source of CPS information.

Conclusion: This study illustrates the need for improving parental knowledge of appropriate child passenger restraint use (especially booster seats) and car seat checks programs. These facts are reinforced by our finding that the use of car seat assistance programs is associated with high levels of appropriate use.

Charlton, Kathryn Marie (Katy)

Project Length	Short
Prior Research Experience	No
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Carlos Estrada
Title	Handoffs, Morning to Night Shift Checkouts: Are We Following National Recommendations?

Abstract

Background: The handoff process is the turning over of patient responsibility from one healthcare provider to another. National organizations have issued guidelines regarding proper handoff techniques, and institutions now face multiple challenges to standardize the process with an ultimate goal of improving patient safety.

Objective: To examine adherence to national recommendations and logistical characteristics of the handoff process.

Methods: We conducted a time-series observational study of the handoff process between resident physicians on inpatient medicine units. We used a five-point Likert Scale (1 = disagree, 5 = agree) to document whether the process adhered Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) recommendations: 1) Interactive communication and opportunity for questions is present; 2) Adequate opportunity to review relevant patient history is available; 3) Interruptions do not interfere with the handoff process; and 4) Process for verification of received information is readily used. We also documented logistical aspects of the handoff process.

Results: Over 9 days, we observed 26 handoffs. Adherence to JCAHO requirements varied greatly; agreement, a score of 4 or 5, was 92% for interactive communication, 92% for adequate opportunity to review relevant history, 58% for interruptions do not interfere, and 0% for verification of received information.The mean duration of the handoff communication was 3:04 minutes (range 8 sec-17min). Most handoffs (65.4%) occurred in the unit's conference room. All handoffs were generated by word processing software and 73% were stored in a computer accessible to members of the team. Both the duration of the handoff encounter and the interactive nature were associated with the on call team, but not the team signing out (Wilcoxon rank sums, p=0.0238 and p = 0.04, respectively).

Conclusions: The current handoff process between resident physicians on inpatient medicine units only fulfilled two of four national recommendations. We provide baseline data to test interventions to improve the handoff process.

Cochran, Michael Andrew (Drew)

Project Length	Short
Prior Research Experience	No
Funding Source	Cunningham Fellowship (Pediatrics)
Advisor	Dr. Walter H. Jonson, Jr.
Title	Age And Body Size Are Major Factors In Pacemaker Lead Longevity In Pediatric Patients

Abstract

The integrity of the lead in pacemaker systems is vital to ensuring delivery of adequate therapy, but in pediatric patients the lead is more at risk of failure than in adults. The objective of this study was to identify patient factors and lead characteristics related to lead abandonment and reduced longevity. We identified 174 patients with 393 leads implanted between 1976 and 2009. Patient demographics, lead characteristics and causes of abandonment were identified. Statistical methods were used to identify factors related to early lead abandonment and decreased longevity. At initial implantation median age was 9.6 years (3 days–48.3 years), median weight was 30.6 kg (2.8–118.6) and median height was 145 cm (53–195). Seventy-seven (44.3%) of the patients were female; 64% of all patients had structural congenital heart defects, 33% had normal cardiac anatomy and 6% had cardiomyopathy. Forty-one of the 174 patients (23.6%) required at least one additional lead implantation procedure. The frequency of patients requiring reintervention was significantly higher in patients under age ten at the time of first implantation. The average time before required reintervention was 14.3 $\pm$ 1.3 years. Of the 393 leads, 84 (21%) were abandoned; 13.0% of endocardial leads were abandoned and 32.7% of epicardial leads were abandoned ($p<0.000$). Mean lead longevity was 17.1 $\pm$ 1.5 years and 13.8 $\pm$ 0.9 years, respectively ($p=0.222$). A significantly higher frequency of lead abandonment was observed in leads with non-steroid eluting electrodes and polyurethane insulation in both endocardial and epicardial leads. While these lead-related characteristics were associated with higher frequency of abandonment, there were no characteristics that significantly influenced lead longevity. Based on these results, we conclude that younger age and smaller body size are the major contributors to both increased frequency in abandonment and shorter longevity of pacemaker leads in this patient population.

Colburn, MaryKathryn Huddleston (MaryKathryn)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	AL Sutton, JM Whitworth, KE Schneider, JM Straughn, Jr.
Title	Therapeutic Effect of Gastrografin Administration in Gynecologic Oncology Patients with Bowel Dysfunction

Abstract

Background: Gynecologic oncology patients suffer from a wide range of bowel dysfunction including small bowel obstruction. A small bowel follow through (SBFT) with the water soluble oral contrast gastrografin is utilized to characterize the presence, location, and extent of bowel dysfunction. Several studies in surgical patients have shown that gastrografin administration in patients with small bowel obstructions reduces the length of hospital stay by accelerating the resolution of partial small bowel obstructions. We sought to characterize the outcomes of gynecologic oncology patients undergoing SBFTs with gastrografin at our institution.

Materials/Methods: Following IRB approval, we identified all gynecologic oncology patients undergoing a SBFT with gastrografin from 2004 through 2009. Abstracted data included patient demographics, diagnosis, history of bowel surgery, and prior admission for bowel dysfunction. We characterized the SBFT as normal, delayed transit, partial obstruction, and complete obstruction. Patient outcomes including surgical intervention rates, time to return of bowel dysfunction, length of stay, and readmission rates were determined and correlated with the SBFT results. Statistical analyses were performed with student t test, Chi square test, and Fisher's exact test.

Results: 70 patients underwent 79 SBFTs with gastrografin to evaluate the extent of their bowel dysfunction. The median age was 66. 67 patients (85%) were diagnosed with malignancy; ovarian cancer (63%) was the most common diagnosis. 42% of patients had been admitted in the prior 30 days for bowel dysfunction. 23% of the SBFTs were normal, 11% had delayed transit, 49% had a partial obstruction, and 16% had a complete obstruction. The median return of bowel function after the SBFT was performed was 10 hrs. The median length of stay was 10 days (range, 1-36). The overall rate of operative intervention was 23%. 69% of patients with a complete obstruction underwent surgery compared to 21% of patients with a partial obstruction ($p = 0.002$). Only 4% of patients with a normal or delayed transit SBFT required surgical intervention. Return of bowel function was significantly longer in patients with complete obstructions compared to patients with partial obstructions (48 hrs vs. 8 hrs; $p = 0.006$). Length of stay was longest in patients with complete obstructions (18 days; range, 7-29). Readmission rates were highest in patients with complete obstructions (39%).

Conclusions: SBFT is an important diagnostic tool to evaluate gynecologic oncology patients with bowel dysfunction. The majority of patients with a complete obstruction will require surgical intervention and have a prolonged hospital stay. Patients with delayed transit or a partial obstruction will often have resolution of bowel dysfunction with conservative management suggesting that gastrografin may provide a therapeutic benefit in resolving bowel dysfunction without operative management.

Corrick, Ryan Marshall (Ryan)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Joseph L. Messina
Title	Tissue-Specific Variation in the Development of Growth Hormone Resistance Due to Injury: Skeletal Muscle vs. Liver

Abstract

Acute growth hormone resistance frequently occurs following severe injury and in critical illness, contributing to a rapid erosion of lean body mass and dysfunction of multiple organ systems. The ability to counteract growth hormone resistance in the critical care setting may have beneficial effects, reducing organ dysfunction, morbidity and mortality. However, the molecular mechanisms contributing to the development of acute growth hormone resistance are poorly defined. We subjected mice to trauma and hemorrhage to determine whether growth hormone resistance occurs following injury. The time of reduced blood pressure following hemorrhage was varied in order to characterize the time course of the development of acute growth hormone resistance. Hepatic growth hormone resistance developed rapidly in response to trauma and hemorrhage, becoming apparent by 30 minutes. Livers from animals subjected to 30 minutes of trauma alone, without hemorrhage maintained full growth hormone sensitivity. The onset of growth hormone resistance was delayed in skeletal muscle, and was not apparent until after 90 minutes of either trauma alone or in combination with hemorrhage. Cardiac muscle maintained sensitivity to growth hormone following either 30 or 90 minutes of trauma alone or trauma and hemorrhage. Liver, skeletal muscle, and cardiac muscle are all important growth hormone target tissues, and their ability to respond to endogenous growth hormone may be an important factor in critical care outcomes. The data presented here indicate tissue-specific differences in the conditions required for growth hormone resistance to occur, suggesting distinct molecular mechanisms in its development.

Cossey, Tiffany Danielle (TC)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	Dr. Brian Sims, MD, PhD
Title	The Epigenetics of Neonatal Neuroprotection

Abstract

Background: Neonatal brain injury is a devastating condition that represents a significant cause of neonatal morbidity and mortality. While there is no cure or effective treatment for ischemic injury, there are therapies that may protect against or decelerate injury. Retinoic acid (RA), a metabolite of vitamin A, has been shown to protect against ischemic injury by mechanisms that are unclear. One potential protective pathway may involve epigenetic mechanisms such as histone deacetylase inhibition.

Purpose: Our study was designed to determine the role of epigenetics in neonatal neuroprotection.

Methods: In vivo studies using carotid ligation and then 8% hypoxia were used in control versus ATRA-treated mice. Animals were sacrificed by approved IACUC methods and brains were placed in 4% paraformaldehyde for 12 hours, then in 30% sucrose for 12-16 hours. 12 micrometer sections were collected using a standard cryostat. In vitro studies using neural stem cells were used in control versus glutamate and glutamate/RA-treated cells, and then a Western blot was performed.

Results: In our hypoxia-ischemia model, HDAC1 showed a 78-fold increase in expression, and is reduced significantly in the presence of RA. In the in vitro study, HDAC expression was not changed during stress.

Conclusion: HDAC1 increases in the hypoxia-ischemia model and decreases in the presence of RA. Also, the HDAC 1/2/3 profile does not appear to change during the in vitro model of excitotoxicity, and the neuroprotective effect of RA was not observed. Further studies are needed to examine specific HDAC isoforms in neonatal brain injury and the role of RA.

Cuddapah, Vishnu Anand (Vishnu)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Harald Sontheimer
Title	Chloride channel regulation by CaMKII in human glioma cells

Abstract

Malignant gliomas, accounting for approximately 70% of malignant primary brain tumors, are characterized by rapid clinical progression and poor prognosis. Present treatment options are largely ineffective and fail to target the unique biology of gliomas. The lethality of these tumors can be attributed to an enhanced ability to invade and proliferate in the narrow extracellular space of the brain, making the tumor diffuse and difficult to resect. This ability of glioma cells to migrate, proliferate, and volume regulate in the brain may be facilitated be the expression of certain ion channels, as suggested by numerous recent studies. Specifically, the expression of potassium and chloride channels, via the extrusion of salt (K^+ and Cl^-) and obligated release of water, endows glioma cells with an ability to rapidly regulate cell volume, which is essential during cell proliferation and invasion. Therefore, understanding the regulation of these ion channels in human glioma cells may lead to more effective clinical management. ClC3, a voltage-gated chloride channel, has been identified as the major Cl^- channel implicated in the migration, proliferation, and volume-regulation of human glioma cells. Here, we find that as resected human glioma tissue increases in grade, the expression of ClC3 also increases, with grade 4 glioblastoma multiforme tissue expressing the most ClC3. Concordantly, we find that several glioblastoma cells lines also express ClC3 via Western blotting. Using whole-cell patch-clamp electrophysiology, we then examined the regulation of ClC3 activity by CaMKII, a serine\threonine kinase that is expressed by human glioma tissue and phosphorylates ClC3 at S109. We found that auto-activated CaMKII phosphorylates ClC3 and potentiates NPPB-sensitive currents that are voltage- and time-inactivating, resembling the pharmacological and electrophysiological signature of ClC3. CaMKII increased ClC3 current density by threefold, and this activation was blocked by AIP, a potent and specific inhibitor of CaMKII. We then stably knocked down ClC3 expression using shRNA and saw a decrease in ClC3 current density, which did not increase after addition of auto-activated CaMKII. These data suggest that CaMKII selectively increases the conductance of ClC3. The functional consequences of this regulation are still under investigation, and preliminary data suggests that ClC3 activation may play a role in glioma cell proliferation and migration.

Dizon, Brian Leonard (Brian)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr John F Kearney
Title	Modulation of Autoimmune Diabetes Development by B Lymphocytes Specific for N-acetyl-D-glucosamine

Abstract

Type I diabetes (T1D) is an autoimmune disease in which pancreatic beta cells are targeted for destruction by the immune system. B lymphocytes are found in the beta islet infiltrates of humans and NOD mice afflicted with autoimmune diabetes, and are critical for the development of disease. Exposure to certain types of bacteria, such as Group A Streptococci (GAS), during childhood is negatively correlated with T1D development. Additionally, immune responses to GAS in mice and humans produce N-acetyl-D-glucosamine (GlcNAc) specific antibodies. Since GlcNAc-specific antibodies have potential autoreactivity to cell types expressing high levels of enzymes regulating GlcNAcylation, such as pancreatic beta cells, we hypothesized that GlcNAc-specific B lymphocytes and secreted antibodies have the capacity to modulate the development of autoimmune diabetes. We generated mice transgenic (Tg) for an immunoglobulin heavy chain that conferred specificity for O-GlcNAc, and treated mice with multiple low doses of streptozocin (MLDS), a drug that leads to accumulation of GlcNAcylated proteins in beta cells. We observed that Tg mice treated with MLDS developed diabetes faster than MLDS-treated littermate (Lm) mice due to insulitis containing T cells and GlcNAc-specific B lymphocytes. MLDS-treated wild type mice that developed diabetes had increased frequencies of endogenous GlcNAc-specific B lymphocytes in pancreatic lymph nodes. Changes in serum GlcNAc-specific antibodies were not detected, suggesting that secreted antibodies did not play a role in diabetes development. To determine whether exposure to GAS could influence the development of autoimmune diabetes, C57BL/6 and NOD mice were immunized with GAS or control bacteria as neonates and monitored for hyperglyemia and glycosuria. C57BL/6 mice and NOD mice immunized with GAS as neonates were resistant to developing diabetes. These findings suggest that a B lymphocyte clone with specificity for O-GlcNAc may exert pathogenic influences on diabetes development by a mechanism dependent on beta cell death and independent of secreted antibodies. In contrast, these same B lymphocytes, when activated by antigen during neonatal development, may protect against autoimmune diabetes by a mechanism dependent on secreted antibodies. This research is supported by AI4782-31 and DK082277-02.

Dobbin, Zachary Christopher (Zachary)

Project Length	Short
Prior Research Experience	yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Danny R. Welch
Title	Formation of kisspeptins from KiSS1 to determine their role in suppression of cancer metastasis

Abstract

In cancer patients, the development of metastatic disease usually signifies a point at which treatment is no longer looking curative but palliative in nature. With traditional intervention, prognosis for metastatic melanoma is extremely poor with a five-year survival rate of 2-3%. In the past two decades, survival for metastatic melanoma has not improved at all indicating the need for new treatments that will specifically target the metastatic nature of this disease. One promising avenue for treatment has been the discovery of metastasis suppressors, especially KiSS1, whose expression levels in melanoma have been inversely correlated to metastatic potential and prognosis of patients., Endogenous KiSS1 expression is lost in metastatic C8161.9 melanoma cells, however, its restoration inhibits metastasis without inhibiting primary tumor formation. To exert its anti-metastatic effect, KiSS1 must be: *1) secreted from the cell into extracellular space;* and, *2) processed into multiple peptides called kisspeptins* as shown in our preliminary data. Of the ten theoretically possible kisspeptins, only the peptide (KP-54) has been investigated for its biological role. Therefore, it is of great importance that the other nine kisspeptins are investigated for their possible role(s) in metastasis suppression. It is our hypothesis that kisspeptins, other than KP54, are responsible for metastasis suppression. This objective is especially important since our previous work showed that KISS1 processing to kisspeptins occurs outside of the cell. cDNA encoding KISS1 wherein the amino acids involved in proteolytic processing are mutated will be created by site-directed mutagenesis. Variant KISS1 will be transfected into C8161.9, stable clones selected and metastatic potential determined. Currently, we have shown the successful creation of three KiSS1 processing variants and have incorporated them into the pcDNA3 plasmid vector. Experiments to determine their biological role and function in metastasis are underway.

Edwards, Adam Larry (Adam)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	
Advisor	H Thomas McElderry
Title	Reimplantation is Often Not indicated Following Cardiac Rhythm Management Device Extraction

Abstract

INTRODUCTION: The number of patients with implantable cardioverter-defibrillators (ICDs) and permanent pacemakers (PPMs) has increased due to expanding indications for cardiac rhythm management devices (CRMDs). With this, so has the number of device and endocardial lead extractions. Reimplantation of CRMD after extraction is commonplace. We aimed to evaluate the indications and medical appropriateness for reimplantation of CRMDs at the time of lead and device extraction. METHODS: We performed a retrospective cohort study of consecutive patients referred to our institution for lead extraction between 1999 and 2008. Demographic information and data regarding extraction and reimplantation history were obtained by review of medical records. RESULTS: One hundred forty-eight leads were removed during 83 procedures (age 60 $\pm$ 18 years, 66% male, 78% Caucasian). Forty-three (52%) PPM and 40 (48%) ICD systems were extracted. Reimplantation of a CRMD occurred in 47 (57%) patients. Of the 36 patients that were not reimplanted with a CRMD, 19 had PPMs and 17 had ICDs. The initial indications among the 19 patients with extracted, non-reimplanted PPMs were symptomatic bradycardia (6), sick sinus syndrome (4), paroxysmal heart block (4), vasovagal syncope (2), and unknown (3). The initial indications among the 17 patients with extracted, non-reimplanted ICDs were ischemic cardiomyopathy (8), non-ischemic cardiomyopathy (6), idiopathic ventricular tachycardia (1), sinus node dysfunction (1) and unknown (1). The most common reasons for not reimplanting PPMs and ICDs were the absence of a current indication and normalization of ejection fraction, respectively. Of the 15 surviving patients with ICDs not reimplanted, only one had received appropriate shock therapy while implanted. CONCLUSIONS: Forty-three percent of patients at the time of device extraction do not meet indications for or are deemed not medically appropriate for reimplantation. Our results indicate that reevaluation of patients at the time of CRMD extraction is imperative prior to reimplantion.

Elkhetali, Abdurahman Said (Abdurahman)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Rotem Elgavish
Title	Normalization of Hippocampus Quantitative Percent Pathology Map Following Temporal Lobectomy.

Abstract

Rationale: Percent pathology mapping (PPM) has previously been demonstrated to correlate with hippocampal cell counts associated with pathology in mesial temporal lobe epilepsy. Metabolic recovery in the contralateral hippocampus following temporal lobectomy has been reported with proton magnetic resonance spectroscopic imaging. The purpose of this study was to evaluate whether the PPM method would identify a similar and earlier normalization of cell counts. Such changes would presumably be reflected in the post-surgical contralateral hippocampal quantitative PPM (qPPM).

Methods: 17 patients with medically intractable mesial temporal lobe epilepsy were studied both one week before and 2 months after anterior temporal lobectomy. 14 age-matched healthy controls were studied for comparison. An MRI sequence was used to generate R2-maps (R2=1/T2) for multiple coronal slices through the head and body of both hippocampi. PPMs were generated for each slice and qPPM values measured for both hippocampi before surgery and the unresected contralateral hippocampus after surgery. Paired and unpaired t-tests were used for statistical analysis.

Results: Mean qPPMs: healthy controls 249.6 (SD 260.9), pre-surgical ipsilateral 3623.5 (SD 2266.4), pre-surgical contralateral 976.6 (SD 720.0), and post-surgical contralateral 403.4 (SD 319.7).). The mean decrease of post-surgical contralateral PPM was 58.7%. 12 of the 14 patients with a post-surgical decrease were seizure free (86%). Two patients had an increase of the post-surgical contralateral qPPM, neither was seizure free. Ipsilateral and contralateral pre-surgical qPPMs were significantly different ($p<0.0001$). Contralateral pre-surgical and post-surgical qPPMs were significantly different ($p=0.001$).

Conclusions: The normalization of the post-surgical contralateral qPPM is consistent with the MRS literature. One potential mechanism is reversibility of a contralateral reactive gliotic process, this conclusion is supported by the short interval between surgery and the post-surgical scan, making a glial process more likely. This study supports the notion that contralateral hippocampal pathophysiology is partially reversible post-surgically and, to our knowledge, is the first study to show contralateral structural changes so soon after surgery.

Ellison, Jim Patrick (Jim)

Project Length	Short
Prior Research Experience	Yes
Funding Source	HSF Community and Rural Health Fellowship
Advisor	John R. Wheat, MD, MPH
Title	National Health Insurance: Alabama Family Physicians' Attitudes

Abstract

Americans are increasingly in need of health coverage, and lack of health coverage is usually associated with adverse health effects. Some policy makers are proposing that a universal health insurance system could provide for those in need. Traditionally physicians' attitudes have helped to derail movements toward universal coverage in the past. Some studies have attempted to gain insight in physicians' attitudes towards universal coverage in the recent past, but none have examined rural primary care physicians' attitudes in depth. This study attempted to do that through a cross-sectional survey of Alabama Family Physicians. From there, the attitudes of this group were compared to current national surveys. It was found that 40% of Alabama Family Physicians are in favor of a national health insurance system compared to a 59% nationwide average reported in the literature. Importantly, there was no difference between rural Alabama physicians' sentiments towards a national health insurance and their urban Alabama counterparts nor does it seem that a physician's practice characteristics influence their thinking on this issue.

Falls, Nicole Margaret (Nicole)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Helen Krontiras MD
Title	Patient Preference May Explain Regional Variation in Mastectomy Rates

Abstract

Background: In 1990 a NIH Consensus Conference recommended “Breast Conservation Treatment (BCT) is an appropriate method of primary therapy for the majority of women with Stage I and II Breast Cancer (BC) and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast”. However, considerable variation in mastectomy rates exists, with the southern US having the highest rates of mastectomy.

Objective: Identify potential reasons for higher mastectomy rates in the South.

Methods: Women with Stage 1 or 2 BC who had undergone surgical treatment for BC at UAB between 2001 and 2004 completed a short, IRB approved questionnaire about factors contributing to their treatment choice.

