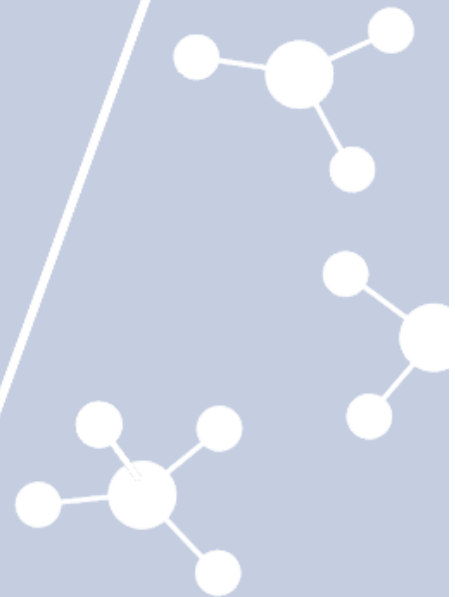


University of Alabama
School of Medicine

Dale J. Benos
Medical Student
Research Day 2011



Design by DK

JUDGES

Dr. Zusasanna Bebok
Dept. of Cell Biology

Dr. Mark Bevensee
Dept. of Physiology & Biophysics

Dr. Edlira Bashari Clark
Dept. of Physiology & Biophysics

Dr. Derek A DuBay
Dept. of Surgery

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Dept. of Cell Biology

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Dept. of Neurology

Dr. Raghavan Raju
Dept. of Surgery

Dr. Elizabeth Sztul
Dept. of Cell Biology

Dr. Qin Wang
Dept. of Physiology and Biophysics

Dr. James Willig
Dept. of Medicine

Dr. Bradford Woodworth
Dept. of Surgery

Oral Presentations

Lecture Room E

Short-term Research

Mata Burke, MS2*

“Gamma-secretase Inhibitors Increase Sensitivity to LDE225, a Smoothened Antagonist, in Chemoresistant Ovarian Cancer Cells In Vitro”

Mentor: Dr. Charles Landen

Kyle Den Beste, MS2

“Epithelial Permeability Alterations in an Air-Liquid Interface Model of Allergic Fungal Rhinosinusitis”

Mentor: Dr. Sarah Wise

Reese Feist, MS2

“Muller Cells and Retinal Pigment Epithelium Contribute to the Myofibroblast Population in Proliferative Vitreoretinopathy”

Mentor: Dr. Clyde Guidry

Akash Kapadia, MS2

“Estrogen Inhibits CRP-Induced Inflammation in Mouse Macrophages in an Estrogen-Receptor Dependent Manner”

Mentor: Dr. Fadi Hage

David Kim, MS2

“Multimorbidity Patterns in HIV+ Patients: The Role of Obesity in Chronic Disease Clustering”

Mentor: Dr. James Willig

Sara Wilkins, MS2

“Defining Variation in Management of Children with Sports-Related Concussion: First Step to Standardization”

Mentors: Drs. Drew Davis, James Johnston, and Chevis Shannon

Oral Presentations

Lecture Room A

Intermediate-term Research

Jennifer Hadley, MSTP (GS2)

“Imaging Biomarkers for the Prediction of Treatment Response in Schizophrenia”

Mentor: Dr. Adrienne Lahti

Joseph Kundukulam, MS3

“Rotator Cuff Crepitance: Can Cuff Tears be Felt?”

Mentor: Dr. Brent Ponce

John-Ryan McAnnally, MS4*

“National Estimates of Mortality from Sepsis and Septic Shock in the Era of Early Goal-Directed Therapy”

Mentor: Dr. Henry Wang

Adam Weber, MS4

“Dual-Energy Single-Source CT for Diagnosis of Adrenal Lesions”

Mentor: Dr. Desiree Morgan

Long-term Research

Juan Calix, MSTP (GS4)

“Ambiguous Serotypes with Serogroups 9 and 11 of Streptococcus pneumoniae are Mediated by Differential Disruption of the O-acetyltransferase wcjE”

Mentor: Dr. Moon Nahm

Vishnu Cuddapah, MSTP (GS4)*

“Kinase activation of ClC-3 Chloride Channels Accelerates Cytoplasmic Condensation During Mitotic Cell Rounding in Human Glioma Cells”

Mentor: Dr. Harald Sontheimer

Poster Presentations

Group A

A-1. Alex Abangan, MS4

“Quality of CPR Performed During In-Hospital Cardiac Arrest at University Hospital, University of Alabama at Birmingham”

Mentor: Dr. Andrew Edwards

A-2. Robin Bishop, MS4

“Predictors of Infant Mortality in Alabama Counties”