Results: 412 women were indentified and 221 returned surveys. There were 54% with Stage I BC and 46% with Stage II BC. 60% underwent BCT and 40% underwent mastectomy. 73% reported that they were presented with multiple options for surgical treatment. 98% reported having adequate decision making time. Participants ranked factors influencing their surgical decision, and fear of cancer recurrence was ranked most influential in treatment choice. Avoidance of radiation was not a significant factor in women choosing mastectomy, as only 5% (n=10) chose mastectomy to avoid radiation. Few disparities were noted as only one patient avoided BCT because of travel distance and only 3 patients were uninsured. While 90% of women undergoing BCT reported being satisfied with physical appearance and outcome, the majority of women having mastectomy (78%) were also satisfied (p=0.01).

Conclusion: Patient preference may explain higher mastectomy rates in the South when compared with other geographical regions even when options are presented. Access to care, avoidance of radiation therapy, surgeon’s recommendations, and insurance status do not appear to account for higher mastectomy rates in this single institution study.

Feng, Alexander Jing (Alex)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Baljendra Kapoor
Title	Absence of Common Carotid Artery: A Case Study

Abstract

Summary: The *absence of the common carotid artery (CCA)* is a rare anomaly. We report the case of a 43-year-old male with uncontrolled life-long epilepsy who underwent a WADA procedure. During the procedure, we discovered the presence of direct origin of the left internal and left external carotid arteries from the aortic arch. We discuss the clinical and embryologic correlations of this anomaly after the case report.

Feng, Alexander Jing (Alex)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Baljendra Kapoor
Title	Bow Hunter's Syndrome: A Case Study

Abstract

Summary: *Bow Hunter's syndrome, a rare form of vertebrobasilar insufficiency*, was successfully treated by surgical intervention. We report two cases (classic and variant) of this rare, but important potentially surgically correctable condition, to make the referring physicians and radiologists aware of the need for dynamic imaging according to the clinical presentation of VBI. The mechanisms, pathophysiology, imaging and treatment options of rotational VBI are discussed.

Gamble, Lena Jeanelle (Lena)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	David Curiel, MD, PhD
Title	Increased oncolytic ability of a double RGD-modified adenovirus in ovarian cancer

Abstract

Ovarian cancer is a leading cause of gynecological cancer mortality in Western countries. Attempts to address the urgent need for effective anti-tumor treatments for ovarian cancer patients include development of oncolytic virotherapy agents targeted specifically to ovarian cancer cells. One major hindrance to effective virotherapy has been suboptimal transduction of ovarian cancer cells due to the sparse presence of the natural adenovirus receptor on cancer cells. Addition of an Arg-Gly-Asp (RGD) motif to the receptor attachment protein of the adenoviral capsid "fiber" increases viral ability to bind and transduce ovarian cancer cells. This RGD modification has been added to the HI-loop domain of the fiber knob in the virus Ad5Δ24,RGD which is designed to conditionally replicate in cancer cells. The safety of Ad5Δ24,$F5_{HI}$-RGD has been tested in a Phase I clinical trial. In order to further improve the ovarian cancer cell infectivity of this agent we created a double RGD-modified virus that incorporated an additional RGD modification at a distinct capsid locale, protein IX (pIX). We have shown that the double-modified virus, Ad5,double RGD increases ovarian cancer transduction over both of the singly modified Ad5,pIXRGD and Ad5,F_{HI}-RGD viruses. Based on these data, we hypothesized that a conditionally replicative version of this virus would more efficiently kill tumor cells than either of the singly-modified control viruses. Using standard molecular biology techniques we added an RGD sequence to the pIX portion of Ad5Δ24,$F5_{HI}$-RGD to yield Ad5Δ24,pIXRGD/F_{HI}-RGD or Ad5,doubleRGD. Preliminary data indicate that the newly created double modified virus carries the RGD motif on both the fiber and pIX proteins. Preliminary data also indicate that the oncolytic ability of Ad5,doubleRGD is better than that of Ad5Δ24,$F5_{HI}$-RGD. The use of double modification may not only allow for increased oncolytic capability of the new agent as an anti-cancer treatment modality but could possibly translate to a less toxic potential therapeutic option for the treatment of ovarian cancer.

Gaston, David Curtis (David)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Jacqueline Nuss Parker
Title	Prior Immunity to HSV-1 Limits Gag-Specific Immune Responses Elicited by a HSV-1 Vaccine Vector

Abstract

As more than 60% of the U.S. population is seropositive for herpes simplex virus type-1 (HSV-1), the impact of pre-existing HSV-1 immunity on the efficacy of HSV-1 derived vaccine vectors is a concern. Previously we demonstrated that J200, a conditionally replication competent, herpes simplex virus type-1 (HSV-1) expressing CMV driven HIV-$1_{89.6}$ Gag, was able to elicit persistent Gag-specific cellular immune responses in mice. The purposes of the current studies are twofold: 1) to determine the impact of prior immunity on J200 with regards to its ability to elicit Gag-specific immune responses in mice, and 2) to determine whether observed inhibition from pre-existing immunity could be overcome by increased vaccine dose, or by co-administration with M002, a similar HSV-1-derived vector engineered to express murine IL-12. Gag-specific, splenic CD8 T-cell responses elicited by J200 in Balb/c mice were diminished to background levels in the presence of HSV-1 immunity, and accompanied by rising serum IgG titers against HSV-1. Neither increased vaccination dose of J200, nor co-administration with M002 was able to overcome inhibition of Gag-specific CD8 responses when challenged six weeks following initial immunization. Additionally, bioluminescence imaging studies demonstrated that luciferase expression from an HSV-1 replication dependent gamma-2 promoter in an HSV-1 vector similar to J200 was undetectable in mice exposed to wildtype HSV-1 four weeks prior, whereas the signal was strong in naïve mice. These data further emphasize the challenges posed by pre-existing immunity to HSV-1 for the optimal use of HSV-1 derived vaccine vectors. Continued investigations into the immunological interactions between HSV-1 derived vaccine vectors and HSV-1 immunity, as well as the development of novel strategies to achieve optimal vaccine vector efficacy, are warranted.

Gladden, James Douglas (James)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Louis Dell'Italia
Title	Inhibition of Xanthine Oxidase Preserves Left Ventricular Function In Volume Over Heart Failure.

Abstract

Background: There is no effective medical therapy to prevent progressive cardiac remodeling and failure in chronic volume overload states. We previously demonstrated short-term inhibition of xanthine oxidase (XO), in the rat, attenuates the response to volume overload; however it unknown whether this benefit will be maintained chronically. In the current investigation we hypothesized that inhibition of XO would prevent progressive remodeling and preserve cardiac function in chronic volume overload in the rat.

Methods: Age-Weight matched Sprague-Dawley rats were randomized to either Sham or aortocaval fistula (ACF) ± allopurinol, (n=7 per group). Allopurinol (100 mg/kg/day) was delivered in standard chow. Echocardiography was performed at 8-weeks post induction of ACF. Statistical analyses were performed using 2-way ANOVA with Student-Newman-Keuls post-hoc testing.

Results: Left ventricular (LV) end-diastolic dimensions were significantly increased in both ACF groups as compared to Sham, confirming significant volume overload. LV end-systolic dimension, a critical marker of adverse remodeling was increased in untreated ACF vs. Sham, however this increase was attenuated in ACF+allopurinol group. LV ejection fraction, fractional shortening, and velocity of circumferential shortening were all significantly depressed in the untreated ACF as compared to Sham, however these indexes of LV function did not differ significantly from Sham in the ACF+allopurinol group (see Table).

Conclusions: Allopurinol treatment attenuates adverse LV remodeling and preserves LV function in the chronic volume overload of ACF in rats. Inhibition of XO may provide a novel strategy for treatment of chronic volume overload states such as MR in humans.

	Sham	ACF	Sham+Allopurinol	ACF+Allopurinol
Body Weight	476±14	459±17	418±15	462±18
Heart Rate	381±11	349±6#	378±10	364±6
LVEDD	8.2±0.3	11.3±0.3#	7.7±0.2	10.9±0.3#
LVESD	4.4±0.2	7.2±0.3#	4.3±0.3*	6.1±0.3#*§
LV EF	76±2	63±2#	74±3*	73±3*
LV FS%	46.6±2	36.6±1#	45.0±3*	44.3±2*
VCFr	9.8±0.5	6.2±0.4#	10.1±0.9*	9.3±0.5*

#=p<0.05 vs. Sham
*=p<0.05 vs. ACF
§=p<0.05 vs Sham+Allopurinol

Griffith, Zachary M (Zach)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Piotr Kulesza
Title	FNA-Based Assay Predicts Therapeutic Response to TRA-8 (Death Receptor 5 Antibody) Treatment

Abstract

INTRODUCTION: Targeted therapies for cancer utilize agents that manipulate specific cellular pathways essential for a malignancy's proliferation and survival. TRA-8 antibody, which binds to Death Receptor 5 (DR5), is one of the newest targeted agents. Nearly all cells express DR5; degree of expression bears no correlation to sensitivity to TRA-8. DR5 induces apoptosis via activation of the Caspase proteases. DR5 directly activates Caspase-8 (receptor-associated protease). The most distal effector is Caspase-3. Activated Caspase-3 cleaves Poly (ADP-ribose) polymerase (PARP), destroying its anti-apoptotic activity. Measuring levels of activated Caspase-8 indicate apoptosis induction, while levels of activated Caspase-3 and PARP reflect apoptosis's terminal events. We hypothesize that TRA-8 binding causes apoptosis in sensitive tumor cells and results in anti-tumor activity *in vivo*, and that we can predict *in vivo* response to TRA-8 therapy by obtaining a Fine Needle Aspirate (FNA) before treatment, and interrogating molecular effects in an *ex vivo* assay.

MATERIALS /METOHODS: Colon and pancreas cancer xenografts were made in nude mice. Tumor tissue from therapy-naïve animals was obtained by FNA. Material was then either exposed to TRA-8 or IgG (control) *in vitro* under tissue culture conditions, and levels of cleaved Caspase-8, Caspase-3, and PARP were assessed by Western blotting. *In vivo* effects were assessed in xenografts treated with 200ug/animal of TRA-8 or vehicle alone. Tumor size and survival were determined.

RESULTS: Treatment with TRA-8 *in vivo* delayed and inhibited tumor growth only in samples which showed cleavage of Caspase-3 and PARP, as predicted by the *ex vivo* assay.

CONCLUSIONS: FNA-based assay can assess molecular effects of TRA-8. In animal models of 5 different colon and pancreas cancers, we were able to predict the *in vivo* effects of therapy before administration of the drug. Thus, the study demonstrates the feasibility of predicting an individual's clinical response to DR5 antibody treatment.

Hadley, Jennifer Ann (Jennifer)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Rotem Elgavish
Title	Implementing a Rat Model of Acute Seizure to Study High Frequency Oscillations

Abstract

Pathological high frequency oscillations (HFOs) can be recorded from intra-cranial electroencephalography (ICEEG) of patients with intractable epilepsy, and from rodent models of epilepsy. They remain have only recently been identified because the sampling rates necessary to detect them are much higher than those currently in clinical use. HFOs appear to occur predominantly in the seizure onset zone (SOZ), but their relationship to the underlying pathology is unknown. We set out to produce an acute seizure model in rodents and to develop a means of analyzing ICEEG data in order to study HFOs, with the ultimate goal being to provide a comprehensive assessment of HFOs and their role in the generation and propagation of seizures.

Methods. Sprague-Dawley rats (weight 250 – 350 g, 30 – 45 days old) were anesthetized using a standard ketamine (70 mg/kg) and xylazine (6 mg/kg) mixture given intraperitoneally. They were secured in a stereotactic frame. 0.25cc lidocaine was injected subcutaneously over the incision site; a 3cm incision was made to expose the skull surface. Two 1mm burr holes were drilled through the skull, at +/- 3mm lateral and 1mm anterior to bregma. Electrodes, made of 30 gauge copper wire, were stripped of insulation 2.5mm from the end and secured such that they rested on the cortical surface. Seizures were stimulated using parameters V: 2 – 8 volts; f: 50 – 200 Hz. ICEEG was acquired using an A/D converter at a 5000 Hz sampling rate and analyzed using a Matlab-based Teager Energy algorithm.

Results. An acute seizure model in rats was successfully implemented and ICEEG recorded. Pathological HFOs were detected using a Teager Energy algorithm and this model can now be used for the further study of HFOs.

Hammond, John Charles (John)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Robert McCullumsmith, MD/PhD
Title	AMPA Receptor Trafficking in Endosomes in Schizophrenia

Abstract

Accumulating evidence suggests that glutamate receptor dysfunction in schizophrenia is not a problem of too much or too little receptor expression, but instead a problem of receptor trafficking. Trafficking of receptors is controlled, in part, by proteins that interact with the AMPA receptor subunits such as SAP97, GRIP1, or PICK1. Turnover of receptors via endosomes is a critical event for regulation of neuronal transmission at the synapse. We postulate that alterations in endosome content may underlie neuropathological alterations in schizophrenia. We hypothesize that there is an increase in AMPA receptor interacting proteins in early endosomes in schizophrenia, suggesting decreased stabilization of AMPA receptors at the synapse in this illness. The aim of this study is to isolate the early endosomes from postmortem human brain tissue and using a modified subcellular fractionation technique to probe for alterations in endosome content and AMPA receptor interacting protein expression. Tissue homogenates were pre-cleared of non-specific binding via incubation with magnetic beads. Using this pre-cleared tissue homogenate, we targeted endosomes for immunoisolation using a magnetic bead-antibody complex (specific binding) or using magnetic beads only (negative control). Captured material was removed from the beads and analyzed by Western blot analysis. Data on expression of EEA1 and AMPA receptor interacting proteins in the early endosome fraction for subjects with schizophrenia and a comparison group will be presented. In schizophrenia compared to control, we found no significant difference in the expression of SAP 97 ($p=0.82$) or GRIP1 ($p=0.37$) in total homogenate in the anterior cingulate cortex. Overall protein expression of SAP97, GRIP1, and PICK1 in anterior cingulate cortex and dorsolateral prefrontal cortex will be presented. In summary, we have developed a modified immunoisolation protocol to isolate early endosomes from postmortem tissue, permitting us to test the hypothesis that there is an alteration in trafficking of AMPA receptor subunits in schizophrenia.

Hollis, Robert Hayne, IV (Bob)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	David Standaert, M.D. Ph.D.
Title	Investigating the Role of Striatal Cholinergic Neurons in DYT1 Dystonia: Validation of a Mouse Model

Abstract

Dystonia is a functional movement disorder characterized by abnormal tonic activation and contraction of muscle. DYT1 dystonia is the most prevalent and severe sub-type of primary dystonia and is known to be caused by a 3-bp deletion in the DYT1 gene that codes for the protein torsinA. While it remains unknown how this mutation in torsinA leads to the pathology of DYT1 dystonia, a dysfunction in normal striatal cholinergic signaling has been suggested. To investigate the role of striatal cholinergic neurons in the pathology of the disorder, the Standaert lab has created a mouse model (ChAT-KO) in which the mouse homologue of the human DYT1 gene, the Dyt1 gene, is selectively inactivated in cholinergic neurons by using a cre-recombinase strategy. To validate this mouse model we hypothesized that torsinA expression would be significantly decreased in striatal cholinergic neurons but not in non-cholinergic striatal neurons in ChAT-KO mice. We used immunoflourescent staining and laser capture microdissection to obtain RNA from striatal cholinergic neurons and from non-cholinergic striatal neurons. Quantitative real-time PCR was used to quantify RNA expression. Preliminary results in a wild type (WT) mouse show that choline acetyltransferase expression is higher in cholinergic neurons compared to non-cholinergic neurons and that levels of torsinA expression are similar. These results illustrate the ability of our methods to selectively obtain and quantify RNA from striatal cholinergic neurons and non-cholinergic striatal neurons. These methods will be used to compare torsinA expression in ChAT-KO mice and WT mice.

Honasoge, Avinash Vinayak (Avinash)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Harald Sontheimer
Title	Characterization of CLC-3 Knockdown Human Glioma Cells

Abstract

Gliomas are cancers that arise from the different types of glial cells or their progenitors, and collectively are the most common type of primary brain tumors. They are among the most deadly cancers, with poor prognosis and few treatment options. Although they rarely metastasize, gliomas are highly invasive and aggressively migrate throughout the intracranial cavity. This migration is helped in part by the ability of glioma cells to substantively and rapidly modulate their cell volumes – a modulation regulated by the efflux of K^+ and C^{l-} ions followed passively by water. Prior studies suggest that K^+ and C^{l-} channels are recruited to the membrane surface where they can facilitate the volume condensation of both dividing cells and hypotonically challenged swelled cells. One such channel, CLC-3, is time- and voltage-inactivating, outwardly rectifying, and NPPB-sensitive. It has been shown to be involved in premitotic condensation, but it is unclear whether it is more generally involved in the regulation of cell volume. To explore this role, we have created a line of CLC-3 knockdown human glioma cells.

We first verified the presence of ClC-3 in the knockdown cells via Western blotting and immunocytochemical staining, analyzing the stains for possible ClC-3 colocalization both at the cell membrane and intracellularly. Then, we used whole-cell patch clamp recordings under Cl^- current isolating conditions by using paxilline to block BK K^+ channels. We compared control and knockdown cells under both isotonic and 10% hypotonic conditions. In agreement with CLC-3 knockout data from mouse atrial myocytes, we found no significant difference between the cell types in either condition, suggesting that while ClC-3 is an essential component of volume regulation in premitotic condensation, it is not required to combat osmotically induced volume changes. Further studies will reveal ClC-3's role in migration and whether compensatory mechanisms upregulate other C^{l-} efflux channels.

Huff, Kayci Renee (Kayci)

Project Length Long
Prior Research Experience Yes

Funding Source

Advisor Phillip D. Smith
Title Mucosal TGF-β;/IL-6 Axis Regulates Effector T cell Function

Abstract

The role of intestinal stroma in T-cell regulation is inadequately understood. Therefore, we investigated whether human intestinal stroma-associated products down-regulate T cell function. We used human blood mononuclear cells and lamina propria stroma (after removal of cells) to recapitulate the intestinal microenvironment *in vitro*. Stroma-conditioned media (S-CM) derived from normal mucosa (normal S-CM) profoundly inhibited CD3/CD28- and mitogen-induced T-cell proliferation and IFN-γ production. In sharp contrast, S-CM derived from inflamed Crohn's disease mucosa (Crohn's S-CM), permitted inducible T-cell proliferation and IFN-γ production. To address this dichotomy, we show that equivalent levels of TGF-β and IL-10 were present in normal S-CM (n=4) and Crohn's S-CM (n= 9), but significantly more IL-6 was present in the Crohn's S-CM than normal S-CM. IL-6-producing mast cells were detected in the lamina propria of Crohn's mucosa but not normal mucosa. Addition of rhIL-6 to normal S-CM reversed the down-regulation of T-cell function mediated by normal S-CM, and pre-incubation of Crohn's S-CM with anti-IL-6 antibodies increased the capacity of Crohn's S-CM to down-regulate pro-inflammatory T-cell function, especially with co-addition of anti-IL-1β antibodies. These novel findings indicate that intestinal stroma/extra-cellular matrix contributes to mucosal homeostasis through cytokine regulation of effector T cell proliferation and cytokine release.

Irons, John Harrison (Harrison)

Project Length	Short
Prior Research Experience	No
Funding Source	Diabetes Research and Training Center
Advisor	Timothy W. Garvey, MD
Title	A skeleton key to insulin sensitivity and inflammation: Osteocalcin effects on cytokine secretion by adipose tissue

Abstract

It has been shown that osteocalcin (a protein secreted by osteoblasts), in particular the uncarboxylated form, (uncOC), can improve insulin sensitivity and regulate adipocyte biology. Furthermore, studies suggest a direct correlation between inflammation, obesity and insulin resistance. In addition, adipocytes have been shown to secrete biologically active molecules, called adipokines, such as tumor necrosis factor-α (TNFα), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), which plays a role in the recruitment of monocytes to sites of inflammation. This led us to hypothesize that osteocalcin (OC) can influence the production of adipose tissue (AT)-derived cytokines. To explore this hypothesis, we performed glucose transport (GT) in isolated adipocytes (IA) from rat periepididymal fat pads. We then measured levels of IL-6, IL-10 and MCP-1 by ELISA in AT and IA treated with 20 ng/mL of carbOC and uncOC for 1 and 3 hours. To assess adipocyte sensitivity in response to insulin we performed dose-response curves to test for effects at submaximal concentrations of insulin and to determine the EC_{50}. Our results showed that 20 ng/mL of OC increased insulin responsiveness and sensitivity as manifest by leftward shift in the dose-response curve and a decline on the EC_{50} (98.3±0.53 x 67.9±1.14, P<0.001). Our findings suggest that IL-10 increases after 1 and 3 hours incubation with uncOC and after 3 hours with carbOC in IA. Conversely, in AT carbOC was more effective to increase IL-10 than uncOC. This same trend was also observed with IL-6 in AT. On the other hand, IL-6 levels were not changed in IA when compared to the control cells. Treatment with uncOC and carbOC resulted in smaller concentrations of MCP-1 at all times both in cells and whole tissue. Our experiments demonstrate that osteocalcin can contribute to improved insulin sensitivity by enhancing the secretion of anti-inflammatory cytokines, such as IL-10, and reducing pro-inflammatory molecules. Decreased MCP-1 levels can minimize macrophage infiltration in adipose tissue resulting in suppressed inflammation. These observations could contribute to a new concept that OC has a direct effect on cellular insulin action and that bone plays a role in the regulation of chronic inflammation seen in obese individuals.

Israel, Daniel James (Daniel)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Baljendra Kapoor and Dr. Jeffery White
Title	Hemoptysis and Bronchial Artery Embolization: A Review of 96 Cases

Abstract

Background: Hemoptysis is the potentially life-threatening coughing up of blood originating from the lower respiratory tract. Though many options – including surgery – currently exist for the treatment of hemoptysis, bronchial artery embolization (BAE) has grown in frequency of use and is considered by many to be the first line of therapy for hemoptysis. It is largely unknown how this procedure may affect different patient populations across the demographics of age, gender, race, and cause of hemoptysis. Methods: Retrospective review of patients' charts was utilized in order to collect data on the aforementioned demographics, the results of each embolization procedure, and the health outcome of each patient. Results: A significant increase in the necessity of additional embolization sessions amongst younger patients was discovered as the average age of individuals who required at least one subsequent BAE was approximately 12 years younger than those whom did not. It was also determined that the necessity for a future BAE increased threefold if a patient required a second BAE. There were no differences in the frequency of additional BAEs found across gender or race. Conclusions: When treating patients with hemoptysis clinicians should be prepared for the increased likelihood that a younger patient will have to undergo an additional BAE following their first and the fact that second BAEs tend to lead to third and forth BAEs.

Iyer, Anand (Anand)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. Ali Ahmed, MD MPH
Title	Uncontrolled Hypertension and Increased Risk for Incident Heart Failure in Older Adults with Hypertension: A Propensity-Matched Prospective Population-Based Study

Abstract

Background: The effect of uncontrolled hypertension on incident heart failure (HF) in community-dwelling older adults with hypertension has not been prospectively examined in propensity-matched studies.

Methods and Results: Of the 5795 Cardiovascular Health Study participants, ≥65 years, 2562 without HF had baseline self-reported physician-diagnosed hypertension and 1391 had uncontrolled hypertension, defined as systolic blood pressure (BP) ≥140 (n=1373) or diastolic BP ≥90 mm Hg (n=18). Propensity scores for uncontrolled hypertension were used to assemble a cohort of 1021 pairs of participants with controlled and uncontrolled hypertension who were balanced on 31 baseline characteristics. Centrally adjudicated incident HF developed in 23% and 26% of participants with controlled and uncontrolled hypertension respectively during 13 years of follow-up (matched hazard ratio {HR} for uncontrolled hypertension, 1.39; 95% confidence interval {CI}, 1.12–1.73; P=0.003). HR's (95% CI's) for incident HF for those with (n=503) and without (n=1539) chronic kidney disease (CKD) were 1.73 (95% CI, 1.26–2.38; P=0.001) and 1.08 (95% CI, 0.87–1.34; P=0.486) respectively (P for interaction, 0.012). Compared with patients with systolic BP <140 mm Hg, HR's (95% CI's) for incident HF associated with systolic BP 140–159 and ≥160 mm Hg were 1.06 (0.86–1.31; P=0.572) and 1.58 (1.27–1.96; P<0.0001) respectively. Among those without CKD, systolic BP ≥160 mm Hg was associated with increased incident HF (HR, 1.33; 95% CI, 1.02–1.74; P=0.036).

Conclusions: Uncontrolled BP has an independent association with new-onset HF in older adults with hypertension, which is more pronounced in those with CKD and with systolic BP ≥160 mm Hg.

Jackson, Justin Myron (Justin)

Project Length	Short
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	Dr. Sadis Matalon
Title	Respiratory Syncytial Virus Predisposes Lung To Injury By Chlorine

Abstract

Introduction: Cl_2 exposure has been shown to cause lung injury by production of reactive oxygen nitrogen species. Respiratory Syncytial Virus (RSV) is the most common cause of lower respiratory tract infections in infants and children worldwide, and is also under-diagnosed as a cause of community acquired lower respiratory tract infection among adults. We hypothesize that RSV infection will render the lung more vulnerable to Cl_2 injury. Methods: BALB/C mice were infected intra-nasally by RSV strain A2 for 96 hours then exposed to 187 ppm Cl_2 for 30 min. Bronchial Alveolar Lavage and flexivent were done 24 hours later, protein concentration, cell counts, cell differentiation and airway responsiveness were measured to evaluate lung injury. Results: Mice infected by RSV then exposed to Cl_2 had significantly higher total cell counts and neutrophils; total airway resistance was also significantly elevated. Conclusion: Pre-existing RSV infection increases lung injury by Cl_2 exposure, suggesting a synergistic effect through enhanced inflammation.

Jaleel, Tarannum

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 short term training grant
Advisor	Dr. Richard Gallo
Title	Antimicrobial Effect of Inactive Vitamin D on Skin

Abstract

In previous studies, it has been shown that keratinocytes stimulated with active Vitamin D have anti-microbial properties against *S.aureus*. Activation of serum 25D3 to 1,25D3 requires two hydroxylation steps that occur in the liver and the kidney. Keratinocytes also express enzymes to activate Vitamin D, specifically CYP27B1 which is a 1-alpha hydroxylase that activates 25D3 by converting it to 1,25D3. It then stimulates keratinocytes to increase the production of cathelicidin, which is a known anti-microbial peptide[AMP]. Cathelicidins serve a crucial role in mammalian innate immune defense against invasive bacterial infections. CD14, which also is induced by this mechanism, acts as a co-receptor for the detection of lipopolysaccharides and other pathogen associated molecular patterns. In this study, we examined the effect of inactive Vitamin D on the AMP activity of human keratinocytes[NHEKs] as well as characterized the effect of stimulation with microbial extracts on the eventual AMP production by NHEKs. We stimulated NHEKs for 24 hours with inactive Vitamin D, inhibitor of Cyp27B1, and *S.aureus* extract and assessed gene expression of cathelicidin and CD14 by RTPCR[Real Time PCR]. We also stimulated NHEKs for 24h with *S.epi, S.aureus*, and MRSA extracts and assessed the ability of supernatant from these NHEKs to kill *S.aureus* delta mprF[more susceptible to AMPs] and MRSA(Methicillin Resistant *S.aureus).* In the last phase we stimulated NHEKs with *S.aureus* extracts, inactive Vitamin D, and inhibitor of Cyp27B1 to assess ability of cell lysates to kill *S.aureus* delta mprF.

The results show a trend towards decreasing bacterial growth and increasing AMP expression in the presence of inactive vitamin D. The supernatant of NHEKs stimulated with bacterial extracts show anti-microbial activity higher than controls. S.aureus extract significantly increases the expression of CD14 and cathelicidin in NHEKs as well as plays an important role in decreasing growth of *S. aureus* delta mprF.

Jarboe, John Stewart (John)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Christopher Willey
Title	Identification of TrkA as a Component of the Radiation-Induced Signal Transduction Pathway

Abstract

Protein kinases have emerged as important targets for treating multiple types of cancer, particularly when combined with other therapies, such as radiation. Because kinases are predominantly regulated post-translationally, genomics and proteomics are indirect methods for assessing kinase activity. Alternatively, a multiplex kinase assay format utilizing peptide arrays is an innovative approach that can provide a global profile of kinase activity ("kinomics") in physiological and pathological states. Here, we have used kinomics to identify novel targets in vascular endothelial cells involved in the response to radiation. Kinomic profiling of human umbilical vein endothelial cells (HUVEC) was performed using PamStation96 microarray (Pamgene, BV) with PTK PamChip. Lysates were prepared 0, 2, 5, 15, 30, and 60 min following 0 or 3 Gy. We identified four distinct sets of differentially phosphorylated peptides in response to irradiation. The most dynamic group represented several receptor tyrosine kinases including ErbB2, EphA and the neurotrophin receptors, TrkA and TrkB. We selected the most robustly phosphorylated peptide (TrkA) for target verification. We plated HUVEC at defined cell numbers and treated them with potent TrkA/Trk family inhibitors for 1 hour prior to irradiation at 0, 3, 5 and 8 Gy. Following 10 day incubation, the surviving fraction (SF) of colonies formed was determined at each condition (Normalized to the SF0 Gy). We found that Trk inhibitors promoted significant radiation protection at nanomolar ranges. Our results provide proof of principle that kinomics can identify novel targets in radiation studies. Inhibition of TrkA resulted in radioprotection and indicates that TrkA is a component of the radiation-induced signal transduction pathway. We are currently working to identify whether activation of TrkA might lead to radiosensitization of vascular endothelial cells. Such a finding might provide a clinically important mechanism through which the tumor vasculature could be targeted in combination with radiation therapy.

Johnson, Erica Monique (Erica)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Foundation for Anesthesia Education and Research
Advisor	Dr. Gwendolyn Boyd, Dr. Sadis Matalon, Dr. Karen Iles
Title	Hypochlorous Acid (HOCl)-Mediated Damage to Human Pulmonary Epithelial Cells

Abstract

Accidental or deliberate release of Cl_2 can cause significant morbidity and mortality. At high concentrations (>50 ppm) Cl_2 molecules or secondary oxidants can penetrate far into the lung and cause extensive damage to the alveolar epithelium leading to inflammation, hypoxemia, pulmonary edema and even death. In the aqueous environment of the lung Cl_2 is converted to HOCl which is thought to mediate much of the damage. To test this hypothesis, and to determine the mechanism(s) of chlorine damage human pulmonary epithelial cells (A549) and rat ATII cells were exposed to increasing concentrations of HOCl (0-500 μM) *in vitro* to model the impacts of chlorine exposure on the alveolar epithelium. Damage (decrease in cell viability) was measured using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Sub-lethal concentrations of HOCl increased whole-cell production of ROS as determined by DCF fluorescence. Mitochondrial ROS production was assayed using MitoSOX Red, which is targeted to the mitochondria and fluoresces when oxidized by superoxide; HOCl also increased mitochondrial ROS production. As ROS production can impact the cellular antioxidant glutathione (GSH) whole-cell GSH was measured following HOCl exposure using the GSH recycling assay. Short exposures depleted GSH which was followed by a subsequent induction. Western blotting confirmed that HOCl increased the amount of both subunits of the rate-limiting enzyme in GSH biosynthesis, glutamate cysteine ligase (GCL). We have determined that HOCl increases ROS and impacts GSH homeostasis. Thus, we have identified a potential mechanism for HOCl-mediated damage to the alveolar epithelium and a potential site of therapeutic intervention (GSH).

Jordan, Stephen James (Stephen)

Project Length	Long
Prior Research Experience	Yes
Funding Source	
Advisor	Julian Rayner
Title	Identification of a Novel Malaria Vaccine: Cross-Reactive Antibodies in a hypoendemic Setting

Abstract

Plasmodium falciparum Merozoite Surface Protein 3 (PfMSP3) is a strong candidate for inclusion in a blood stage vaccine cocktail. Like many merozoite surface proteins, PfMSP3 is polymorphic and vaccine development to date has focused largely on the C-terminal domain, which is more conserved. However, field data suggests that the PfMSP3 N-terminus is much more immunogenic than the C-terminus, and antibodies against the N-terminal domain can correlate with protection from severe malaria. Given that the PfMSP3 N-terminus is polymorphic, it will only be useful as a vaccine target if cross-reactive antibodies can be generated to provide protection against different antigenic variants.

To establish whether such cross-reactive antibodies develop *in vivo*, we have conducted a systematic study of antibody dynamics generated against each PfMSP3 domain in individuals living in a malaria-hypoendemic environment in the Peruvian Amazon. ELISA assays were carried out using two different PfMSP3 N-terminal antigens, based on the currently circulating genotypes present at the study site, as well as a PfMSP3 C-terminal antigen conserved in both alleles. Given the low transmission dynamics (less than one infection per person per year), individuals are usually infected with clonal *P. falciparum* infections spaced many months apart. All the infection samples used in the study have been previously genotyped for PfMSP3 allele and sequence diversity, allowing us to compare the immune response against both the currently infecting PfMSP3 antigen sequence and a PfMSP3 antigen that the individual has not been exposed to for at least one year.

By measuring the strength and isotype profile of antibody responses against each antigen, we have found that there is a level of cross-reactivity between PfMSP3 N-terminal alleles that is equivalent to the reactivity against the PfMSP3 C-terminal antigen and supports the development of a novel N-terminal based PfMSP3 vaccine.

Kozak, Michael

Project Length	Intermediate
Prior Research Experience	Yes
FundingSource	NIH T35 short term training grant
Advisor	Michael Mugavero
Title	Computer-administered Assessment of Mental Health and Substance Abuse Disorders in an HIV Clinic

Abstract

Introduction: Patient Reported Outcomes (PROs) capture data through computer-administered surveys at the point of care. This methodology provides a new paradigm for information capture. Few studies compare PRO data to routinely captured clinical data for domains of interest (e.g., depression). Further, little is known about the prognostic value of PRO data versus clinical data in reference to clinical outcomes.

Methods: A retrospective cohort study included HIV-infected patients at the UAB 1917 HIV/AIDS Clinic receiving antiretroviral (ART) therapy who had completed at an initial PRO between April 2008 and July 2009. In April 2008, the 1917 Clinic initiated PRO capture as a part of routine clinic visits using touch screen computers. Questions assess depression (PHQ-9) and substance abuse (ASSIST). Multivariable logistic regressions were used to evaluate the relationship between these psychosocial domains and self-reported antiretroviral medication adherence (ACTU-4) while controlling for other sociodemographic and clinical factors.

Results: Among 785 study patients, the mean age (+/- SD) was 44.8±10 years, 52% were white, 78% were male, and 19% were uninsured. Diagnostic information capture differed significantly ($p<0.05$). Differences in detection included depression [(n=318, 41%) Chart vs. (n=100, 13%) PRO], current SA [(n=102, 13%) Chart vs. (n=45, 6%) PRO], prior SA [(n=48, 6%) Chart vs. (n=244, 31%) PRO]. In multivariable logistic regression analysis using PROs, significant relationships between depression (OR=1.88, 95%CI=1.09-3.22) and current substance abuse (OR=3.22, 95%CI=1.56-6.67) with ART non-adherence were observed. In contrast, significant relationships were not observed between either depression or substance abuse and ART non-adherence when using medical record diagnoses.

Conclusions: Our data suggest PRO capture of important psychosocial domains may have enhanced prognostic capacity beyond medical record diagnosis when implemented in routine clinical care settings. Electronically administered PROs may prove to be complementary and potentially transformative health informatics technology for the capture of clinical data in routine care settings.

Levin, Elina (Elina)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Steven Rowe, MD
Title	Mucociliary and ion transport in human airway epithelial cells: Effects of a CFTR Potentiator.

Abstract

The relationship between ion and mucus transport in cystic fibrosis (CF) is crucial to understanding the mechanistic basis underlying CF, and could reveal how novel modulators of cystic fibrosis transmembrane conductance regulator (CFTR) dependent ion transport result in clinical benefit. Mutations in CFTR in CF are thought to result in reduced mucus clearance and airway obstruction through volume depletion of the airway surface liquid, and collapse of the mucociliary clearance apparatus. Using fully differentiated primary respiratory human epithelial cells from CF and normal patients, we observed a marked difference in the ion transport properties and mucociliary transport rates (MCT) of CF versus normal patients. CFTR-mediated ion channel activity was measured using short-circuit current measurements under voltage clamp conditions and quantified by the response to the cAMP agonist forskolin. MCT was analyzed using the linear velocity of fluorescent microspheres and time frame imaging. We then evaluated the effects of VX-770, a CFTR potentiator currently in Phase III testing in CF patients harboring the G551D-CFTR, a mutation that confers a severe channel gating defect. VX-770 (10μm) potentiated wild-type CFTR dependent ion transport by augmenting the response to forskolin by 100% ($p < 0.05$). Moreover, MCT rates were robustly augmented by addition of VX-770 (20-fold increase in basal transport rate after 24 hours, $p<0.001$). This was accompanied by an apparent increase in the airway surface liquid volume, (~10μL in control treated cells vs, ~ 30μL in VX-770 treated cells). These results suggest the mechanism by which VX-770 ion transport properties result in an increase in lung function after 14 days of treatment in CF subjects with the G551D CFTR mutation is a potent mobilization of inspisated mucus. As noxious exposure from tobacco smoke has been reported to reduce CFTR dependent ion transport in vivo, we also studied these effects in our model. CFTR dependent anion secretion was reduced by 35% with 24 hour exposure to 2% smoke extract, and was dose dependent ($p<0.05$). MCT also decreased (5 fold over control with 4% CSE, $p<0.05$) with the addition of CSE. Our model suggests the presence of a tightly controlled relationship between MCT rate and CFTR dependent ion transport. Moreover, augmented CFTR dependent ion transport with VX-770 in CF results in a clinical benefit likely through conferring a robust increase in MCT, and could also apply to other disease with reduced CFTR function, such as smoke induced lung disease.

Lewis, Travis Benjamin (Travis)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	David G. Standaert, MD/PhD, David T. Curiel, MD/PhD
Title	Coxsackie and Adenovirus Receptor Expression Dictates Neuronal Tropism in the Mouse Substantia Nigra

Abstract

Adenovirus (Ad) incorporates many useful properties as a gene therapy vector, including large packaging capacity, persistence without integrating into the host genome, and an array of tropism modifications capable of changing its cellular targeting. In this regard, we considered its utility as a gene therapy vector in Parkinson disease (PD). A number of clinical trials utilizing adeno-associated virus (AAV) are currently underway, providing rationale to continue development of enhanced delivery vectors. Inherent limitations with AAV prompted us to explore the utility of Ad in this context, including understanding its capacity to deliver payload to degenerating neurons of the substantia nigra (SN). To investigate this, we first assessed the native distribution of Ad5 delivered stereotactically to the C57BL/6 mouse SN. Close analysis showed no SN colocalization. To understand the basis for these results, we assessed the distribution of the coxsackie and adenovirus receptor (CAR), the natural receptor for Ad serotype 5 (Ad5). Evaluation of CAR expression showed minimal staining in the SN. This finding provides rationale to explain why Ad5 is not seen to infect SN neurons, but does not discount the possibility that SN neurons have an intrinsic resistance to Ad5 infection. We utilized the hCAR transgenic mouse—used to predict the outcome of Ad infection once an appropriate targeting modification is developed—to answer this question. Dual immunofluorescence showed that delivery of Ad5 to the SN of the hCAR mouse expands Ad tropism to multiple CNS cell types, including SN neurons. Thus, the limiting factor in Ad gene therapy for PD is surface receptor binding, not an intrinsic property of SN cells. Based on these results, our lab is assessing the ability of tropism-modified Ad vectors to infect SN neurons in non-transgenic mouse brain. This work represents the starting point for the development of viable Ad-based PD gene therapeutics.

Lin, Victor

Project Length	Long
Prior Research Experience	Yes
FundingSource	NIH Medical Scientist Training Program Grant
Advisor	Fang-Tsyr (Fannie) Lin
Title	TRIP6 Mediates Cell Cycle Progression Through $p27^{KIP1}$

Abstract

TRIP6 is a focal adhesion molecule belonging to the zyxin family of LIM-domain containing proteins. In addition to localizing to focal adhesions and actin stress fibers in the cytosol, it is also known to shuttle to the nucleus, which suggests a regulatory role in addition to any structural role it may play. TRIP6 is highly expressed in several cancer tissue types and knockdown of TRIP6 in multiple cancer cell lines results in a phenotype that includes prolonged time to confluence and impaired adhesion and motility. Cell cycle analysis of synchronized and propidium iodide-stained U373-MG human glioma cells revealed a delay in S-phase entry when TRIP6 was knocked down versus scrambled siRNA control. Additionally, western blot analysis of similarly synchronized cells showed that the CDK inhibitor $p27^{KIP1}$, an important prognostic factor in a variety of cancers, is highly expressed in siTRIP6-expressing cells. We show that $p27^{KIP1}$ binds directly to TRIP6 and that TRIP6 expression mediates the nucleocytosolic shuttling of $p27^{KIP1}$, but does not regulate its transcription. As $p27^{KIP1}$ is able to regulate the G1/S checkpoint, we hypothesize that TRIP6 facilitates S-phase entry by modulating $p27^{KIP1}$ function.

Lopker, Michael John, Jr (Mike)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. George Shaw
Title	Identification, Molecular Cloning and Characterization of Mucosally Transmitted SIVsmE660

Abstract

Background: Single genome amplification (SGA) followed by direct amplicon sequencing of plasma vRNA or PBMC vDNA allows for the unambiguous identification of transmitted/founder (T/F) viruses responsible for productive SIV/HIV infection (J Exp Med 206:1117, 2009; ibid 206:1273, 2009). Molecular clones of mucosally transmitted SIVsm strains could facilitate transmission, pathogenesis and prevention research in the SIV-rhesus macaque model, especially for SIVsmE660 where wide variability in virus replication patterns and clinical outcome follows low-dose mucosal inoculation of the uncloned virus isolate.

Methods: SGA-direct amplicon sequencing of plasma vRNA was performed so as to infer T/F viral genomes in two Indian rhesus macaques acutely infected by low-dose rectal inoculation of SIVsmE660. Proviral genomes corresponding to T/F viruses were molecularly cloned by amplifying, cleaving and ligating into low-copy plasmid vectors 5' and 3' half-genomes from PBMC-associated vDNA. Large-scale preparations of cloned viral DNA were resequenced to confirm their identity prior to transfection into 293T cells.

Results: Proviral clones pE660.CG7G.ir1 and pE660.CG7V.ir1 were 10,283 and 10,286 nt in length, 99.5% identical, and contained nine intact canonical structural and regulatory genes. Transfection of 293T cells yielded virions that were infectious and replication competent in JC53bl-13 cells and in human and rhesus CD4+ T-cells, where virus titers reached 2x10e9 vRNA/ml six days after inoculation at an MOI of 0.01. 10e9 virions corresponded to 100ng p27, 10e6 I.U. in JC53bl-13 cells, and 10e4 I.U. in rhesus PBMCs.

Conclusions: Infectious molecular clones of mucosally transmitted SIVsmE660 viruses responsible for productive clinical infection were generated and their genomic integrity and biological functionality confirmed. This proof-of-concept result opens the way for the identification, cloning and in vitro and in vivo testing of novel, genetically-diverse T/F strains of SIVsm for transmission, pathogenesis and prevention research. pE660.CG7G.ir1 and pE660.CG7V.ir1 may serve as genetically-defined heterologous challenge strains for SIVmac239 vaccinated animals.