Mentor: Dr. Tom English

A-3. Valerie Gribben, MS4*

“Illness and Injury in Mary de Morgan’s Fairy Tales”

Mentor: Dr. Hughes Evans

A-4. David Hardin, MS2

“Rural Alabama: Observations of Diversity in Medical Practices and Health Care Challenges”

Mentor: Dr. John Wheat

A-5. Rachel Martin, MS3

“High-Fidelity Simulations for Orthopedic Residents: Medical Complications and Systems Challenges”

Mentor: Dr. Marjorie Lee White

A-6. Harry Saag, MS4

“Impact of Healthcare Reform on UAB Hospital”

Mentor: Dr. Benjamin Taylor

A-7. Keri Sewell, MS3

“Perceptions and Barriers to Usage of Generic Medications in a Rural African-American Population”

Mentor: Dr. Monika Safford

A-8. Julie Turner, MS4

“Breadth versus Depth? Repeated Versus Mixed Case Selection in Pediatric Resident Simulation”

Mentor: Drs. Nancy Tofil and Marjorie Lee White

Poster Presentations

Group B

B-1. Daniel DiToro, MSTP (MS2)

“Role of TCR Specificity in CD4 T Cell Differentiation”

Mentor: Dr. Casey Weaver

B-2. Brian Dizon, MSTP (GS5)

“Neonatal Exposure to Bacterial Carbohydrate Antigens Exerts Long-Lasting Effects on Clonal B Cell Responses”

Mentor: Dr. John Kearney

B-3. Laura Dover, MS2

“Lymphocyte Activation Gene-3 Modulation Potentiates Immunogenesis of GM-CSF-Secreting Whole-cell Cancer Vaccines in HER-2/neu Tolerized Mice”

Mentor: Dr. Elizabeth Jaffe

B-4. Ian Flaniken, MS2

“Assessing the Role of DNA Damage Response in a Human Disease Model”

Mentor: Dr. Frederick Goldman

B-5. David Gaston, MSTP (GS4)*

“A Conditionally-Replicating oHSV Vector Dually Encoding IL-15 and IL-15 Receptor Alpha for Malignant Glioma Therapy”

Mentor: Drs. Jacqueline Parker and Richard Whitley

B-6. Abhay Kulkarni, MS2

“Therapeutic Antitumor Activity of Allogeneic Gamma Delta T-cells”

Mentor: Dr. Richard Lopez

B-7. Katie Poholek, MSTP (GS2)

“The Role of Interleukin-21 in the Pathogenesis of Inflammatory Bowel Disease”

Mentor: Dr. Laurie Harrington

B-8. Jeff Singer, MSTP (MS2)

“The HAT-BAC Mouse Model: A New Tool in Functional Genomics”

Mentor: Dr. Casey Weaver

Poster Presentations

Group C

C-1. John Frederick, MS3

“Anti-CD147 Inhibits Proliferation by Down Regulation of EGFR in Cutaneous Squamous Cell Carcinoma”

Mentor: Dr. Eben Rosenthal

C-2. Ellie Killian, MS4

“Receptor Concordance in Triple-Negative Breast Cancer (TNBC) Recurrences”

Mentor: Dr. Helen Krontiras

C-3. Danuel Laan, MS2

“Novel Compounds Which Inhibit Epidermal Growth Factor Dependent Cancer Growth”

Mentor: Dr. Gary Piazza

C-4. Patrick McCabe, MS2

“Bladder, Bowel, and Sexual Dysfunction Symptoms One to Five Years after Intensity-Modulated Radiation Therapy for Prostate Cancer”

Mentors: Drs. Patricia Goode, Rojymon Jacob, and David Redden

C-5. Shyam Patel, MS2

“Efficiency of PSA-AV Score as a Predictor for a Positive Prostatic Biopsy when Compared to Age-Adjusted PSA and Non-adjusted PSA Methods”

Mentor: Dr. Rizk El-Galley

C-6. Nick Piazza, MS2

“Phosphodiesterase-5 (PDE-5) as a Potential Target and Marker of Lung Cancer”

Mentor: Dr. Isam-Eldin Eltoun

C-7. Tim Stooksberry, MS2

“The Risk of Prostate Cancer in Patients with Zigzag PSA Patterns”

Mentor: Dr. Rizk El-Galley

C-8. Terence Zimmerman, MS2*

“The Prognosis of Bone Invasion in Small Squamous Cell Carcinomas of the Oral Cavity”

Mentor: Dr. Eben Rosenthal

Poster Presentations

Group D

D-1. Alana Bates, MS2

“Determining Body Mass Index Trends in Young Adult Survivors of Congenital Heart Disease”