Love, Christopher Scott (Scott)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	
Advisor	Dr. John Arnold (NMCSD) and Dr. David Kimberlin (UAB)
Title	Comparison of Maternal and Child Hepatitis B Antibodies at 18-48 Months Postpartum

Abstract

Objective: Worldwide, as many as 2 billion people may be infected with Hepatitis B. Since the implementation of recommendations to immunize routinely against hepatitis B in 1991, there has been a 67% reduction in HBV infections in the United States. In order to prevent both perinatal infection and primary infection in young adults, the immunization program targeted newborns, infants, and adolescents. The infant HBV vaccine schedule consists of 3 injections and is generally completed around 6 months of age. Maternal antibodies generally persist for at least 6 months. The potential for inactivation of Hepatitis B vaccine components by maternal antibody has been suggested.

Methods: Children 18 to 48 months of age who were having blood drawn for clinically indicated reasons, or who were undergoing routine anesthesia were eligible. Blood was simultaneously collected from child/mother pairs and tested for the presence of quantitative HBsAb, qualitative HBcAb, and qualitative HBsAg. The quantitative HBsAb levels between mothers and children were compared.

Results: 41 mother/infant pairs were recruited. Five pairs were excluded due to lab errors, previous infection, or inability to draw blood. Of the 36 mother/infant pairs included, the overall vaccine efficacy was 88%. There were no detectable differences in vaccine efficacy between mothers who did and did not have HBsAb. The average HBsAb in children of mothers with levels of HBsAb exceeding 500 were lower than those mothers whose HBsAb was between 1 and 500 (98 IU/L vs 326 IU/L, p=0.045).

Conclusions: Although this study was limited by small size and was not prospective, our data support the concept that maternal antibody may interfere with antibody production following the infant Hepatitis B immunization series. While there was no difference in non-responders to vaccine, the association between high maternal HBsAb and lower infant HBsAb warrants further study.

Love, Rozalyn Grace Farmer (Rozalyn)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Kimberly H. Hoover, MD; Kerri S. Bevis, MD
Title	Medical Student Knowledge, Experiences, and Attitudes about Midwifery

Abstract

OBJECTIVE: To examine the relationship between medical student knowledge and attitudes about midwifery at an urban academic medical center.

METHODS: An anonymous electronic survey containing 27 questions evaluated 1) students' knowledge and experience with midwifery 2) their attitudes regarding midwifery practice, and 3) their interest in further education in this area. Wilcoxon Rank-Sum and Chi-square tests evaluated the difference in attitudes among informed and uninformed students.

RESULTS: The survey was sent to 688 undergraduate medical students with a response rate of 32% (n=223). Forty-nine students (22%) were considered informed and were likely to be older, in their clinical years of training, and have completed their OB/GYN clerkship ($p<0.01$). No statistically significant difference between level of knowledge and attitudes were demonstrated; however, only 2% of students correctly answered >50% of the knowledge questions. Forty-nine percent of students indicated interest in attending an out-of-hospital birth during medical school and 47% felt discussion of midwifery should be included in the pre-clinical curriculum.

CONCLUSION: Medical students are poorly informed about midwifery practice. Therefore, no statistically significant difference between knowledge and attitudes was found. Despite limited background education, students are interested in learning opportunities that include out-of-hospital birth and midwifery care.

Love, Rozalyn Grace Farmer (Rozalyn)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Alice R. Goepfert
Title	Pregnancy Outcomes in Single Active-Duty Military Women

Abstract

OBJECTIVE: To determine pregnancy outcomes in active duty (AD) single and married women at a large military treatment facility.

METHODS: This cohort study reviewed delivery records from 2004-2008 for AD nulliparous women with singleton births at Naval Medical Center San Diego. Total prenatal visits, total weight gain, pregnancy complications, delivery at <37 weeks gestation, mode of delivery, birth weight <2500g, 5 min APGAR score <7, neonatal intensive care unit (NICU) admissions, and type of feeding were evaluated to determine the effect of marital status.

RESULTS: Two thousand six hundred and nine deliveries met inclusion criteria for this study. Thirty-nine percent of births occurred in single women (n=1,017). Single women were significantly younger (23 v. 25 yrs), have less total weight gain than married women (37lbs v. 38lbs), fewer prenatal visits (9 v. 10 visits), fewer cesarean births (22% v. 27%), and are more likely to bottle-feed (15% v. 10%); all with $p<0.05$. No statistically significant difference was found between single and married women in pregnancy complications, birthweight <2500g, deliveries at <37 weeks, 5 min APGAR score <7, and NICU admissions.

CONCLUSION: In this large contemporary study, the prevalence of births to single AD women is high. This study confirmed that marital status does not significantly impact pregnancy outcomes in AD women. Targeted efforts to improve breastfeeding rates among single AD women are indicated. Further research is needed to investigate the propensity for increased weight gain and cesarean section rates among married active-duty service women.

Mason, Alexis Tanishia (Alexis)

Project Length	Short
Prior Research Experience	Yes
Funding Source	HSF Community and Rural Health Fellowship
Advisor	John Wheat, MD, MPH; James Leeper, PhD
Title	Agromedicine for the Deep South

Abstract

The Alabama Agromedicine Project was initiated by Dr. John Wheat and Dr. James Leeper to address health care concerns and risks of Alabama's farm community. This research takes a partnership approach involving academics with both the farm community and other agencies in the conduct of the research and use of its findings. The Rural Medical Scholars Program, Alabama Cooperative Extension System (ACES), and West Alabama poultry farmers were initial partners. Starting in a largely Caucasian farm population in West Alabama, the project produced a questionnaire that was approved and piloted with poultry farmers. The questionnaire takes a broad approach to soliciting farmer concerns about health, risks, and medical care. A policy committee that represents the farmers directed and reviewed the pilot study, endorsed continued use of the questionnaire, and suggested that the African American farm community be included. This poster details my experience in helping to establish a relationship with the African-American farming community, solidify a questionnaire, obtain pilot information, and report results of this pilot study. It also includes the continuation of the project after the former was completed and future steps. This information should have special relevance for these agromedicine partners and for expansion of this approach throughout Alabama and the Delta Region.

Mayhew, David L.

Project Length	Long
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Marcas Bamman, PhD
Title	The mRNA Translation Factor eIF2Bε is Translated by an Internal Ribosome Entry Site (IRES)

Abstract

mRNA translation occurs by either a 5'-cap-dependent or cap-independent (IRES-dependent) mechanism, which are regulated by distinct mechanisms. The eukaryotic initiation factor (eIF) 2B is a 5 subunit complex that is required for cap-dependent translation initiation. The ε subunit of eIF2B is the catalytic subunit of the complex, and its cellular content has been shown to significantly affect overall protein synthesis rates, which is dysregulated in cancer and muscle atrophy. Moreover, eIF2Bε content is itself regulated at the level of translation. Preliminary evidence in our lab suggested that eIF2Bε translation does not occur by a canonical cap-dependent mechanism. Therefore, we hypothesized that eIF2Bε was translated by an IRES. The 5' untranslated region (UTR) of mouse or human eIF2Bε was cloned into a bicistronic reporter driving firefly luciferase expression, while renilla luciferase expression was driven by cap-dependent translation on the same mRNA molecule expressed in C2C12 myoblasts. Both 5'UTRs displayed IRES activity that was dynamically regulated in response to various cell stresses that are known to decrease cap-dependent translation rates. ER stress induced by tunicamycin or thapsigargin caused as much as a 30-fold increase in IRES activity, while rapamycin treatment increased IRES activity by 1.4-fold. Analysis of the 5'UTR of eIF2Bε revealed a stretch of 24 bases that was 100% identical among 7 mammalian species, while the remainder of the 5'UTRs showed less identity. Deletion of this consensus region resulted in 96% reduction in IRES activity, suggesting this region is required for full IRES activity. This is the first evidence that the translation of eIF2Bε, which affects overall cap-dependent translation rates, is translated by a cap-independent mechanism in response to cell stresses, and this activity is regulated by a consensus region in the 5'UTR. Identification of this mechanism of eIF2Bε translation will provide novel targets to combat oncogenic growth and muscle atrophy.

McAnnally, John-Ryan Griffin (John-Ryan)

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Henry Wang, M.D., M.P.H.; Randolph Devereaux, M.P.H.
Title	Impact of Population Characteristics and Area Healthcare Resources on Mortality Variation in the US

Abstract

BACKGROUND: While mortality rates vary widely across the United States (US), the population and societal characteristics associated with this variation remain unknown. Knowledge of the factors underlying mortality variation could identify areas for individual or community mortality reduction efforts. We sought to determine the association between population and area healthcare resource characteristics and all-cause mortality in the US.

METHODS: We identified US all-cause mortality rates using the Centers for Disease Control and Prevention Compressed Mortality File (CMF), a national registry of all US deaths. We combined data from 1999-2005, calculating age-adjusted mortality incidence at the county level. Using 2000 data from the HRSA Area Resource File (ARF), we determined county-level population and healthcare resource characteristics, including the number of minority, unemployed, impoverished (persons below poverty threshold), uninsured and undereducated populations (highest education <12th grade), and the numbers of doctors, hospitals, critical care hospitals and hospital beds per person. Using multivariate linear regression, we determined the associations between county-level population and area healthcare resource characteristics and all-cause mortality, defining significant associations as characteristics with $p<0.05$.

RESULTS: County-level all-cause mortality varied across the US (median 1,126 per 100,000, IQR 997-1,213.6, range 469.7-2,245.6). County-level population and area healthcare resource characteristics also varied across the US: minorities median 9,035 per 100,000(IQR 2,923-26,206), unemployed 1,205(484-2,688), impoverished 3,817(1,678-8,555), uninsured 13,818(10,807-17,215) and undereducated 48,283(44,195-53,810), number of doctors 99.6(55.4-184.6), number of hospital beds 198(0-402), and number of critical care hospitals 0.24(0-2.18). On multivariate analysis, poverty ($p<0.001$), education ($p<0.001$), insurance status ($p<0.001$) number of doctors ($p<0.05$), and number of critical care hospitals ($p<0.005$) were independently associated with mortality.

CONCLUSIONS: Poverty, education, insurance status, and the availability of doctors and critical care hospitals are associated with mortality. Population characteristics and healthcare access may explain variations in US mortality.

McClugage, Samuel Gardner, III (Trey)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Corinne Griguer, Ph.D
Title	Mitochondria Dysfunction and Multidrug Resistance in Human Gliomas

Abstract

Mitochondria play a central role in cellular energy production, apoptosis and free radical generation. Because of these important roles, malfunctions of mitochondria have been associated with the development of many cancers, including gliomas. Glioblastoma multiforme (GBM), in particular, is the most common primary intracranial neoplasm and its almost uniform lethality is exemplified by a median survival of 12-15 months in diagnosed patients. Typical treatment uses a combination of surgery, radiotherapy and chemotherapy (Temozolomide), however recurrence still occurs in nearly 90% of GBM patients. One cause of this poor outcome is the development of a multidrug-resistance (MDR) phenotype, associated with proteins such as Major Vault Protein (MVP). Due to the over-expression of MVP in several P-glycoproteins (P-gp)-negative chemoresistant cancer cell lines, MVP has been linked to MDR. Accordingly, high levels of MVP were found in tissues chronically exposed to xenobiotics. Using mitochondrial DNA (mtDNA) knock-down glioma (ρ0) cells, we tested whether mtDNA plays a role in the development of the MDR phenotype, in particular with resistance to temozolomide (TMZ). We showed that mitochondria-depleted glioma cells were up to 10 times more resistant to TMZ-induced apoptosis than parental sensitive cells. Sensitivity was also restored in trans-mitochondrial cybrids. Affimetrix gene array indicated that transcripts for major MDR proteins, in particular Major Vault Proteins (MVP), were significantly up-regulated in ρ0 cells ($p<0.01$), which was confirmed using standard western blot and immunocytochemistry techniques. We next tested whether MVP expression correlated with the degree of TMZ resistance by generating TMZ-resistant glioma cells from sensitive cells. TMZ resistant cells expressed higher levels of MVP compared to the sensitive parental cells. These studies provided new insight into the role of mitochondria in controlling the MDR phenotype via MVP. Our results are relevant to understanding the drug resistance response in cancer cells and could affect patient care by identifying novel predictors of MDR in glioblastoma patients.

McCluskey, Suzanne Michelle (Suzanne)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Max Cooper, M.D. and Goetz Ehrhardt, Ph.D.
Title	Development of Novel High-Avidity Fusion Proteins

Abstract

Joining the Fc-domain of immunoglobulin G (IgG) with a fusion partner of interest is a common technique to generate recombinant proteins. Detecting the binding of the dimeric IgG-fusion proteins to cell surface molecules typically requires a relatively high affinity for the cell surface receptor. Here we demonstrate that fusion of the extracellular domain of PD1L to the multimeric variable lymphocyte receptor (VLR), a sea lamprey derived analog to mammalian antibodies, results in high-avidity proteins that interact specifically with PD1 expressing cells from human tonsillar tissues.

To generate these novel high-avidity fusion proteins, a portion of the VLR invariant stalk region was combined with the extracellular domain of PD1L using recombinant DNA technology. A 6-His epitope tag was inserted between the two gene segments to facilitate purification of the recombinant protein. Once the DNA constructs were generated, they were cloned into the expression vector pcDNA3.1 and were transfected into 293-T cells. The resulting fusion proteins were analyzed via SDS-PAGE western blots to verify their expression, secretion, and multimerization. The PD1L/VLR-B fusion proteins were used to stain cell lines transfected with PD1 and primary tonsillar lymphocytes, which endogenously express PD1. The cells were co-stained with lineage markers and analyzed by flow cytometry.

Our results demonstrate that the VLR-B stalk is a suitable scaffold for fusion partners that contain immunoglobulin domains. The strong binding observed with these recombinant proteins makes them ideal tools for the analysis of low-affinity interactions that may not be seen using the standard IgG-based fusion proteins. This proof of concept study shows that high-avidity VLR-B fusion proteins may be useful in several areas of molecular and cellular biology and may prove to have biomedical applications as well.

McNeil, Whitney

Project Length	Short
Prior Research Experience	No
FundingSource	Departmental or Mentor funds
Advisor	Stefan Kertesz, M.D.
Title	Survey of Homeless Service Agents: Homeless Access to Health Care

Abstract

Background: In 1995 and 2005, surveys were administered to homeless persons in the Birmingham area to assess their access to healthcare. There was an increase for 32% to 54% in homeless persons who reported having trouble receiving the care that they needed. Objective: Survey homeless service agencies in Greater Metropolitan Birmingham to assess how easy or difficult it is for their homeless clients to obtain access to health care. Methods: A survey was created and electronically distributed through Surveymonkey.com to homeless service agencies. The agencies first rated how easy or hard it was to get care for their clients based on a list of common health problems. They were then asked to rank how easy or hard it was for their clients to get healthcare based on health care providers. A total of 13 surveys were collected from agencies over a one month period.

Results: When asked how often they encounter obstacles seeking care, 38.5% occasionally encounter obstacles when seeking care and 23.1% encounter obstacles several times a day. Healthcare problems that were rated as “very difficult” for patients to obtain care were: long term care, specialized doctors, dental, psychiatric, and medications. When asked “why was it difficult to get care” at health care providers, responses included: transportation, cost, and long weight. Conclusion: There are specific health care problems that are more difficult for homeless persons in the Greater Metropolitan Birmingham to obtain care for. Also, there are health care establishments that are very difficult and others that are very easy for the homeless population to obtain care from. We were also able to identify some of the specific obstacles that contribute to the difficulty in the homeless patient’s ability to gain access to health care.

Merino, Aimee Marie (Aimee)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Kaslow
Title	KIR Gene Polymorphisms in HIV-1 Infection

Abstract

Killer Immunoglobulin-like receptors play an important role in innate and acquired immunity as receptors on natural killer cells and some subsets of T cells. Genetic polymorphisms in these genes have been implicated in both autoimmune and infectious diseases. Recent work has indicated that certain KIR genes or haplotypes influence various aspects of HIV-1 pathogenesis; including risk of acquisition, viral load, and time to progression to AIDS.

This study analyzed 506 Zambian couples that were serodiscordant for HIV-1 at the time of enrollment. Clinical data was collected quarterly for HIV status, the presence of genital ulcers and/or inflammation, and viral load (in seropositive participants). In cases of transmission, viral strains between the donor and recipient partner were compared to ensure that transmission occurred within the couple. None of the participants were on anti-retroviral therapy throughout the study period.

A KIR SSP kit was used to determine the presence or absence of 17 KIR genes and allelic variants of 2 KIR genes (*KIR2DS4* and *KIR2DP1*). Genes were tested for effects on transmission and viral load. We discovered that the allele *KIR2DS4*001* is associated with an increased risk of HIV-1 transmission (RH=1.641, ρ=0.010), even after controlling for other salient factors (genital ulcers, viral load). Our analysis did not reveal a statistically significant affect of *KIR2DS4*001* on viral load. It is uncertain how *KIR2DS4*001* might affect HIV-1 transmission or if it is actually serving as a marker of another gene. We are currently working to determine the mechanism of this finding with the hope that a better understanding of how host genetics affect HIV-1 transmission will aid future vaccine development.

Miller, William Ryan (Ryan)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Stuart J. Frank
Title	Liberation of Growth Hormone Binding Protein and its Effects on Growth Hormone Signaling

Abstract

Growth hormone (GH), a key regulator of postnatal growth, elicits its effects by binding to the extracellular domain (ECD) of the GH receptor (GHR) found on tissues like liver, muscle, and fat. This interaction activates cytoplasmic tyrosine kinase, JAK2, and the intracellular signal transducer and activator of transcription (STAT)-5 to affect gene expression. Cellular response to GH is greatly influenced by receptor abundance, as well as the circulating level GH binding protein (GHBP), which is liberated by cleavage of the ECD of the GHR via metalloproteolytic cleavage. GHBP acts as a soluble receptor, reducing the amount of GH available to bind to the GHR. GH has also been shown to stabilize the GHR, preventing cleavage by metalloproteases such as TNF-α converting enzyme (TACE).

Our aim was to develop reagents for the purpose of examining GHR cleavage in an *in vivo* mouse model and to characterize GHBP's effect on GH signaling. In efforts to characterize the shedding of GHBP and its effects on GH signaling, either C14 cells (a human fibrosarcoma cell line that stably expresses rabbit GHR and JAK2) or 3T3-F442A cells (a preadipocyte cell line that expresses endogenous GHR) were treated with PMA or PDGF to liberate GHBP and the media were harvested. Separate cells were treated with these media to determine the effect of GHBP on GH signaling. Western blot analysis of cell lysates showed that the presence of GHBP led to a decrease in STAT5 phosphorylation in response to GH. GH treatment also lead to an increase in receptor abundance following metalloproteolytic cleavage due to stability of the engaged receptor.

Milteer, Hugh B, Jr (Hugh)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Robert Bourge
Title	Low Risk of Intracerebral Hemorrhage With Adjunctive IIb/IIIa Inhibitors in Ad-hoc Carotid Stenting

Abstract

Background. The adjunctive use of glycoprotein IIb/IIIa inhibitors in pre-procedural anti-platelet therapy in carotid artery stenting (CAS) has been widely reported to cause an increase in complications, particularly intra-cerebral hemorrhage. We hypothesize that the adjunctive use of IIb/IIIa inhibitors in carotid stenting does not increase the risk of intracerebral hemorrhage.

Methods. A retrospective review was conducted on 469 consecutive patients who underwent ad-hoc CAS between August,1999 and December, 2008 at Baptist Medical Center – Princeton, Birmingham, Alabama. Of these, 454 patients were administered a IIb/IIIa inhibitor as adjunctive anti-platelet therapy. Patients were eligible if they had neurologic symptoms and >50% stenosis of the common or internal carotid artery or no symptoms and >80% stenosis. Except where contraindication precluded their use, all patients received anti-platelet therapy consisting of aspirin and a thienopyridine (ticlopodine or clopidogel) and IIb/IIIa inhibition with either eptifibatide (n=454) or abciximab (n=2). Anti-coagulant therapy consisted of bivalirudin, heparin or a combination of both. All but 11 of the cases since 2002 were performed with cerebral protection catheters.

Results. There was one (0.22%) case of intracerebral hemorrhage. He was a 70 year old Caucasian male with a positive history of multiple strokes and was symptomatic for multiple risk factors and comorbidities. Anti-thrombotic therapy consisted of 325mg of aspirin, 600mg of clopidogrel, a single bolus and infusion of bivalirudin as well as adjunctive use of a single bolus of eptifibatide. A right carotid artery stent was successfully deployed. The patient exhibited signs of altered consciousness approximately 30 minutes post-procedure and a CT showed a massive ipsilateral intracranial hemorrhage. Other complications in the series included death (0.88%), ischemic stroke (1.32%), trans-ischemic attack (TIA) (1.10%), hyperperfusion syndrome (1.54%), and access site bleeding (3.29%).

Conclusions. Peri-procedural antithrombotic therapy consisting of aspirin, thienopyridine, bivalirudin and eptifibatide does not increase the risk of intracerebral hemorrhage.

Mitra, Arnab (Arnab)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Christine Curcio
Title	Correlation of SD-OCT Imaging and Histological Staining in Pathology Identification in ARMD eyes

Abstract

Objective: Macular Degeneration is one of the leading causes of vision loss in the elderly. The two forms, dry and wet (exudative), can present with distinct features of pathology in the retinas and maculas of donor eyes. Some of these features can include geographic atrophy and the presence of drusen-like deposits.

Spectral Domain Optical Coherence Tomography (SD-OCT) imaging is a relatively new modality and has become more prominent in non-invasive detailed imaging of the retina. Its main advantage over other current techniques is the speed in which the device can capture the image with an adequate resolution.

The purpose of this project was to establish conditions for sequential SD-OCT imaging and histological analysis of ARMD-affected donor eyes, preliminary studies to identify specific ARMD pathology by SD-OCT and histology (e.g., drusen, basal deposits, sub-retinal debris, fibrovascular scar).

Methods: Trephined pieces of eye donor tissue (including the macula and optic nerve head) were sutured into a tissue holder. This holder was oriented properly and placed into another holder with a 60D lens, which was aligned in the path of the light beam from the SD-OCT imaging device. Section and volume scans were performed with each sample of tissue. These images were then saved and analyzed.

Results: Upon analysis of the images captured, the distinct layers of the retina were seen with striking clarity. Normal donor eyes were imaged to visualize certain features that could serve as landmarks for each tissue specimen. Some of the latter that were observed include the optic nerve head with surrounding vasculature and arcuate fibers. Geographic atrophy and edema were observed in diseased eyes. Retinal layers and topographic features could be identified with agreement among observers.

Conclusion: The method used in this experiment is a useful way of determining the SD-OCT correlation to histologically-defined features in normal and ARMD retinas.

Moseley, Carson Edward (Carson)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. Robert G. Webster & Dr. Peter C. Doherty
Title	TNF/iNOS-producing dendritic cells—the necessary evil of lethal influenza virus infection

Abstract

Recently, a new H1N1 Swine-Origin Influenza Virus (S-OIV) was isolated from humans in North America and has subsequently developed into the first influenza pandemic of the 21st century. While seasonal influenza epidemics generate a heavier disease burden among geriatric and infant populations, pandemic influenzas—including S-OIV—often cause more severe disease in young, immuno-competent individuals. This paradox has led to the hypothesis that pandemic and other highly pathogenic influenza viruses induce immune-mediated pathology, characterized by the exuberant production of cytokines and chemokines and the enhanced recruitment of innate inflammatory cells.

Here, we show that challenging mice with virulent influenza A viruses, including H1N1 and H5N1 strains, causes the increased selective accumulation of a particular dendritic cell subset, the TNF/iNOS-producing dendritic cell (tipDC), in the pneumonic airway. These tipDCs are required for the further proliferation of influenza-specific $CD8^+$ T cells in the infected lung, because blocking their recruitment in $CCR2^{-/-}$ mice decreases the numbers of $CD8^+$ effectors and ultimately compromises virus clearance. However, diminution rather than total elimination of tipDC trafficking by treatment with the type II diabetes drug pioglitazone moderates the potentially lethal consequences of excessive tipDC recruitment without abrogating $CD8^+$ T cell expansion or compromising virus control. Targeting the tipDCs in this way thus offers a new possibility for therapeutic intervention in the face of a catastrophic pandemic.

Muzaffar, Wasef Kabiruddin (Wasef)

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Silvio Litovsky
Title	Predictive Value of the Extent of Fibrosis in the Progression of Dilated Cardiomyopathy

Abstract

Dilated cardiomyopathy is a primary myocardial disease characterized by dilatation and impaired ventricular systolic function. Fibrosis has been well described in these hearts but the effect, if any, of this pathologic feature on the progression of pump failure and risk of sudden death is unknown. The main objective of this retrospective project is to compare the speed of progression of disease (as assessed between the beginning of symptoms and the listing for transplantation) and the requirement of defibrillator therapy between the patients with the highest magnitude of myocardial fibrosis with those with the lowest degree of fibrosis. To that effect, fibrosis was quantified by histomorphometry utilizing the Bioquant Image Analysis Software on picrosirius red stained sections of left ventricular free wall and septum (average of 5 sections per patient). Thirty consecutive patients that underwent allograft cardiac transplantation between 2004 and 2009 at the University of Alabama at Birmingham for terminal dilated cardiomyopathy were studied. The patients were divided in 2 groups, one half with the highest and one half with the lowest degree of fibrosis. Preliminary data analysis indicate that patients with the highest degree of fibrosis had a longer time course between diagnosis and transplantation than patients with less fibrosis suggesting that fibrosis per se does not portend a worst prognosis. In addition, patients with the highest extent of fibrosis had more prevalence of diabetes and chronic renal failure but less mitral regurgitation than patients with less fibrosis. Since the vast majority of the patients of both groups received a cardioverter defibrillator, no significant difference in the use of the device was noted between the two groups. If confirmed in larger number of cases, the study might have major implications since 1. Anti-fibrotics like TGF-β antagonists have been proposed to delay progression of the disease and 2. The factor/s responsible for the occasional major improvement of patients with advanced heart failure weaned off mechanical support is/are yet not understood.

Nguyen, Nguyet Anh (Nicki)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	John Shacka
Title	Characterization of the Autophagic Lysosomal Pathway in Traumatic Brain Injury

Abstract

Traumatic Brain Injury (TBI) affects 1.4 million people each year and is associated primarily with mild behavioral and cognitive changes, in addition to a predisposition for developing neurodegenerative disease. Neuronal damage occurs from shearing forces of injury and is characterized by diffuse axonal injury (DAI), as indicated by the aberrant localization of amyloid precursor protein (APP) to axons, as well as multiple types of neuron death. The autophagy lysosomal pathway (ALP) is a highly regulated macronutrient recycling pathway and when altered has been shown to contribute to cell death. Alterations in the ALP have been documented in experimental models of TBI but whether the ALP contributes to TBI-induced neuropathology is unclear. The tumor suppressor protein p53 has also been shown to be altered following TBI and may regulate the ALP as well as neuron death. We hypothesize that the ALP regulates neuronal injury following TBI which is in part p53-dependent. Retinoic acid-differentiated SH-SY5Y human neuroblastoma cells were grown in elastic wells, and injury (ranging from 0-42 psi) was applied using a mechanical stretch injury device. Cells were lysed 24h after injury for western blot analysis. LC3-II, the lipidated and cleaved form of LC3 and selective marker of autophagic vacuoles (AVs), was increased following stretch injury. Damage regulated autophagy modulator (DRAM), a protein that senses macroautophagy and is required for p53-dependent cell death, p53 phosphorylation and total p53 all appear to increase following stretch injury. Results also indicate injury-dependent increases in APP, suggesting possibly the onset of DAI. Together these findings support a role for alterations in the ALP in an in vitro model of TBI, which may be related to alterations in p53 and the onset of DAI. Ongoing studies are being performed to delineate the ability of p53 and the ALP to regulate DAI and neuron death following TBI.

Niyongere, Sandrine

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES program
Advisor	Dr Hui Xu
Title	The role of Slit2 expression in the activation of epithelial-mesenchymal transition in tumor samples

Abstract

Epithelial-mesenchymal transition (EMT) is a developmental program that is often activated during cancer invasion and metastasis, and plays an important role in normal embryogenesis. Recent studies have found that tumor metastasis is often enabled by EMTs in which cancer cells exhibit self-renewal capability that is seen in normal stem cells in order for the cancer cells to metastasize. During the activation of EMT, it has been found that certain epithelial markers on cells are elevated such as SNAI1, TWIST1, and SLUG while others markers such as E-cadherin are reduced. *Slit2* is a secreted glycoprotein that regulates cell migration and is a part of the *Slit* gene family. Several studies have shown that *Slit2* expression is silenced in several cancers such as cervical, colon, breast, and lung cancer. It has been shown that expression of *Slit2* inhibits tumor cell invasion and migration as well as promotes programmed cell death. We used tumor tissue samples that had been transfected and are expressing *Slit2*. We hypothesize that the tumors expressing *Slit2* will suppress the activation of EMT since *Slit2* inhibits tumor cell invasion and migration as well as induces programmed cell death[2]. Using immunohistochemistry and western blot analysis, the level of expression of previously reported epithelial markers indicating EMT activation were measured in tumor tissue samples in order to determine if *Slit2* expression will reduce the expression of these epithelial markers. The results were inconclusive on whether *Slit2* expression prevents activation of EMT. Further experiments need to be conducted using more sensitive antibodies for these epithelial markers as well as optimizing the protocol for immunohistochemistry in order to evaluate the role of *Slit2* expression on EMT activation.

Nolte, Ryan Nicolas

Project Length	Short
Prior Research Experience	Yes
FundingSource	NIH T35 short term training grant
Advisor	Shannon M. Bailey, PhD
Title	Increased Arginase 1 Protein in Nonalcoholic Fatty Liver Disease and Implications for Nitric Oxide B

Abstract

Decreased nitric oxide (NO) bioavailability has been implicated as a key mediator in obesity and diabetes related pathologies in the vasculature, kidney, and liver. Liver NO concentration is determined by its production and degradation. Arginase 1 (Arg1), a key enzyme of the urea cycle, hydrolyzes arginine to urea and ornithine in liver. Thus, Arg1 has the potential to decrease hepatic NO levels. Previously, we reported disrupted NO metabolism in nonalcoholic fatty liver disease (NAFLD); however, the effect on Arg1 is unknown. Herein, we test the hypothesis that NAFLD mediated disruption in NO metabolism and signaling may be related to an increase in Arg1 protein. For this, Arg1 protein levels were measured in liver samples from Zucker fatty rats +/- pioglitazone (PGZ) treatment (10 mg/kg/day for 3 weeks). For comparison, liver Arg1 levels were also measured in *ob/ob* mice and C57BL/6 mice fed a high fat diet (HFD) for 8 and 16 weeks. PGZ treatment decreased serum glucose, insulin, free fatty acids, and triglyceride levels in Zucker fatty rats to control levels. Liver Arg1 levels were significantly elevated in Zucker fatty rats compared to controls, with PGZ having no effect on Arg1. Arg1 levels were also increased in liver from *ob/ob* mice with smaller increases observed in liver of C57BL/6 mice fed a HFD for 8 and 16 weeks. In conclusion, these studies show for the first time an increase in Arg1 protein in multiple models of NAFLD. This finding suggests that obesity and/or diabetes may reduce hepatic levels of NO due to decreased arginine availability following increased arginine degradation via Arg1. Alterations in arginine metabolism may be an important factor in the initiation and progression of NAFLD. Therefore, Arg1 represents a promising new target for further investigations aimed at identifying the molecular mechanisms of NAFLD pathobiology.

Nwaobi, Sinifunanya Elvee (Sini)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. David Standaert and Dr. Andrew West
Title	Neuroinflammatory role of LRRK2 in Parkinson's Disease

Abstract

Mutations in leucine-rich repeat kinase (LRRK2) gene is the most common genetic cause of late-onset Parkinson's disease (PD). The exact function of LRRK2 as well as its role in the pathology of PD remains unclear. Here, we begin to examine a potential neuroinflammatory function of LRRK2. Based on the pathological role of monocytes and microglia cells in PD and their expression of LRRK2, we utilized a human acute monocytic leukemia cell line (THP-1) to study the effects of LRRK2 on cytokine expression. By use of lipopolysaccharide, we induced a highly immunogenic response within THP-1 cells. mRNA was isolated and changes in LRRK2 and various cytokine expression were measured using quantitative polymerase chain reaction (Q-PCR). Lentiviral knock down of LRRK2 allowed us to compare expression of various cytokines with and without LRRK2. Our data show that with the significant knock down of LRRK2, there is a striking reduction in the expression of several cytokines. This study suggests that there is a neuroinflammatory function of LRRK2 and opens the door for greater exploration into the specific role of LRRK2 in PD.

Odom, Carl Irwin (Carl)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. James Markert and Dr. Jackie Parker
Title	Construction of a Conditionally Replicating HSV Vector that Expresses IL-15 As a Vaccine Adjuvant

Abstract

The overall objective of the laboratory is to construct novel, $\gamma_1$34.5-deleted Herpes Simplex Virus Type 1 (HSV-1) vectors that express a variety of immune-modulating genes for use as anti-tumor agents or vaccine adjuvants. One example is M002, a $\gamma_1$34.5-deleted HSV engineered to express murine IL-12. Tumor-bearing mice treated with M002 demonstrated significantly improved survival versus treatment with non cytokine-expressing viruses. The multifunctional cytokine interleukin 15 (IL-15) is thought to potentiate a more durable anti-tumor effect through the induction of immunologic memory against tumor cells. Tumors treated with IL-15 have demonstrated increased anti-tumor activity, reduced metastasis, and prolonged survival in animal models.

The goal of this project was to construct a $\gamma_1$34.5-deleted Herpes Simplex Virus Type-1 (HSV-1) that expresses the immunomodulatory protein IL-15 for evaluation as a tumor vaccine adjuvant. The first step was to construct shuttle plasmids that specifically targeted two separate loci within the HSV-1 genome: (1) the diploid $\gamma_1$34.5 gene and (2) the U_L3/U_L4 intergenic region. Successful construction of these shuttle plasmids was confirmed by restriction enzyme digest analysis and PCR amplification. These plasmids were then co-transfected with viral DNA from the parent virus and recombinant viruses selected for IL-15 by loss of dsRed or Green Fluorescent Protein (GFP) expression. A total of three rounds of plaque selection and purification has been completed and candidate recombinant viruses are currently being confirmed using Southern blot hybridization analysis.

Once the genotype of the recombinants has been confirmed correct, the virus will be characterized for both in vitro and in vivo IL-15 expression, and its efficacy tested in vivo as a tumor vaccine adjuvant.

Orr, Mary

Project Length	Short
Prior Research Experience	
Funding Source	NIH T35 Summer Training Grant, IDSA ERF Medical Scholarship
Advisor	Herrick J. Siegel, MD, Associate Professor of Surgery
Title	Factors associated with missed outpatient HIV visits: First steps in developing a clinical prediction rule

Abstract

Introduction: Factors related to appointment adherence in an HIV setting are largely unknown, and "no show" visits are common. Patient Reported Outcomes (PROs) capture computer-administered surveys at the point of care, and may provide a fast and simple method to identify patients at increased risk for a next visit "no show."

Methods: A retrospective cohort study at the UAB 1917 HIV/AIDS Clinic included patients who completed at least one PRO and had a subsequent appointment between April 2008 and July 2009. The PRO uses validated measures of medication adherence (ACTU-4), substance abuse (ASSIST), and tobacco use among other domains. Univariate analysis of sociodemographic and psychosocial factors identified variables associated with a "no show" appointment status after completing a PRO at the previous visit. A multivariate logistic regression model then analyzed statistically and clinically significant factors.

Results: Among 844 study patients, 128 patients (15%) had a "no show" visit. A multivariate analysis modeling "no show" status included age, race/ethnicity x sex relative to white male [black/other male OR=1.91, 95%CI=1.17-3.26, white female 2.42, 1.14-5.12, black/other female 2.27, 1.24-3.26], insurance status, substance abuse, tobacco use, a prior appointment visit status ["no show" OR=2.14, 95%CI=1.36-3.38)], and not currently taking ART [OR=1.88, 95%CI=1.19-2.96]. The Hosemer Lemeshow goodness-of-fit P-value is 0.37, and the C-statistic is 0.69 for the multivariate model, indicating reasonable fit and model discrimination.

Conclusion: Race/ethnicity and sex other that white males, prior appointment "no show" status, and patients not currently taking ART are significantly associated with subsequent "no show" visit status. These variables represent a first step in creating a point-of-care appointment adherence prediction rule. With increased emphasis on expanding HIV adherence beyond medications to include retention in care, such a prediction rule may have important implications for future research and clinical care.

Pardi, Brandon Michael (Brandon)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Herrick J. Siegel, MD, Associate Professor of Surgery
Title	Use of Foam Acetabular Components for Periacetabular Bone Loss with Primary Total Hip Arthroplasty

Abstract

The management of extensive bone loss in the periacetabular region remains a challenging problem. Frequently, concurrent problems are also present including leg length discrepancy, soft tissue contracture and poor regional vascularity. This study evaluates the use of foam metal backed components in the reconstruction of patients with massive bone periacetabular bone loss due to trauma, chronic infection and metastatic bone disease. Between January 2004 and January 2008, 39 patients were included and followed for a minimum of 1 year. The patients were reconstructed using titanium foam acetabular cups. A review of medical records, clinical examinations and imaging studies were performed. Functional outcome was assessed using the Harris (0-100 scale, 100 being best) and Oxford Hip Scores (12-60 scale, 12 being best), radiographic assessment to determine loosening and osteolysis, as well as perioperative complications were recorded. Functional results were excellent (Oxford <15; Harris >90) in 35 patients, good in 3 patients (Oxford 16-30; Harris 80-90), fair in 1 patient (Oxford 32, Harris 74). One patient was treated for a deep infection. The components were retained in this patient and he was successfully treated with intravenous antibiotics and surgical debridement. Two of 39 exhibited a Trendelenburg gait. Thirty-six of 39 patients were ambulating without assistive devices at 1 year and of the 33 patients with 2 year follow up all were ambulating without assistive devices. Leg length discrepancy was able to be corrected in 37 of 39 to within 1 cm (range 2 – 5 cm; avg. 3.1 cm). Two of 33 patients had radiographic loosening; both were noted to be loose within the initial 3 months following surgery. All 22 hips (100%) with 4 year follow up were radiographically stable. Foam metal backed acetabular implants appear to enhance initial stability and maintain durable bone ingrowth in patients with severely compromised periacetabular bone.

Parrish, Nicholas Fredric (Nick)

Project Length	
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Beatrice Hahn
Title	A rev1-vpu polymorphism in HIV impairs envelope glycoprotein expression and pseudovirion infectivity

Abstract

Functional analyses of Human Immunodeficiency Virus Type 1 (HIV-1) envelope glycoproteins (Envs) commonly include the generation of pseudoviruses which are produced by co-transfecting an *env* expression vector with an *env*-deficient proviral backbone. Here we show that a polymorphism in the intergenic region between the first exon of *rev* (*rev1*) and *vpu* can reduce Env expression from *rev-vpu-env* cassettes and generate pseudovirions with markedly impaired infectivity. Characterizing a panel of transmitted/founder Envs, we identified six subtype C constructs that were defective in the pseudotyping assay; however, two of these ostensibly defective Envs produced fully infectious virus when expressed in the context of their cognate proviruses. To explain these paradoxical results, we compared the gene arrangement of defective and functional *rev-vpu-env* cassettes. This analysis revealed that all defective constructs exhibited a polymorphism that placed *rev1* and *vpu* into the same reading frame without an intervening stop codon. Disruption of this *rev1-vpu* fusion gene by frameshift, in-frame stop codon, or abrogation of the *rev* initiation codon restored pseudovirion infectivity to wildtype levels. In contrast, introduction of the *rev1-vpu* fusion gene into wildtype constructs severely compromised their function. The phenotypic defect was not due to reduced *env* or *rev* transcription, mRNA stability, or a dominant negative effect of the expressed fusion protein. Instead, the defect was caused by inefficient Env translation from fusion gene containing *rev-vpu-env* transcripts. These findings indicate that the *rev1-vpu* polymorphism does not adversely affect viral replication *in vivo*, but impairs Env expression from subgenomic expression *in vitro*. This can cause problems in studies requiring Env *trans* complementation, such as analyses of co-receptor usage and neutralization properties, since about 19% of subtype C and 3% of subtypes A viruses encode this polymorphism. A simple solution to this problem is to eliminate the *rev* initiation codon in the forward primer when amplifying *rev-vpu-env* cassettes because this increases Env expression independent of the polymorphism.

Pattanaik, Elora (Ellie)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Myriam Peralta, M.D.
Title	Use of Exclusion Diets on Children with Autism Spectrum Disorders (ASD)

Abstract

The number of children diagnosed with Autism Spectrum Disorder (ASD) is increasing. No definite cure exists for ASD; therefore, an increasing number of parents seek alternative therapies. One proposed therapy is use of exclusion diets, such as the gluten-free and/or casein-free diet. Currently, there is no scientific evidence on benefits of the use of this diet. We explored the use of exclusion diets in children diagnosed with ASD, impact on the family, and perceived benefits of the diet.

Children diagnosed with ASD by an expert in autism were eligible for the study. Children were between 2-14 years of age. Parents of these children were contacted; those who agreed to participate were interviewed regarding use of the diet and other forms of therapy. Data was entered and analyzed with parametric and non-parametric tests using SPSS.

28 parents of children with ASD participated in the survey. 15 (53%) reported to have never tried the diet; 13 (46.4 %) have tried the diet; 5 (17.9%) were currently on the diet. There were no significant differences in socio-demographic characteristics of the group who had tried the diet and the group who had not tried the diet, except for race; 11 of the 13 (84.6%) who had tried the diet were of Caucasian race. Comparing the group who had tried the diet and discontinued versus those still on the diet, we found no major differences in socio-demographic characteristics. Neither group reported improvements in communication, cognition, motor, tactile sensitivity, or empathy. The group still on the diet reported improvements in attention and anxiety. In those who had tried the diet, difficulties were reported regarding financial restrictions, accessibility of gluten/casein-free products, and the effect on family members' diets. A significant number of parents of children with ASD have tried the gluten-free and/or casein-free diet. A majority of these parents discontinue the diet, due to lack of improvement in addition to the mentioned difficulties associated with using the diet.

Pickens, Mekeisha Renae (MeKeisha)

Project Length	Short
Prior Research Experience	No
Funding Source	Diabetes Research and Training Center
Advisor	Dr. Nefertiti H. Durant
Title	WALKFIT: The Efficacy of Moderate Intensity Exercise in the Promotion of Weight Loss and Prevention

Abstract

Obesity rates continue to rise in the US, particularly among African American women. Increasing physical activity in this vulnerable population may both decrease early adulthood weight gain as well as the risk of chronic diseases such as type 2 diabetes that would occur later in adult life. The aims of this study were: (1) To assess the effects of a supervised moderate-intensity exercise program on fat mass, waist circumference (WC) and Body Mass Index (BMI) in African American women and (2) To assess associations between factors that may moderate the effect of supervised exercise. Eligible female African American UAB students aged 19-30 with a BMI $\geq$ 25 kg/m^2 were randomly assigned to the exercise intervention or control group. Controls received informational brochures on the benefits of exercise. The intervention group walked three miles per day four days per week at a moderate intensity pace for three months. All participants were instructed to keep their diet the same. Pre- and post-measures evaluated for all participants included: assessment of WC, body composition (DEXA scan), and BMI as well as surveys on diet, sedentary behavior, and daily PA. Independent, two-sample *t*-test analysis revealed that the amount of moderate to vigorous physical activity (MVPA) in days per week increased in the intervention group (3.2 ± 1.0; n = 6), while the amount of sedentary behavior (screen time) decreased in the intervention group (-1.2 ± 6.5 n = 6) (p=0.006). There were no significant differences in BMI, WC, or fat mass. Future studies should examine whether longer moderate intensity PA interventions in this population with and without dietary components would additionally produce the desired anthropometric outcomes of decreased BMI, WC, and fat mass.