Mentor: Dr. Walter Johnson

D-2. Katie Billue, MS4

“A Web-Based Diabetes Intervention for Physician: A Cluster-randomized Effectiveness Trial. A Closer Look at Medication Intensification in Rural Primary Care Practices”

Mentor: Dr. Carlos Estrada

D-3. Jonathan Black, MS3

“Impact of Obesity on Outcomes in Cardiac Rehabilitation”

Mentor: Dr. Vera Bittner

D-4. Matt Breland, MS2

“Impact of Follow-up on Clinical Outcomes after Laproscopic Roux-en-Y Gastric Bypass”

Mentor: Dr. Jayleen Grams

D-5. Andrew Klinger, MS2*

“Contribution of Food Additives to Daily Sodium and Phosphorus Intake in Diets Rich in Processed Foods”

Mentors: Drs. Orlando Gutierrez and Emmy K. Bell

D-6. Elizabeth Luke, MS2

“Perceptions of the Effects of a Peer-Delivered Diabetes Intervention on Healthy Eating Habits of the Peer’s Families”

Mentor: Dr. Monika Safford

D-7. Elizabeth Ma, MSTP (MS1)

“Monomeric and Oligomeric Catechin and Epicatechin in Commercial Grapeseed Extract Dietary Supplements”

Mentor: Dr. Stephen Barnes

D-8. Brittany Richardson, MS2

“Diabetes Connect: African American Patients’ Perceptions of the Community Health Worker Model for Diabetes Care”

Mentor: Dr. Andrea Cherrington

D-9. Alexander Taylor, MS4

“Diabetic Patients Presenting for Retinal Surgery- A High Risk Population”

Mentor: Dr. Gwendolyn Boyd

D-10. My-Hanh Thi Vu, MS2

“Determining Common Parental Styles for Obese Adolescents at a Weight Management Clinic”

Mentors: Drs. Stephanie Wallace and Heather Austin

Poster Presentations

Group E

E-1. Emily Blosser, MSTP (GS3)

“Maternal Antibiotics Increase Risk of Klebsiella Late-Onset Sepsis in Neonatal Mice”

Mentor: Dr. David Randolph

E-2. Suzanne McCluskey, MS4*

“Challenges and Missed Opportunities in the Diagnosis of Acute HIV”

Mentor: Dr. Sonya Heath

E-3. Okechukwu Mgbemena, MS2

“HIV-1 Cryptic Epitopes Induce a Lower Magnitude by Similar Functional Avidity Responses When Compared to Traditional Epitopes”

Mentor: Dr. Paul Goepfert

E-4. Aimee Merino, MSTP (GS5)

“HLA-B Signal Peptide and Common Motifs in Heterosexual HIV-1 Acquisition”

Mentor: Dr. Richard Kaslow

E-5. Sara Stone, MS2

“HIV Modulation of HLA-E Surface Expression of CD4 T Cells”

Mentor: Dr. Paul Goepfert

E-6. Morgan Wilbanks, MS3

“Dysuria in the Emergency Department: A Missed Opportunity for Chlamydia Diagnosis?”

Mentor: Dr. William Geisler

E-7. Susan Wiltrakis, MS2

“Comparing the Glasgow Coma Scale and Infant Face Scale in Pediatric Patients with Influenza Infection”

Mentor: Dr. David Kimberlin

E-8. Adam Zelickson, MS2

“Detection and Quantification of Bacterial Load in open Fracture Models: Investigation of Desferrioxamine as a Novel Treatment for Open Fractures with Osteomyelitis”

Mentor: Dr. Shawn Gilbert

Poster Presentations

Group F

F-1. Amanda Brito, MS2

“Mucoïd Streptococcus pneumonia in Cystic Fibrosis”

Mentor: Dr. Marilyn Crain

F-2. Michael Chestnut, MS3*

“Resveratrol Enhances Airway Surface Liquid Depth by Increasing CFTR Channel Open Probability”

Mentor: Dr. Brad Woodworth

F-3. Justin Jackson, MS4

“Effects of Inter Alpha Trypsin Inhibitor on Amiloride Sensitive Epithelial Sodium Channels (ENaC)”

Mentor: Dr. Sadis Matalon

F-4. Erica Johnson, MS4

“Effects of Respiratory Syncytial Virus (RSV) and Chlorine Exposure on Pulmonary Epithelium”

Mentor: Dr. Sadis Matalon

F-5. Eric Kebbel, MS2

“CFTR Modulation by the Tobacco Smoke Toxin Acrolein”