Planz, Virginia Barnes (Virginia)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Mark Lockhart and Dr. Lincoln Berland
Title	Common Bile Duct Dilatation in Post-cholecystectomy Patients

Abstract

Background: Compensatory dilatation of the common bile duct in post-cholecystectomy patients has been a controversial issue in the surgical, radiographic, and sonographic literature. Further study is needed to define the normal limits of common bile duct diameter in post-cholecystectomy patients with long-term follow-up. Unlike prior sonographic studies, our review examines the common bile duct before and greater than two years after cholecystectomy, offering long-term follow-up after surgery. Also, our comparison of CT and ultrasound measurements of the common bile duct has not been previously done, and it may add useful information in the evaluation of these patients.

Purpose: This retrospective review will evaluate the diameter of the common bile duct in patients pre- and post-cholecystectomy with at least two years of sonographic follow-up post-surgery to determine the normal diameter of the common bile duct in post-surgical patients.

Method: Abdominal sonograms obtained previously in the Department of Radiology during the years of 2002-2008 will be reviewed on the KinetDx archive system, and sonographic or CT images and reports as well as laboratory analysis (liver enzymes, bilirubin, etc.) will be reviewed on Centricity/Horizon/CDA. Patients who have had an abdominal sonogram and another abdominal sonogram or abdominal CT within two years of their cholecystectomy are included in this study, and their imaging and medical records will be reviewed. The common bile duct diameters of patients without cholecystectomy will be compared to those who have had interval cholecystectomy and also compared to patients who have had remote history of cholecystectomy. Comparison of abdominal sonographic and CT measurements will be made in the few that have both study types.

Results: During the years 2002-2008, 32,814 sonographic studies were obtained. Of those studies, 1412 had at least two abdominal ultrasounds within an interval of two years or greater. The vast majority, 82.6%, had an intact gallbladder. Of the minority without a gallbladder, 80.5% also had at least one abdominal CT study. At the time of writing this abstract, all studies are still undergoing evaluation.

Poholek, Catherine Helen (Katie)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Laurie E. Harrington, Ph.D.
Title	The Role of Twist1 in the Regulation of Inflammation During Colitis

Abstract

Inflammatory Bowel Disease (IBD) is a group of chronic inflammatory disorders that result from a dysregulation between intestinal flora and the mucosal immune system and affect an estimated 1-2 million people in the United States. Current treatment options have unsatisfactory results, significant side effects, and are non-curative. Th1 and Th17 CD4+ T cells have been implicated in the disease pathogenesis of IBD but the regulation of these cell populations remains unclear. The aim of this study was to examine the role of a potential regulator of inflammation and its effects on the pathogenesis of IBD. *Twist1* is a transcriptional repressor that has been implicated in the immunomodulation of Th1 cells. Here we use two murine models of IBD to investigate the role of *twist1* in colitis. In one model the regulatory cytokine IL-10 is knocked out and mice spontaneously develop colitis. In another model $CD4^{+}CD45Rb^{hi}CD25^{-}$ cells are transferred into Recombination Activating Gene (RAG)-deficient mice and mice develop colitis within eight weeks. In this study we examined the expression of *twist1* in various CD4 cell populations by inducing CD4 naïve cells towards a specific phenotype using a cocktail of cytokines. *Twist1* was found to be upregulated in chronically activated Th1 cells by Real-Time PCR and Western blotting. We also examined lymph nodes and colons of mice with colitis for expression of twist1 by immunofluorescence. Our data suggest that *twist1* is upregulated in chronically stimulated Th1 cells in a colitis setting. We believe this upregulation may be the body's attempt at regulating or reducing inflammation in the diseased state. Further investigation into the role of *twist1* in colitis and other autoimmune-mediated diseases may yield clinically relevant data that could lead to new and more efficacious treatments for colitis.

Qadri, Muhammad Yawar (Yawar)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dale J Benos
Title	Acid Sensing Ion Channel-1 Inhibitors

Abstract

Acid sensing ion channels (ASICs) are a family of proton gated cation channels expressed predominantly in neuronal tissue. These pH sensors are capable of transducing changes in the extracellular [H^+] into changes in membrane potential and intracellular cation concentration, primarily sodium but in some cases also calcium. These capabilities, combined with neuronal expression, have implicated them in fundamental processes such as the sensing of pain or taste as well as important pathologies in the CNS such as ischemic stroke and invasive cancer. The known pharmacological inhibitors of the ASICs are limited to naturally occurring peptides and small molecules. However, the clinical utility of peptides for treatment of the CNS disorders is limited and the small molecule inhibitors lack the specificity and potency of the peptides. This work leverages computational methods and recent crystal structures of chicken ASIC-1 to identify small molecules that are capable of inhibiting human ASIC-1. Using homology modeling and protein docking, a model of hASIC-1 was docked with the well described peptide inhibitor Psalmotoxin-1, a toxin found in the venom of the Chevron Tarantula. The predicted docking site was verified with mutagenesis and electrophysiology to be formed by the interaction of hASIC-1 subunits. Small molecule docking was then performed with a known small molecule inhibitor, amiloride, and other structurally related molecules. From the docking reports, predictions regarding the relative potency of the drugs were functionally tested. Reagents previously classified as inhibitors of sodium transporters were found to also inhibit hASIC-1. From the functional and computational results, as well as prior published data, putative interaction sites for amiloride have been defined. These results demonstrate that computational methods can be used to help identify novel small molecule ASIC-1 inhibitors.

Record, Jessica (Jessica)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Aaron Hamvas, MD (Washington University in St. Louis School of Medicine)
Title	Detection of Rare, Surfactant Associated Gene Variants in Adults with Interstitial Lung Disease

Abstract

Rare mutations in the genes encoding surfactant protein C (*SFTPC*) and ATP-binding cassette family submember A3 (*ABCA3*) have been associated with interstitial lung disease (ILD) in children and lethal surfactant deficiency in newborns. One common mutation, a valine substitution for glutamate (E292V) has been identified in 3.8% of a newborn respiratory distress syndrome cohort. Population-based analyses of *SFTPC* and *ABCA3* have demonstrated that the frequency of deleterious variants in *SFTPC* is rare, but may be as high as 2% for *ABCA3*. The prevalence of variants in these genes in children or adults with ILD is unknown. Pooled sample next generation sequencing was used to determine the frequency of genetic variants in *SFTPC* and *ABCA3* in adults with ILD compared to a control group and population-based frequencies. Computerized algorithms (SIFT and PolyPhen) were used to predict functional effects of the amino acid changes encoded by non-synonymous single nucleotide polymorphisms (SNPs). In *SFTPC*, a total of 42 SNPs (25 promoter, 3 non-synonymous, 14 intronic) and a total of 7 insertion/deletions (3 promoter, 4 intronic) were found. In *ABCA3*, a total of 81 SNPs (4 splice site, 8 synonymous, 7 non-synonymous, and 62 intronic) were found. Out of these, the rare *SFTPC* variant L181V was only present in 2 cases and thus may be associated with ILD in adults. Rare functional variants in *ABCA3*, especially R709W, are also over-represented in adults with ILD. Assuming rare variants are all on unique alleles in *ABCA3*, 17% of ILD patients have a deleterious *ABCA3* mutation, while only 4% carry a deleterious mutation in the controls. In a previous observation, the population based frequencies of functional mutations in 1100 individuals from the state of Missouri was only 2%, which strongly suggests that these *ABCA3* mutations are linked to developing ILD later in life.

Reeves, Shari Nichelle (Shari)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Cunningham Fellowship (Pediatrics)
Advisor	Brian Sims MD PhD
Title	Cystine Glutamate Exchanger Upregulation by Retinoic-Acid

Abstract

Background: The incidence of neonatal brain injury is devastating in its lasting medical implications and in the lack of treatment options available. A possible therapeutic strategy may be found in retinoic acid, a lipophilic molecule that has been investigated for its neuroprotective properties. Preliminary experiments in our lab have shown that all-trans retinoic acid (ATRA) upregulates the cystine glutamate exchanger, system Xc. System Xc couples the cellular intake of cystine, the precursor for the antioxidant glutathione, with the release of glutamate. Studies have shown glutathione to be an important antioxidant necessary for the defense of brain cells from oxidative stress and glutamate-mediated excitotoxicity.

Purpose: We hypothesize that retinoic acid confers neuroprotection through the upregulation of System Xc.

Methods: B104 neuroblastoma cell cultures were plated on T25cm flasks for 24 hours prior to treatment. ATRA was added at 100nM concentration and cells were harvested at the appropriate time point. Experimental paradigms included either treatment with the system Xc inhibitor S4CPG, glutamate, or kainic acid. Standard Western Blot analysis was performed using xCT, glutathione, and cleaved-caspase 3 primary antibodies.

Results: B104 neuroblastoma cells showed an increase in expression of xCT in the presence of ATRA. This increase was also correlated with an increase glutathione production and neuroprotection. In the presence of a system Xc inhibitor, retinoic acid failed to induced and increase in glutathione production.

Conclusions: All-trans retinoic acid causes an upregulation in system Xc that we believe is correlated with glutathione mediated neuroprotection. Inhibition of system Xc prevents ATRA induced glutathione upregulation and neuroprotection.

Reish, Nicholas Joseph (Nicholas)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Gavin Rumbaugh
Title	Low expression of SynGAP1 as a model of abnormal neocortical development

Abstract

Intellectual disabilities, autism and certain psychiatric illnesses are believed to arise from abnormal development of brain circuits. The refinement of connections in sensory cortices is dependent upon NMDA receptor (NMDAR) activation. As such, these channels and associated signaling pathways are attractive candidates to control processes that underlie the wiring of neocortical circuits during critical periods of brain development. However, it is still an open question how association areas of the cortex connect to each other during childhood. SynGAP, a synaptically enriched protein with both RasGAP and RapGAP activity, is downstream of NMDARs and regulates synaptic structure and function. In addition, this protein has been implicated as a cause of non-syndromic mental retardation and is reduced in persons with schizophrenia. Therefore, we broadly hypothesize that this protein is critical for functional connectivity between brain regions during development, and, as a consequence, the emergence of normal behaviors during childhood. To begin to test this hypothesis, we subjected SynGAP heterozygous mutant mice to a battery of tests designed to uncover behavioral abnormalities that model autism and schizophrenia. The results from this extensive behavioral testing demonstrated an array of abnormalities. The behavioral endophenotype of the SynGAP mutant was strikingly similar to that of mice with reduced function or expression of NMDARs. Some of these abnormities included reduced pre-pulse inhibition, enhanced startle responses, reduced socialization, novelty-induced hyperactivity and severely deficient spatial working memory. In addition, these mice were less responsive to psychomotor effects of NMDAR antagonists, further suggesting that some of these abnormal behaviors are related to NMDAR hypofunction. Functional analysis of prefrontal cortex in brain slices demonstrated that circuits in this area have abnormal spread of neuronal activity between layer5/6 and layer 2, indicating these cortical micro-circuits are disorganized. Interestingly, many of these abnormal behaviors were present as early as 3-4 weeks of age, suggesting that SynGAP is necessary for the development of circuits that control fundamental behaviors. Our immediate future studies are aimed at understanding how the brain adapts during development to abnormal levels of SynGAP proteins by comparing structural and functional measures of circuits before, during and after the critical period of development.

Rodriguez-Feo, John Anthony, III (John)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Rena Stewart
Title	Development of an Infected, Open Fracture Model with MRSA and Acinetobacter in a Rat

Abstract

Background

High-energy open fractures are common injuries where current treatment is sub-optimal and frequently plagued with complications including poor function, osteomyeltitis, and possible amputation. Making matters more complex, multiple-drug resistant bacteria have emerged as a difficult problem in today's world of healthcare.

Objective

The purpose of this study was to create a model that reliably reproduces an infected, open fracture in a small, cost-effective mammal that may be used to evaluate various treatment options with relevance to both civilian and military injuries.

Methods

The surgical procedure consisted of creating a mid-diaphysis femur fracture using a drop weight apparatus, tissue ischemia at fracture site using compression, and periosteal stripping using cautery. The defect was then stabilized and innoculated using *Acinetobacter buamannii* and MRSA. Phase I determined the appropriate dose for osteomyelitis where Phase II repeated the procedure using dose information from Phase I. A control receiving no bacteria was also conducted. Radiographs on post-operation day 0, 7, 14, 21, and 28 and microbiological and histopathlogical analysis on the femurs after sacrifice on day 28 were used to determine osteomyelitis.

Results

Phase I: A 50% mortality rate at and above the critical threshold of MRSA $1x10^6$ CFU/mL and *A. baumannii* at $1x10^6$ CFU/mL was observed. A high dose group of MRSA at $1x10^6$ CFU/mL and *A. baumannii* at $1x10^5$ CFU/mL and a low dose group of MRSA at $1x10^5$ CFU/mL and *A. baumannii* at $1x10^5$ CFU/mL were selected for further testing.

Phase II: The high dose group exhibited the greatest amount of radiographic signs of osteomyelitis at 79%. 43% of the low dose group and 0% of the control group exhibited signs of osteomyelitis at 3 weeks. Four-week radiographs along with microbiologic and histologic results are not currently available.

Conclusion

Our results show a reliable, reproducible, cost-effective open fracture model for use in a small mammal.

Roebuck, Natalie Victoria (Natalie)

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Nathaniel Robin M.D.
Title	Timing of cleft palate surgery and speech outcome.

Abstract

BACKGROUND: The predominance of current literature supports the concept that palate repair prior to one year of age produces the best outcomes. The purpose of this study was to look at a population of patients with delayed closure of cleft palates and compare their outcomes to those of populations closed prior to one year, with emphasis on fistula rate and speech outcome.

METHODS: A retrospective, time-series cohort of 93 consecutive patients greater than the age of recommended closure at time of primary two-flap palatoplasty (average age 37.5 months). The main outcome measures were immediate postoperative complications, oronasal fistula rate, and speech. A perceptual speech evaluation was performed by two speech pathologists and included hypernasality, nasal emission, articulation, intelligibility, and overall velopharyngeal competence. The need for secondary palate surgery for velopharyngeal insufficiency was also analyzed.

RESULTS: There were some differences in postoperative complications between the two study groups. Postoperative morbidity in the delayed closure population occurred in 3 patients (3.2 percent) and consisted of three patients with a fistula in the junction of the hard and soft palate and no airway or bleeding complications. This is compared to two patients with oronasal fistulas (1 percent) in the early closure population. Including the patients with fistulas, there were 6 patients (2.8 percent) overall in the earlier closure group with complications. The remainder consisted of two patients with respiratory compromise and two patients who required reoperation for bleeding. Perceptual speech evaluation demonstrated significantly better speech outcomes in early closure (83.3 percent in the early closure versus 57.5 percent in the delayed closure, $p = 0.05$) but no significant differences between the rates of secondary palate surgery for velopharyngeal insufficiency (10 percent versus 6.7 percent, $p = 0.483$).

CONCLUSIONS: This study demonstrates that delayed closure of cleft palates does not significantly alter the outcomes of speech development and postoperative morbidity. This is despite the study design limitations, such as experience bias and follow-up differences.

Rutherford, John Matthew (Matt)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Rita Cowell
Title	Transcriptional regulation of parvalbumin

Abstract

Schizophrenia is recognized as a functional deficit of cerebral cortex, as working memory (a product of prefrontal cortex) is deficient across schizophrenia subtype. Adverse events in development have been widely accepted to play a role in schizophrenia etiology. Cortical development occurs throughout childhood and adolescence. Sensory cortex has well-described "critical periods" of plasticity during which patterns of connectivity are established, followed by relative inflexibility for the duration of life. These occur early in life; critical periods for higher order processes later in development have been hinted at for higher-order processes. Involvement of abnormality in such a critical period in prefrontal cortex has been proposed for schizophrenia.

Parvalbumin, whose expression is consistently reduced in schizophrenic brain, is a calcium-binding protein characteristic of a particular GABAergic interneuron subtype, which synapse on the somata and axon initial segment of pyramidal cortical neurons. Parvalbumin buffers calcium at presynaptic terminals, giving this subtype a characteristic fast-spiking, non-accommodating output. These characteristics provide parvalbumin+ neurons with control of critical period closure in visual cortex. Thus, alteration of parvalbumin expression might contribute to cortical abnormalities in patients with schizophrenia.

We have found that regulation of parvalbumin is responsive to the transcriptional coactivator PGC-1α (peroxisome proliferator activated receptor γ coactivator 1α), which itself follows a distinct developmental time course in rat. Mice lacking PGC-1α show greatly reduced cortical parvalbumin expression, and cells transfected with PGC-1α experience a robust upregulation of parvalbumin.

Here we explore PGC-1α's regulation of parvalbumin expression in SH-SY5Y (a neuroblastoma) cell line. To do this, we want to determine both the genomic elements required for PGC-1α-dependent induction and the factor(s) that mediate this process.

Saag, Harry Switow (Harry)

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Crayton Fargason
Title	Children's Hospital of Alabama and the Case Mix Index

Abstract

The Case Mix Index (CMI) is a metric that reflects the severity of illness (SOI) of patients treated at a hospital. Its purpose is to answer the question, “How sick are the patients in this hospital?” The CMI is used for several purposes, most importantly, for re-imbursements from 3rd party payers and to normalize hospital quality data for benchmarking comparisons. Children's Hospital (CH) in Birmingham, Alabama serves as a tertiary care referral center for the state and southeast. Remarkably, its CMI was the lowest in the nation among all Children’s Hospitals (N=40) in 2007. Thus, it was suspected that CH was underreporting the true acuity of its patients leading to an inappropriately low CMI.

The first step was to identify how other hospitals were reporting the SOI of their patients compared to CH. It was determined that other institutions were more accurately coding their patients illnesses to the maximum extent possible under coding guidelines, whereas CH was routinely under-coding their patients. Evaluation of UAB hospital’s coding process was initiated to learn how they ensured the accuracy of their CMI reporting. Columbia Children’s Hospital in New York was also evaluated to assess their process, as they have one of the highest CMI’s in the nation.

The findings were compiled into a presentation describing CH’s difficulties in accurately reporting the hospital’s CMI as well as how other hospitals managed these issues. Suggestions regarding what CH could do to improve its operations were included. This information was presented to CH physicians during their monthly medical forum meeting; to the residents during their weekly conference; and to CH’s upper administration, including their CFO and COO. Several of the proposed changes have already been implemented. Improved accuracy of CH’s CMI is anticipated and the change in ranking among other Children’s hospitals in the network will be used as the primary metric of success.

Schreeder, Daniel Martin (Daniel)

Project Length	Long
Prior Research Experience	No
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Randall Davis
Title	Biological characterization of Fc Receptor-like 6 (FCRL6) – an inhibitory receptor for MHC class II

Abstract

Members of the Fc receptor-like (FCRL) family are cell-surface proteins with ancient conservation, distinct lymphocyte expression patterns, and tyrosine-based signaling capabilities that imply a fundamental role for them in modulating immune responses. Though they share many features with the Fc receptors (FCR) for IgG and IgE, FCRLs have not been found to bind immunoglobulin. In these studies, we sought to characterize the cellular expression pattern, the binding partner, and the function of a recently identified FCRL family member, human FCRL6.

By developing FCRL6-specific monoclonal antibodies (mAbs) we determined that FCRL6 is distinctly expressed by cytotoxic lymphocytes, namely NK cells, $CD8^+$ T cells, gd T cells, and rare cytotoxic $CD4^+$ T cells. Using a cell-based GFP reporter system to assay FCRL6 surface receptor engagement we were able to identify that FCRL6 binds to HLA-DR, an MHC class II molecule. This was interaction was confirmed by generating a panel of HLA-DR-reactive mAbs that blocked the FCRL6 interaction and by demonstrating specific binding of a soluble FCRL6-Fc molecule to HLA-DR transductants. Furthermore, we found that by blocking the FCRL6/HLA-DR interaction, $CD8^+$ T cell function could be enhanced in response to antigenic peptide stimulation. Additionally, forced expression of FCRL6 in a human NK cell line inhibited its killing of HLA-DR-expressing cells. Collectively, these studies demonstrate that FCRL6 is an inhibitory receptor for MHC class II expressed by cytotoxic lymphocytes. These findings reveal an intriguing evolutionary relationship between receptors for immunoglobulin and MHC and demonstrate that NK cells and $CD8^+$ T cells, whose activities are traditionally considered to be governed by MHC class I interactions, are also functionally regulated by MHC class II. This newfound interface may have important implications for better understanding HLA class II disease association and its manipulation could be of therapeutic benefit to patients with disorders of cell-mediated immunity.

Schuster, Daniel (Daniel)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Bradford A. Woodworth, MD
Title	Quercetin Increases Transepithelial Chloride Transport in Primary Murine Nasal Epithelial Cultures

Abstract

Objectives: Evidence indicates that decreased mucociliary clearance (MCC) is a major contributing feature of rhinosinusitis. Increasing epithelial chloride (Cl^-) secretion represents a method for promoting MCC through augmentation of the airway surface liquid. Several naturally occurring flavonoid compounds have demonstrated the capacity to increase transepithelial Cl^- transport. Quercetin is a flavonoid compound that exhibits well-known antioxidant and anti-inflammatory activity. However, the Cl^- secretory properties of quercetin have yet to be fully investigated.

Methods: Well-characterized primary murine nasal septal epithelial cultures were mounted in modified Ussing chambers for examination using pharmacologic manipulation of ion transport. Short-circuit current measurements representing transepithelial Cl^- transport were measured in response to the administration of quercetin to the mucosal and serosal sides of the cultured monolayers and compared to controls.

Results: The changes in Cl^- stimulated current (ΔI_{SC} -expressed as mA/cm^2) in cultures exposed to quercetin (26.26+/-8.03) were significantly greater than the DMSO control solution (2.02+/-1.18, p=0.00003). Furthermore, quercetin increased ΔI_{SC}, after the administration of forskolin, a cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel activator, when compared to forskolin alone (23.23+/-5.44 vs. 2.47 +/- 1.62, p=0.000004). Total inhibition of Cl^- transport by the specific CFTR inhibitor INH-172 was greater in the quercetin treated cultures compared to DMSO controls (-27.07+/-8.89 vs. -15.71+/-8.35, p=0.0039), indicating that CFTR is the ion channel being activated by quercetin.

Conclusion: Quercetin significantly increased transepithelial Cl^- transport in this culture model of nasal epithelium. Further research efforts are required to determine whether this could be effective in promoting MCC in sinus and nasal disease.

Scott, Adam Wesley (Adam)

Project Length	Short
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Debasish Chattopadhyay
Title	A Fragment-Based Approach to Discovering Novel Antifolates

Abstract

Methotrexate (MTX), a classical antifolate inhibitor of human dihydrofolate reductase (hDHFR), is widely used in chemotherapy of breast cancer. However, drug resistance and toxicity of MTX poses major challenges in the continued use of MTX and related drugs. The use of hDHFR inhibitors with novel scaffolds, different from the typical 2,4-diaminopyrimidine or 2,4-diaminopteridine scaffolds of currently used antifolates, will circumvent the problem of MTX drug resistance. Applying a fragment-based drug discovery strategy will allow identification of novel scaffolds and development of potent antifolates. We have prepared highly purified functional recombinant enzyme and optimized an *in vitro* enzyme activity/inhibition assay for rapid screening of inhibitors. We have obtained a portion of a high quality fragment library which was used for screening. We have identified two small fragments that effectively inhibit hDHFR, at relatively low concentrations compared to other small fragments. We then prepared purified hDHFR for crystallization with one of the inhibitory fragments. Crystallization experiments have yielded micro-crystals after some optimization. Further work is needed in order to obtain high quality crystals and perform X-ray crystallography studies to determine the binding site and mode of the fragment and analyze the enzyme-inhibitor complex. Once the structure is resolved, the inhibitory fragment may be optimized by chemically linking selected fragments that bind to neighboring pockets or by chemical modification of a single fragment using medicinal chemistry tools, thus developing potentially therapeutic agents against breast cancer.

Seibert, Allan Michael (Allan)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Louis J. Dell'Italia
Title	Left Ventricular Strain is Reduced in Remote Non-Diseased Segments Following Myocardial Infarction in Patients with Type-2 Diabetes Mellitus.

Abstract

Background: Type-II diabetes mellitus (DM) is a strong risk factor for adverse left ventricular (LV) remodeling and heart failure (HF) following myocardial infarction (MI). Alteration of LV strain following MI occurs in both diseased and remote non-diseased myocardial segments and is associated with adverse LV remodeling. In the current study we use tissue-tagged magnetic resonance imaging (MRI) to evaluate differences in LV strains in diseased and remote non-diseased segments in post-MI patients with and without DM that may potentially underlie the increased propensity of post-MI DM patients to develop HF.

Methods: Fifty-one DM and 41 non-DM patients underwent cardiac-MRI within one week of MI. Three dimensional circumferential and longitudinal LV strains were calculated and averaged for each patient over diseased (distal to >55% vessel stenosis) and remote non-diseased LV segments.

Results: There were no significant differences in age, blood pressures, LV ejection fraction (51.8±1.8 vs. 55.0±1.6%), radius to wall thickness ratio (3.4±0.1 vs. 3.2±0.2), or number of diseased cardiac segments per patient (6.6±0.6 vs. 6.1±0.5) between DM and non-DM groups, respectively ($p>0.05$ in all cases). There were no significant differences in the strains of diseased areas in DM and non-DM groups. DM patients however, demonstrated significantly reduced circumferential and longitudinal strains in non-diseased areas compared to non-diseased areas in non-DM patients (10.06±0.53 vs 11.54±0.43, $p=0.04$ and 8.82±0.47 vs 10.23±0.41, $p=0.03$, respectively).

Conclusions: When compared to non-DM patients, DM patients demonstrated significantly reduced circumferential and longitudinal strain in remote non-diseased myocardial segments post-MI. Reduced strains in remote non-diseased myocardium may contribute to the increased incidence of adverse remodeling and heart failure in post-MI DM patients.

Singhal, Sara Sonali (Sara)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. Justin Baker
Title	The Impact of Palliative Care Consultations on End-of-Life Decisions in Pediatric Cancer Patients

Abstract

Pediatric palliative care (PPC) focuses on maximizing quality of life, easing suffering, emphasizing healing, and addressing end-of-life care issues for patients with life-threatening conditions and their families regardless of disease trajectory. Much of PPC used at cancer institutions, such as St. Jude Children's Research Hospital (SJCRH), focuses on end-of-life care (EOLC). PPC consultations at SJCRH are performed by the Quality of Life Service (QoLS), which uses EOLC as a tool to facilitate "good deaths" for the patients-deaths involving minimal suffering, symptom palliation and control, spiritual and religious support, and bereavement services. This study assessed the impact of palliative care consultations on major EOLC decisions in 64 children who died between the years of 2007 and 2009 at SJCRH. Retrospective chart review of various EOLC measures and decisions was performed in the patient cohort and compared to those from a historical cohort collected prior to the initiation of QoLS. The study shows increased documentation of EOLC discussions after QoLS implementation. Furthermore, there are also documented increases in Do not Resuscitate (DNR) orders and hospice use, with specific increases in days spent with a DNR order or on hospice prior to death. There were also increases in the documentation of bereavement services and sibling counseling. Additionally, there was extensive documentation of changes in care interventions and specific symptoms for the weeks preceding initial QoLS consult, following initial QoLS consult, and last week of life. Finally, the study also showed documentation of specific goals of treatment, specifically for chemotherapy administered in the last week of life with the documented goal of palliation. Ultimately, the study shows that the QoLS has impacted EOLC at SJCRH by improving documentation of major EOLC issues, suggesting that the QoLS has positively impacted EOLC decisions at SHCRH by facilitating "good deaths" for the patients in the cohort.

Smith, Haller Jackson (Haller)

Project Length	Short
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Andrey Frolov
Title	Effects of exogenous MEK expression on resistance to tyrosine kinase inhibitors in GIST

Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the GI tract. Over 80% of GISTs contain an activating mutation in *KIT*, a receptor tyrosine kinase that modulates activity of several pathways linked to cell proliferation and survival. One such pathway is the MAP kinase cascade, which includes activation of ERK by MEK, leading to transcription of genes promoting cell proliferation. The first-line treatment for inoperable or recurrent GISTs is currently tyrosine kinase inhibitors (TKIs), which specifically target KIT signaling. Previously, it was determined that down-regulation of *SPRY4A*, *FZD8*, and *PDE2A* and upregulation of *MAFbx* were markers of response to TKIs in GIST. Although most patients respond well to TKI therapy initially, many eventually develop refractory disease. The goal of this study was to determine whether exogenous activation of the MAP kinase cascade could contribute to the development of this secondary resistance to TKI therapy in GIST.

Western blotting for ERK was used to demonstrate that an adenoviral vector could be used to introduce exogenous MEK expression in the only two available human GIST cell lines, GIST T1 and GIST 882. This increased expression was shown to persist in the presence of a TKI, showing that it was not linked to KIT signaling.

RT-PCR was used to determine the effect of exogenous MEK on the genetic markers of response to TKI therapy. Increased expression of MEK had the opposite effect of TKIs in GIST cells, up-regulating expression of *SPRY4A*, *FZD8*, and *PDE2A* and down-regulating expression of *MAFbx*. Treatment with a TKI in GIST cells expressing exogenous MEK had no significant effect on expression of *MAFbx* or *SPRY4A*, and it increased expression of *PDE2A*. This indicated an abnormal response to treatment in these cells.

A MTT proliferation assay was used to determine the effects of exogenous MEK expression on cell growth. Overexpression of MEK led to increased proliferation in human GIST cells. In the presence of TKI, GIST cells that overexpressed MEK exhibited an abrogated response to treatment compared to normal counterparts, although this was not statistically significant. These results indicate that increased activity of the MAP kinase cascade could potentially promote resistance to TKI therapy in human GIST cells.

Stanley, Jennifer Anne (Jennifer)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Ralph Sanderson
Title	Syndecan-1 Shedding Diminishes Its Nuclear Levels: Mechanism for Stimulation of Myeloma Tumor Growth

Abstract

The progression of multiple myeloma is promoted by the combined actions of syndecan-1 and heparanase. Syndecan-1 is a heparan sulfate proteoglycan that localizes to two myeloma cellular compartments: the cell surface and the nucleus. Heparanase, an enzyme that cleaves heparan sulfate chains, accelerates shedding of synedecan-1. These high levels of shed syndecan-1 dramatically condition the tumor microenvironment to enhance growth, angiogenesis, and metastasis. Additionally, high levels of heparanase expression in myeloma cells are associated with a decrease in levels of nuclear syndecan-1. Lower levels of nuclear syndecan-1 likely lead to enhanced transcription through the action of topoisomerase-1 and histone acetyltransferase. In this study, we hypothesized that shedding of syndecan-1 from the cell surface controls the level of sydnecan-1 in the nucleus. To examine this, syndecan-1 shedding was induced by treatment of cells with bacterial heparitinase (HepIII), which can strip heparan sulfate chains from the cell surface. Using confocal microscopy, ELISA and flow cytometry we discovered that following exposure to HepIII: 1) the rate of syndecan-1 shedding from the cell surface was increased, 2) the level of nuclear syndecan-1 was dramatically reduced, and 3) cell surface staining for syndecan-1 was enhanced. We conclude that stimulation of syndecan-1 shedding is associated with a decrease in levels of nuclear syndecan-1. This suggests that during myeloma progression, shedding of syndecan-1 not only influences the tumor microenvironment but also increases tumor cell transcriptional activity. Together these actions may promote the aggressive phenotype seen with multiple myeloma.

Stephens, Lauren A (Lauren)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Mark O. Bevenesse
Title	Altered Bicarbonate-dependent pHi Regulation in a Cortical Collecting Duct Cell Model of ARPKD

Abstract

Polycystic kidney disease (PKD) is a genetic disorder affecting nearly 600,000 people in the US and the fourth leading cause of kidney failure. In both autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD), ductal epithelia including collecting tubules of kidney are less differentiated, more prone to remodeling, and display mispolarity and dysregulated ion transport. We used fluorescence imaging with the pH-sensitive dye BCECF to examine the regulation of intracellular pH (pH_i) in both cilium-deficient ("mutant") and cilium-competent ("rescued") cortical collecting duct principle cell monolayers derived from a mouse model of ARPKD that lacks the *Tg737* gene. We characterized HCO_3^--dependent pH_i regulation by examining pH_i recoveries following NH_4^+ prepulse-induced acid loads elicited by exposing both the apical and basolateral membranes simultaneously to a 5% CO_2/33 mM HCO_3^- solution in the presence of 50 μM HOE-642 ± 200 μM DIDS. As previously reported, HOE nearly blocked the pH_i recovery from an acid load in both cell monolayers bathed in HEPES-buffered solutions. However, subsequently switching to the HCO_3^- solution (with HOE) elicited a faster pH_i recovery in the rescued vs. mutant cells. DIDS applied to the basolateral (but not apical) membrane inhibited the HCO_3^--induced pH_i recovery. In the linear part of the pH_i recovery, total acid extrusion (J_H) in the pH_i range: 6.38-6.9 was 61 μM/s (19%) less in the mutant vs. rescued cells. In the pH_i range: 6.5-6.88, reduced DIDS-sensitive and -insensitive J_H contributed equally to the reduced total J_H in the mutant cells. According to immunohistochemistry data from xz-plane images of folder filters, the DIDS-insensitive, electroneutral Na/HCO_3 cotransporter NBCn1 is expressed to a lesser extent on the apical membrane of the mutant vs. rescued cells. Reduced activity/expression of HCO_3^- transporters in the mutant cells may compensate for the increased NHE-mediated Na^+ reabsorption in this cell model of ARPKD.

Stoddard, Mark Bevan (Mark)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. John Kearney
Title	Tracking Intraperitoneal IL-10-producing Regulatory B cells in vivo.

Abstract

Regulatory immune cells may play a key role in the pathogenesis of important autoimmune and the immune response to infection. Recent studies have postulated the existence of small (approximately 3%) regulatory B cell populations isolated from mouse splenocytes that produce the anti-inflammatory cytokine IL-10. These populations may include CD1d(high)CD5(+) B1a, marginal zone (MZ), or follicular (FO) B cells. IL-10 production is protective in certain inflammatory disease models and may play a role in immunogenesis.

In this study, we track these B cell populations using BCR transgenic mice specific for phosphorylcholine (PC) on *Streptococcus pneumoniae* (T15 mice) and alpha *Enterobacter cloacae* (J558 mice) that were crossed with Thy1.1 expressing IL-10 reporter mice. Thy1.1, T15/Thy1.1, and J558/Thy1.1 transgenic mice were immunized intraperitoneally with heat-killed *S. pneumoniae* or *E. cloacae*. Spleen and peritoneal samples were obtained and antigen-specific cells were monitored via flow cytometric analysis using anti-idiotype antibodies for T15 mice (AB1.2 antibody) and J558 mice (EB3-7 antibody).

Results from the Thy1.1 mice showed a 60% to 90% increase in IL-10 producing cells in the B1a, B2, and B1b B cell populations isolated from the peritoneal cavity on day three post-immunization. The T15/Thy1.1 mice showed a 23% increase in IL-10 generating antigen-specific B1b cells on day three post-immunization. J558/Thy1.1 mice generated IL-10 in 26% of antigen-specific B1a cells and 17% of B1b cells on day one post-immunization.

In conclusion, a substantial sub-population of B-cells appeared to respond to antigenic stimulation by producing IL-10. These cells were found in the peritoneal cavity rather than the spleen, suggesting a possibly anti-inflammatory role for intraperitoneal regulatory B cells. Previous investigations have not involved intraperitoneal administration of antigen and have not focused on intraperitoneal B cells. This study also suggests that the chronology and B cell sub-populations involved in responses may be antigen specific.

Sullivan, Brian Patrick (Brian)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	J. Scott Magnuson, M.D.
Title	The Utility of Computed Tomography Surveillance for Recurrent Head and Neck Squamous Cell Carcinoma

Abstract

Title: The Utility of Computed Tomography Surveillance for Primary Site Recurrence of Squamous Cell Carcinoma of the Head and Neck

Educational Objective: At the conclusion of this presentation, the participants should be able to understand the utility of computed tomography (CT) in evaluating head and neck tumor recurrences at the primary site and determine which situations may benefit from post treatment CT scans.

Abstract – Maximum 250 words

Objectives: The utility of computed tomography (CT) scans in evaluating neck node metastasis has been shown. This study aims to evaluate the utility of CT compared to physical examination (PE) in evaluating primary site recurrences.

Study Design: A retrospective cohort study.

Methods: Patients who received both CT scans and PE after primary treatment for squamous cell carcinoma of the upper aerodigestive tract (oropharynx, hypopharynx, and larynx) were identified. Each individual CT scan and PE was evaluated for its ability to detect a patient's recurrence status. Positive test results were compared to subsequent biopsy results to determine their validity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each test. Recurrence rate and mortality were calculated for each site and the entire group.

Results: 131 patients underwent a total of 886 PE and 346 CT scans during the 2 year follow-up. The overall recurrence rate was 26.7%. The recurrence rate by site was 40.5% for larynx, 16.6% for hypopharynx and 18.3% for oropharynx. The sensitivity for PE and CT was 84.0% and 66.7%; for specificity, 98.7% and 90.7%; for PPV, 65.6% and 31.8%; for NPV the values were 99.5% and 97.7% respectively.

Conclusions: Due to the low sensitivity and PPV of CT scans compared to physical examination in evaluating primary site tumor recurrences, the utility of computed tomography for surveillance may be limited.

Sultan, Faraz (Faraz)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	J. David Sweatt
Title	Active DNA Demethylation Regulates Long-Term Memory

Abstract

Long-term memory formation depends upon a myriad of complex biochemical and synaptic phenomena that are subserved by stable changes in gene expression and synaptic strength. Recent pioneering work has implicated molecular epigenetic mechanisms in memory-associated gene regulation. Such epigenetic factors include post-translational modifications of histone proteins and covalent modification of DNA itself. *De novo* DNA methylation in the hippocampus involves the addition of a methyl group to key cytosine residues in CpG sites and has been shown to be necessary for long-term contextual fear memory. However, the same paradigm is also associated with demethylation at key memory-associated loci. Since little is known about DNA demethylation, the mechanism behind these changes remains elusive. Recent novel studies uncovered the role of the Growth arrest and DNA damage-inducible protein 45 (Gadd45) family in base excision and repair-mediated DNA demethylation. One isoform, Gadd45b, acts as a neuronal activity-inducible immediate early gene (IEG) in the hippocampus. In this study, we hypothesize that Gadd45b regulates long-term memory formation and memory-associated DNA demethylation.

Tate, Tyler

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center
Advisor	Michael Mugavero
Title	Temporal Changes in Obesity in an HIV Clinic

Abstract

Introduction: The success of antiretroviral therapy (ART) has led to dramatic reductions and changes in causes of morbidity and mortality in HIV-infected individuals. As rates of cardiovascular disease and diabetes have increased, modifiable risk factors such as obesity have gained importance. Methods: Retrospective study of BMI trends in the UAB 1917 HIV/AIDS Clinic population between January 1, 2000-December 31, 2008. BMI was classified as: underweight (BMI<18.5), Normal weight (BMI 18.5-24.9), Overweight (BMI of 25-29.9) and obese (BMI>30). Objectives**:** (1) Describe clinic level temporal trends in BMI; (2) Perform descriptive analyses (chi-square, ANOVA) comparing characteristics of treatment naïve patients starting ART per BMI category; (3) Determine factors associated with change in BMI in the overall and male and female population (linear regression) adjusting for sociodemographic and clinical characteristics at 6 and 24 months after ART initiation. Results**:** We observed an increase in the overall prevalence of obesity in our HIV-infected cohort (n= 2,826) from 2000-2009 (15% vs. 22%). Obesity was more common in women (26% 2000 vs. 39% 2009) than in men (11% 2000 vs. 17% 2009). In bivariate analyses of naïve patients stratified by BMI category at ART initiation, we found statistically significant associations with overweight/obesity (p=<0.01) for female sex, diabetes mellitus, and hypertension. Overall, the mean (± standard deviation) change in BMI at 6 and 24 months following ART initiation was 1.1 (± 2.6) and 1.6 (± 3.5), respectively. In adjusted linear regression analyses at 6 and 24 months, lower baseline CD4 count (p=<0.01) and boosted protease inhibitor use (p≤0.05) were associated with statistically significant increases in BMI. Discussion**:** The prevalence of obesity has increased in our HIV-infected patients since 2000, particularly among women. Following ART initiation increases in BMI are observed among those with lower baseline CD4 counts and in patients treated with a boosted protease inhibitor.

Thomas, Evan

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	John Fiveash
Title	COMPARISON OF SINGLE & MULTI-ARC SINGLE-ISOCENTER VOLUMETRIC ARC RADIOSURGERY TO TRADITIONAL GAMMA K

Abstract

Purpose: Volumetric modulated arc therapy (VMAT), a recent adaptation of intensity-modulated radiation therapy has been shown capable of equal or improved performance in prescription volume coverage, homogeneity, and conformity while reducing monitor units and treatment time for cranial lesions. A study of a novel VMAT planning approach using a single-isocenter in simulated patients with three cranial metastases revealed that equivalent conformity to that of multi-isocenter plans can be achieved with significant reduction in treatment time. This investigation studied whether similarly equivalent conformity could be achieved for patients with greater than 3 cranial metastases in both single and multi-arc single-isocenter plans, and how the resultant conformity and treatment times compared to that of gamma knife treatment plans used in actual patients.

Methods and Materials: Planning data from patients treated with gamma knife radiosurgery with greater than three cranial metastases not requiring dose-sparing considerations were gathered. The lesions were re-contoured in Varian RapidArc to an identical gross tumor volume (GTV) and re-planned with a single isocenter in both single and multi arc formats. New plans were judged for clinical acceptability and all plans evaluated according to Paddick and Radiation Therapy Oncology Group (RTOG) conformity index scores, Paddick gradient index scores, and 12-Gy isodose volumes.

Results: Forthcoming

Thorpe, John Bannon, II (Bannon)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Brent A. Ponce
Title	The Effect of Screw Reinsertion on Pull-out Strength of Screws: Are We Making Trouble?

Abstract

Introduction: The effect of screw removal and reinsertion in metaphyseal and diaphyseal bone has not been critically analyzed. Within surgery, screws are frequently exchanged, creating the potential for weakening a screw's purchase and therefore, reducing the repair construct's stability. This is especially true in osteoporotic bone. As the frequency, cost, and difficulty in treating geriatric fractures continues to increase, it is important to definitively investigate this issue.

Methods: Twelve embalmed cadavers provided 24 femora for testing. The distal femur and femoral shaft were used for metaphyseal and diaphyseal testing respectively. In each specimen, two cortical screws (4.5 mm diameter), one single and one double insertion, were inserted at 50% maximal torque. A template was used to ensure consistent placement and sufficient spacing of screw holes. Specimens were fixed in a custom fixture to align the screw axis with the actuator of the Material Testing System. The screws were pulled out at a rate of 1 mm/sec with the data sampled at a frequency of 100 Hz. Maximum pullout strength (Fmax) was determined and statistical analysis was performed. BMD values were obtained on all specimens prior to testing.

Results: Difference in average pullout strength between single and double insertions did not show statistical significance in the metaphyseal region (43 N decrease, $p = 0.26$) or the diaphyseal region (192 N decrease, $p = 0.41$). In the metaphyseal region, the results showed that pull-out strength and stiffness significantly correlated with BMD ($p = 0.0029$ & 0.0048 respectively), but they did not correlate in the diaphyseal region ($p = 0.63$ & 0.47 respectively).

Conclusion: Repeated insertion of screws *does not* significantly decrease the pull-out strength of screws.