Mentor: Dr. Brad Woodworth

F-6. Ashley Shafferman, MS2

“Prolyl Endopeptidase Expression in Human Airway Epithelial Cells and its Regulation by LPS”

Mentor: Dr. Amit Gaggar

F-7. Alex Smith, MS2

“Relationship between the Viscoelastic Properties of Cystic Fibrosis and Chronic Obstructive Pulmonary Disease Airway Mucus”

Mentor: Dr. Steven Rowe

Poster Presentations

Group G

G-1. Drew Cochran, MS4

“Increased Superoxide Dismutase Activity in Endothelial Cells Treated with Liposomes”

Mentor: Dr. Sadis Matalon

G-2. Ryan Corrick, MSTP (GS4)*

“Acute Hepatic Growth Hormone Resistance Following Injury”

Mentor: Dr. Joseph Messina

G-3. Nicholas Deep, MS3

“Micro-anatomy of the Renal Sympathetic Nervous System: A Human Postmortum Histologic Study”

Mentor: Dr. Farrell Mendelsohn

G-4. Samuel Douglas, MS2

“Echocardiographic Assessment of Aortic Size and Morphometry in a Population of Children With and Without Congenital Heart Disease or Connective Tissue Disease”

Mentor: Dr. Walter Johnson

G-5. Woody Farrington, MS4

“A Retrospective Analysis of Aortic Remodeling Following TEVAR in Acute and Chronic Dissection”

Mentor: Dr. William Jordan

G-6. Travis Hull, MSTP (GS1)

“Cardiomyocyte-Specific Heme-Oxygenase-1 Overexpression in Cardiac Transplantation”

Mentor: Dr. Anupum Agarwal

G-7. Donny Kakati, MS4

“Direct Regulation of Myocardial Glycogen Metabolism by the Cardiomyocyte Circadian Clock”

Mentor: Dr. Martin Young

G-8. Jon Lockhart, MS2

“FOKLF1: A New Target for Sickle Cell Disease and β Thalassemia Therapy”

Mentor: Dr. Tim Townes

G-9. Pratik Patel, MS2

“Effects of Background Velocity Error and Breath-Hold Techniques on Blood Flow Quantification Using Phase Contrast MR Imaging”

Mentor: Dr. Steven Lloyd

G-10. Efe Sahinoglu, MS2

“Anti-inflammatory Effect of O-GlcNAcylated NF κ B, p65”

Mentor: Dr. Suzanne Oparil

Poster Presentations

Group H

H-1. Asher Albertson, MSTP (GS4)*

“HCN Channels Modulate Synaptic Transmission onto Layer V Basket Cells”

Mentor: Dr. John Hablitz

H-2. Avinash Honasoge, MSTP (GS2)

“Proton Concentration Modulates the Rate of Glioma Invasion via a pH-sensitive K⁺ Conductance”

Mentor: Dr. Harald Sontheimer

H-3. Jarrod Meadows, MSTP (GS1)

“Epigenetic Control of Homeostatic Plasticity”

Mentors: Drs. John Hablitz and David Sweatt

H-4. Katie McQueen, MS2

“Expression and Regulation of Astrocytic Proteins During the Development of Rats”

Mentor: Dr. Michelle Olsen

H-5. Sini Nwaobi, MSTP (GS3)

“Alterations in Astrocytic Gene Expression Following Pediatric Traumatic Brain Injury”

Mentor: Michelle Olsen

H-6. Libby Van Gerwen, MS2

“Comparison of Language Skills and Educational Development in Post-Cochlear Implant Children with Non-Syndromic Deafness due to GJB2 Gene Mutations to That of Their Hearing Peers”

Mentor: Dr. Nathaniel Robin

H-7. Stacey Watkins, MSTP (GS3)

“Hydrodynamic Cytoplasmic and Nuclear Changes Aid Cell Invasion”

Mentor: Dr. Harald Sontheimer

H-8. Dylan Whisenhunt, MS2

“Length-Dependent Behavior of Beta Amyloid Polypeptide Within the Lipid Bilayer Immediately Following Generation by Gamma Secretase”

Mentor: Dr. Jere Segrest

Poster Presentations

Group I

I-1. Heather Allen, MSTP (GS2)

“Complement Activation in Response to Overexpression of Alpha-Synuclein in the Substantia Nigra”

Mentor: Dr. David Standaert

I-2. Stephanie Brosius, MSTP (GS1)

“Generation of LAMP-1 Knockdown and Overexpression Cell Lines for Study of ASYN Clearance”