Tonks, Stephen Andrew (Stephen)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Louis Dell'Italia
Title	Post-translational Modification Increases Xanthine Oxidase Activity in Volume Overload

Abstract

Introduction**:** Oxidative stress has been implicated as a major factor in the pathophysiology of chronic heart failure. We have shown xanthine oxidase (XO), an oxidative enzyme, protein expression is increased in humans with volume overload (VO), and XO inhibition in an animal model of VO delays the onset of heart failure. XO's enzymatic activity can be increased via two possible mechanisms, either proteolytic cleavage or transient disulfide bond modification. It is unknown how myocardial XO is changed in response to VO. Therefore, using a relevant animal model we investigated the pathway by which XO is activated.

Methods**:** An aortacaval fistula (ACF), an established model of volume overload, was induced in male age-weight matched Sprague Dawley rats. Either standard tissue collection or cardiomyocyte isolation was performed at 24 hours of ACF. XO assays included, western blot, real-time PCR, XO activity by substrate utilization.

Results**:** XO activity was increased in left ventricular homogenate of ACF animals compared to sham (921 ± 49 vs 691 ± 71 μU/mg, $p<0.05$). Isolated myocytes from ACF also showed an increase in XO activity (69 ± 6 vs 92 ± 4 μU/mg, $p<0.05$). Xanthine dehydrogenase gene/ beta actin internal control was not different between Sham and ACF groups (8.9 ± 1 vs 13.8 ± 2.9 copy # x 10^5, $p=0.17$). Proteolytic cleavage was assayed by western blot using a polyclonal rabbit antibody directed to XO and demonstrated no difference between 145kD, 125 kD, and 85 kD bands.

Conclusions**:** The volume overload of ACF results in increased XO activity in the heart. XO gene expression and proteolytic enzyme cleavage are not changed. Therefore, it can be concluded, XO activity is increased via post-translational disulfide bond modification in acute myocardial volume overload. These findings provide mechanistic insight into heart failure treatment paradigms currently being investigated.

Vullaganti, Sirish

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Louis Dell'Italia
Title	The Combined Effect of Age and Volume Overload on Cardiac Compensation and Mitochondrial Function

Abstract

BACKGROUND: Age is known to play a crucial role in the pathogenesis of cardiovascular disease by augmenting oxidative stress while diminishing protein synthesis and repair in the vasculature. In particular, volume overload (VO) due to acute or chronic dysfunction of the aortic and mitral valves is becoming an increasing problem in our elderly population. There is currently no recommended medical therapy to attenuate the left ventricular (LV) remodeling and progression to heart failure in VO. Studies in the aortocaval fistula rat model of VO (ACF) have demonstrated the presence of oxidative stress in the LV of the ACF rat after just one day of VO. Mitochondria, which play an important role in myocardial contractility, are known to be sensitive targets of such oxidative stress in both VO and aging. However, the combined effect of acute VO and aging on LV cardiac mitochondrial function currently remains unknown.

METHODS: Young (3 months old) and old (18 months old) rats were either subjected to VO by ACF or given a sham surgery. Echocardiographic LV dimensions and high-fidelity LV pressures were obtained at the time of sacrifice after 24 hours and both subsarcolemmal mitochondia (SSM) and intermyofibrillar mitochondria (IFM) were isolated from the excised hearts. Respiratory function of the LV mitochondria was analyzed using a polyarographic measurement of oxygen consumption with a Clark-type oxygen electrode.

RESULTS: LV end-diastolic (ED) dimension increased 15% 24 hrs after ACF in both sets ($p < 0.05$) documenting similar LV dilatation in both age groups. LV fraction shortening (FS) and rate corrected circumferential shortening (VCFr) were increased in ACF rats vs. sham in young rats, but did not change vs. shams in old rats. There were similar 3-fold increases in LV end diastolic pressure in young and old ACF rats vs. shams. SSM respiration showed a significant drop in state 3 in young ACF rats, while both sham and ACF old rats demonstrated a significant decrease in state 3 respiration compared to young shams. Analysis of IFM demonstrated an overall decrease in state 3 within both sham and ACF old vs. young rats.

CONCLUSIONS: Younger animals developed a more profound compensatory contractile response in acute VO compared to old rats, which may be due to the greater impairment of IFM in older vs. young rats. The age disparity in mitochondrial respiration of IFM, which are in close proximity to the myofibrils, may underlie the greater propensity to develop heart failure in the aging heart.

Ward, Paul Wofford (Paul)

Project Length	Short
Prior Research Experience	yes
Funding Source	CaRES Program
Advisor	Dr. Karen Iles
Title	The Effects of Cadmium on Human Bronchial Epithelial Cells, A Novel Mechanism for Cadmium Induced Pulmonary Dys-Function

Abstract

Cigarette smoking is the greatest risk factor for developing lung cancer. One of the toxic components of cigarette smoke (CS) is the heavy metal/carcinogen Cadmium (Cd). Unlike many of the toxins in CS, Cd bio-accumulates. Cd also modulates the expression of cytoprotective/stress response genes such as heme oxygenase-1 (*ho-1*) and *gclc/gclm*, which code for the rate-limiting enzyme in glutathione (GSH) biosynthesis. We hypothesize that Cd increases ROS production directly by targeting mitochondria and indirectly by disrupting cellular iron homeostasis via the up-regulation of HO-1. Further, that the accumulation of ROS damages DNA, and inhibits the DNA-repair enzyme OGG1, exacerbating DNA damage**.** For these studies mice were given $CdCl_2$ (0-50 mg) intra-nasally, or, human bronchial epithelial cells (HBE1) were treated with $CdCl_2$ (0-500 M) for various lengths of time. The effect of Cd on cell viability, ROS production, HO-1 mRNA and protein, GSH and OGG1 regulation were measured *in vitro* and/or *in vivo*. Increasing concentrations of Cd decreased cell viability and increased mitochondrial and whole-cell ROS production in cells. At concentrations of Cd that increased ROS, OGG1 mRNA was down regulated. Low dose/short exposures to Cd induced GSH in HBE1 indicative of cellular stress vs. depletion following longer exposures. HO-1 mRNA and protein were significantly increased in both cultured cells and in lung homogenates exposed to Cd. The increase in HO-1 was followed by an increase in the labile iron pool. These data suggest a novel mechanism (i.e. disruption of iron homeostasis) in Cd-induced pulmonary dysfunction and DNA damage.

Warmus, Brian Andrew (Brian)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Erik Roberson
Title	Investigating the Anatomy Underlying Behavioral Symptoms in Frontotemproal Dementia

Abstract

Behavioral variant Frontotemporal Dementia (FTD) is a progressive clinical syndrome. It normally appears in the patients' mid-forties to early-sixties and is characterized by personality changes, social disturbances, obsessive-compulsive behaviors, disinhibition, and emotional problems. Patients display frontal and temporal brain atrophy. Patients can have either Tau-positive or TAR DNA binding protein (TDP)-positive histopathologies. Several mutations have been found in the microtubule associated protein tau (*MAPT*) gene that lead to Tau-positive tangles. One of these mutations, V337M, was discovered in a family with FTD who lived in Seattle, WA. The Roberson lab is studying a transgenic mouse line with the human Tau V337M mutation (Tg-hTau-V337M). The mice have age-dependent facial lesions caused by compulsive grooming and demonstrate disinhibition in the elevated plus maze, which do not appear in the age-matched non-transgenic (NTg) and wild type human Tau (Tg-hTau-WT) transgenic mice. Tg-hTau-WT mice have the unmutated human Tau gene and do not demonstrate the behavioral abnormalities seen in Tg-hTau-V337M mice. Many human patients with OCD show significant improvement when deep brain stimulators are placed in the ventral striatum (VS); this is thought to correct the aberrant signaling and suggests obsessive-compulsive behaviors are related to abnormal networks within the VS. Similar evidence has been shown in Tg-hTau-V337M mice; extracellular field potentials were recorded from VS and Tg-hTau-V337M display significantly larger field excitatory postsynaptic potential amplitude than Tg-hTau-WT. Thus, it is an important question to investigate the anatomical basis for the differences in physiology within the VS. We hypothesize that physiological abnormalities are caused by Tau-induced changes in postsynaptic densities (PSD) and/or dendritic spines. In this study, we analyze PSDs with electron microscopy and dendritic spines with Golgi staining. We predict that PSDs are larger and/or spines are more numerous and robust in Tg-hTau-V337M as compared to controls.

Watkins, Stacey Michelle (Stacey)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Harald Sontheimer
Title	Biophysical and Biomechanical Aspects of Glioma Invasion

Abstract

Malignant gliomas are among the deadliest cancers with very limited treatment options. Contributing to their dismal diagnosis is the inability to surgically resect these tumors as individual glioma cells diffusely invade the surrounding brain. These invading cells encounter a tortuous extracellular space necessitating profound changes in cell shape and presumably cell volume. However, whether and how cell regulate shape and volume is poorly understood. Hence the main objective of this study was to examine specific biophysical and biochemical changes that permit glioma cells to journey through the confines of the brain. Based on prior findings we hypothesize that cell volume decreases as cells invade and that this is due to the release of Cl^- and K^+ along with obligated water. To examine this hypothesis we established an ex-vivo invasion model that mimicked the spatial constraints of glioma invasion while allowing us to image the process in real time. Specifically, we used a transwell assay system in which GFP-tagged glioma cells were challenged to traverse through 8.0 μm pores from one compartment to another. During this process, cells were maintained in a climate controlled environment and imaged throughout using a laser scanning confocal microscope. Image stacks, created from various time points of the migration sequence, allowed for 3D volume reconstruction to calculate accurate volumes and allowed us to assess global volume changes as cells entered the pores, traversed and exited the barrier. To examine whether the cell nucleus underwent volume alterations, a nuclear dye was loaded into GFP-tagged cells prior to migration experiments to create simultaneous image stacks to determine nuclear volume changes during the migration experiment. Various chemoattractant molecules were examined including serum, scatter factor and epidermal growth factor, single or in combination. The data obtained thus far indicated an unexpected increase in the overall cell volume just before migration was initiated and as glioma cells extended the initial process into the pores. Thereafter, cell volume decrease markedly, up to 50% until cell exited the pores. Treatment with the Cl^- channel inhibitors DIDS or NPPB markedly reduced the number of cells that successfully traversed the barrier. Moreover, immunostainings of cells actively transversing the barrier showed the clustering of ClC-3 Cl^- channels on the leading edge of the invading cells. This data suggests that a local release of Cl^- at the leading edge may cause the gradual reduction in cell volume as cells invade through a tortuous microenvironment. These studies offer an elegant model system in which to study the regulation of this process and signaling processes involved in greater detail, which in turn may aid in the development of future anti-invasive therapies.

Weber, Adam

Project Length	Short
Prior Research Experience	Yes
FundingSource	Departmental or Mentor Funds
Advisor	Glenn Fleisig
Title	Injurious Effect of the Curveball: A 10-Year Longitudinal Study

Abstract

Background: There is a long-standing belief that the curveball is particularly dangerous for youth baseball pitchers. This idea is based on the premise that in order to generate enough spin to cause the ball to break, the pitcher's elbow must withstand damaging stress and torque. While the curveball does require slightly different arm mechanics than the fastball, there is no evidence affirming that breaking pitches put greater stress on the elbow. The literature is inconsistent in its assessment of the curveball as a risk factor for elbow pain.

Methods: 546 male prospective youth league pitchers were surveyed in 1999, the initial year of the study. The mean age of subjects at the beginning of the study was 11.95 years old (range 8.1-16.5). Each year, the subjects were contacted by phone to answer a survey regarding positions played, innings pitched, pain, doctor visits and treatment methods. After two consecutive years of not playing baseball, subjects were retired from the study. The data were collected and all subjects who neither played pitcher or catcher for at least one year were removed from the data pool. The remaining subjects were divided into a healthy and injured group (had surgery or retired from playing due to injury). The healthy group was divided into casual (1-3 seasons pitched) and success (4 or more seasons pitched) subsets. Casual, success and injured groups were the further divided into subgroups depending on whether or not they threw a curveball or not. For each subgroup average values for age at the beginning of the study, years pitching, age at first curveball and innings per year pitched.

Results: 15 of the 25 pitchers (60%) in the injured group threw the curveball, while 148 of the 151 pitchers (98%) in the success group threw the curveball. The mean age in 1999 for the injured group was 12.4 and the mean age for the success group was 11.7. The average age for first throwing the curveball was 13.6 for the injured group and 13.5 for the success group. The only significant difference between the injured and success groups was that the success group averaged 26.1 innings per year and the injured group averaged 11.4 innings per year.

Conclusion: These preliminary results indicate that the curveball is not an independent risk factor for elbow injury in youth pitchers. Additional data analysis is required to determine if the curveball is a secondary risk factor. A longitudinal biomechanics study is needed to determine what specific kinetic and kinematic aspects of the throwing motion are responsible for producing elbow injury in youth baseball pitchers.

Wells, Ryan

Project Length	Long
Prior Research Experience	Yes
FundingSource	NIH Medical Scientist Training Program Grant
Advisor	Michael Niederweis
Title	MmpS4 and MmpS5 are OMPs of Mycobacterium tuberculosis Required for Growth Under Low Iron

Abstract

Mycobacterium tuberculosis (*Mtb*) is able to cause disease by preventing phagosomal maturation to phagolysosomes. Despite its ability to survive within the phagosome, this environment is inhospitable to pathogens because of low pH, the presence of reactive nitrogen and oxygen species, as well as a paucity of nutrients and trace element required for growth. Iron acquisition by pathogenic bacteria is necessary for their survival and bacteria compete with the host for their iron needs by producing and secreting low molecular weight, high affinity iron chelators called siderophores. The phagosomal environment is believed to be particularly low in iron due to the host immune response. *Mtb* synthesizes two siderophores—mycobactin and carboxymycobactin, which are lipophilic and hydrophilic, respectively. The mycobacterial secretion system for these siderophores is unknown. Furthermore, once loaded with their iron cargo, an uptake mechanism for the iron-loaded siderophores is largely unknown. The ability of *Mtb* to acquire and utilize iron within iron limiting phagolysosomes is a virulence factor.

It is hypothesized that MmpS4 and MmpS5 are involved in the secretion of mycobacterial siderophores. An *Mtb* strain lacking the iron-regulated genes, *mmpS4* and *mmpS5* (*DmmpS4/S5*), has been constructed. This strain is unable to grow *in vitro* under low iron conditions, while *Mtb* wt as well as each single deletion strain (*DmmpS4* and *DmmpS5*) retain this ability. Furthermore, media that has been conditioned by growing either *Mtb* wt, *DmmpS4*, or *DmmpS5* is able to rescue the growth of *DmmpS4/S5* under low iron conditions. Subcellular fractionation along with proteinase K surface accessibility assays show that MmpS4 and MmpS5 are outer membrane proteins (OMPs). Taken together, this data supports the hypothesis that MmpS4 and MmpS5 are OMPs involved in the secretion of mycobacterial siderophores.

Whitley, Sarah Kern (Sarah)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Casey Weaver
Title	Regulation of IL-17 Transcription in CD4+ T Cells

Abstract

Proper cytokine expression and commitment to T_H lineages is regulated at the level of transcription. The transcription factors T-bet and GATA-3 dictate commitment to the Th1 and Th2 lineages, respectively, and elucidating how and where these transcription factors act to remodel cytokine loci and direct lineage commitment has been an area of intense investigation. It is clear that distal *cis* -regulatory elements aid in the chromatin remodeling that establish and maintain lineage-specific patterns of gene expression. Here we used a PCR-based approach to map DNase-hypersensitive sites spanning almost 1Mb up- and downstream of the *Il17a* and *Il17f* cytokine loci. Using this method we have identified many regions with CD4+ T cell subset-specific epigenetic modifications. A subset of these sequences enhanced IL-17 expression in a mouse thymoma cell line and in primary Th17 cells, indicating that they represent functional *Il17* enhancers. Further studies have employed chromatin immunoprecipitation to map the binding pattern of the Th17 lineage-specific transcription factor STAT3 to these sites during both primary and secondary responses to antigen. Our findings suggest that proper expression of *Il17* is achieved through collective action of transcription factors at multiple distal regulatory elements present in a region of about 850 kilobases flanking the *Il17a* and *Il17f* genes.

Wilks, Gavin Ray (Gavin)

Project Length	Short
Prior Research Experience	Yes
Funding Source	HSF Community and Rural Health Fellowship
Advisor	John Wheat
Title	Variables Affecting Readiness of Alabama Family Physicians to Retire

Abstract

It is well documented that the United States is facing a shortage of physicians, especially those practicing primary care, specifically family physicians. A primary driving force behind the current and forecasted shortage is physician retirement. The objective of this study is to further understand variables that are associated with the retirement plans of family physicians practicing in Alabama. It was found that approximately 30% of respondents are planning to retire within 10 years, with only age and years of clinical practice being associated with their readiness to retire. However, contrary to anecdotes about physicians remaining in rural practice longer than urban counterparts, this report finds no evidence to suggest that rural physicians plan to work longer than urban physicians. This is an important workforce finding.

Yang, Sherry Wei (Sherry)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Joanne T. Douglas, Ph.D.
Title	A Dual-Action, Armed Replicating Adenovirus for the Treatment of Ovarian Cancer

Abstract

Ovarian cancer is the leading cause of gynecological cancer deaths in the U.S.A. Current treatments have limitations and new therapies are needed. Conditionally replicating adenoviruses (CRAds) are designed to selectively lyse cancer cells. In clinical trials, CRAds have exhibited limited efficacy, and thus need to be armed with therapeutic transgenes to increase their antitumor efficacy. One target for therapeutic transgenes is the tumor microenvironment. The degradation of the extracellular matrix (ECM) is an essential step in ovarian tumor growth and angiogenesis. Matrix metalloproteinases (MMPs) are endogenous proteases that degrade ECM components and are upregulated in numerous tumors. Tissue inhibitors of metalloproteinases (TIMPs) are endogenous inhibitors of MMPs that can limit tumor growth and angiogenesis. We hypothesize that a TIMP-armed CRAd will inhibit the progression of ovarian cancer in two ways: (i) viral replication will directly lead to tumor cell lysis and (ii) TIMP production from infected cells will inhibit cancer progression through both MMP-dependent and MMP-independent pathways.

To validate this hypothesis, we have constructed CRAds (Ad5/3-CXCR4-TIMP) in which the viral E3B region has been replaced with TIMP-1, -2, or -3. Selectivity of replication is conferred by the CXCR4 promoter, which is highly active in ovarian cancer but not in the liver. Transductional selectivity is conferred by replacement of the Ad5 knob with that of the Ad3 knob, so that viral infection is mediated by binding to the Ad3 receptor, which is overexpressed on ovarian cancer cells. We have shown that the TIMP produced is functional. Moreover, expression of TIMP inhibits neither the oncolytic potency nor selectivity of replication of Ad5/3-CXCR4-TIMP. The efficacy of Ad5/3-CXCR4-TIMP will be evaluated *in vivo* in a murine model of intraperitoneally disseminated ovarian cancer. These studies will elucidate the potential of this novel agent for the treatment of ovarian cancer in humans.

Yuskaitis, Christopher Joseph (Chris)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Richard S. Jope
Title	Lithium rescues biochemical and behavioral phenotypes in a mouse model of Fragile X Syndrome

Abstract

Fragile X syndrome (FXS) is the most common form of inherited mental retardation in addition to being one of the few known genetic causes of autism. Lithium, a selective glycogen synthase kinase-3 (GSK3) inhibitor, has recently been identified as a potential therapeutic in FXS. Therefore, we tested the hypothesis that chronic, therapeutically relevant lithium treatment rescues a deficit in inhibitory serine-phosphorylation in GSK3 and FXS-associated behaviors in C57Bl/6 *Fmr1* knockout mice. Using western blot analysis, we found that impaired inhibitory serine-phosphorylation of GSK3 is a robust phenotype in C57Bl/6 *Fmr1* knockout mice brains, and that chronic lithium treatment reversed the hyperactive GSK3 in the brains of *Fmr1* knockout mice. Chronic, therapeutically relevant lithium treatment also rescued altered behaviors exhibited by *Fmr1* knockout mice including open field activity, elevated plus-maze, and passive avoidance. Moreover, chronic lithium treatment increased brain derived neurotrophic factor (BDNF) levels in *Fmr1* knockout mice brains, similar to previous reports in wild-type mice, suggesting that increasing BDNF levels may contribute to the therapeutic effect of lithium. Taken together, these findings support the hypothesis that impaired inhibitory regulation of GSK3 contributes to the pathogenesis of FXS and support GSK3 as a potential therapeutic target for patients with FXS.

Zimmerman, Jacquelyn Winifred (Jackie)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Boris Pasche
Title	A Novel Therapeutic Approach to Breast Cancer Using Amplitude Modulated Radiofrequencies

Abstract

Despite advances in targeted chemotherapy and radiation, breast cancer continues as the second leading cause of cancer death in women. Recently, we have seen both partial and complete tumor responses in patients with refractory metastatic breast cancer when treated with Low Energy Emission Therapy (LEET) via an intraubuccal administration system. The battery powered OncoBionic P1 device used to administer the therapy delivers an electromagnetic field dose that is 100 to 1000 times less than that delivered by cellular phones. The U.S. FDA does not consider this a significant risk device, as there have been minimal adverse side effects reported by patients. Although there have been both objective and subjective tumor responses to this therapy, its mechanism of action is unknown. Therefore, we are attempting to replicate patient responses in both *in vitro* and *in vivo* models to dissect the molecular events leading to the arrest of tumor cell growth. We used MCF-7 cells in our initial *in vitro* experiments, since they parallel the ER/PR positive, ERBB2 negative tumors that responded in patient studies. Cells were exposed to either a previously determined set of breast tumor specific frequencies or a set of dummy frequencies at least 5 Hz of the breast tumor specific frequencies. Treatments were given in three one-hour increments daily for a total of one week, to mimic daily patient treatment. Following 21 total hours of exposure, we ran a proliferation assay to examine relative differences in ATP between the two groups. This assay demonstrated less ATP to a statistically significant degree in the cells exposed to tumor specific frequencies, corresponding to fewer viable cells. These preliminary results have encouraged us to plan functional *in vitro* studies to further explore the mechanism of action and an *in vivo* mouse model to investigate tumor response in mice with tumor xenografts.

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