Mentor: Dr. John Shacka

I-3. Anna Edmiston, MS2

“Functional and Psychological Recovery Following Spinal Cord Injury: Systematically Evaluating the Effects of Exercise Rehabilitation in a Rat Model”

Mentor: Dr. Candace Floyd

I-4. David Figge, MS2

“Chronic Cocaine Administration Causes Epigenetic Alterations within the Nucleus Accumbens”

Mentor: Dr. David Sweatt

I-5. Mikael Guzman Karlsson, MSTP (GS1)

“Assessing G9a-p65/RelA Interactions during Memory Consolidation via In Situ PLA”

Mentor: Dr. Farah Lubin

I-6. Travis Lewis, MSTP (GS5)

“Transduction of Dopamine Neurons by Adenoviral Vectors is Modulated by CAR Expression: Rational for Tropism Modified Vectors in PD Gene Therapy”

Mentors: Drs. David Standaert and David Curiel

I-7. Cody Smith, MS3

“Role for MEG in Surgical Management of Lesional Epilepsy”

Mentors: Drs. Jeffrey Blount and Robert Knowlton

I-8. Brian Warmus, MSTP (GS2)*

“Repetitive Behavior and Salience Network Dysfunction in a Mouse Model of Frontotemporal Dementia”

Mentor: Dr. Erik Roberson

Poster Presentations

Group J

J-1. Alexander Bray, MS2

“Characterization of the Susceptibility of Pediatric Medulloblastomas to Neuroattenuated HSV Infection”

Mentor: Dr. Richard Whitley

J-2. Nicole Brossier, MSTP (GS5)

“Role of Ras Isoforms in Malignant Peripheral Nerve Sheath Tumors”

Mentor: Dr. Steven Carroll

J-3. Phillip Cezayirli, MS2

“Glioblastoma Multiforme Patient Prognosis: Can Change in Peritumoral Cerebral Blood Flow Predict Survival?”

Mentors: Drs. Burt Nabors and Asim Bag

J-4. John Jarboe, MSTP (GS3)*

“MARCKS is a Novel Prognostic Factor for Tumors with Un-methylated MGMT Status among the Proneural Subtype of Glioblastoma Multiforme”

Mentor: Dr. Christopher Willey

J-5. Samina Karim, MS2

“CMV Infection Enhances Immune Evasion of Glioma-derived Cell Lines to In Vitro Expanded/ Activated V δ 1+ T Cells via Down-regulation of NKC2D Ligands”

Mentor: Dr. Lawrence Lamb

J-6. Joi Nichols, MS4

“Exposure of Neural Stem Cells to Billirubin and Treatment with Theophylline”

Mentor: Dr. Brian Sims

J-7. Nicholas Reish, MSTP (GS5)

“Uncovering Klotho in the Retina”

Mentor: Dr. Alicia Gross

J-8. Evan Thomas, MSTP (GS3)

“Dose Rate Effect on Apoptotic Activity in Irradiated Glioma Cell Lines”

Mentor: Dr. John Fiveash

J-9. Adam Weber, MS4

“Corneal Opacity as a Prognostic Factor in Endophthalmitis”

Mentor: Dr. Richard Feist

Poster Presentations

Group K

K-1. Amber Bishop, MS4

“Pediatric Medical and Trauma Resuscitation Teamwork Survey”

Mentor: Dr. Marjorie Lee White

K-2. Jeff DeMedicis, MS4

“Physical Therapy in the Hospital. Importance of Functional Assessment”

Mentor: Dr. Cynthia Brown

K-3. Katy Hines, MS4

“Grandparent Caregivers’ Knowledge Deficit Regarding Child Safety and Development”

Mentor: Dr. Amanda Soong

K-4. Walter Parker, MS3

“High-Fidelity Simulation as Part of Teen Trauma Prevention”

Mentors: Drs. Marjorie Lee White and Nancy Tofil

K-5. MeKeisha Pickens, MS4*

“Randomized Trial Comparing Two Mass Casualty Triage Systems in Simulated Pediatric Mass Casualty Incident”

Mentor: Dr. Marjorie Lee White and Dr. Nancy Tofil

K-6. Erinn Schmit, MS4

“Neonatal Intubations Among Pediatric Providers”

Mentors: Drs. Marjorie Lee White and Nancy Tofil

K-7. Lauren Stephens, MS3

“Validation of the Acute Care Mobility Assessment in Older Adults”

Mentor: Dr. Cynthia Brown

Poster Presentations

Group L

L-1. Laura Allen, MS2

“Predictors and Outcomes of Surgical Intervention for Birth-Related Brachial Plexus Palsy”

Mentor: Dr. John Wellons, III

L-2. Ashley Bentley, MS4

“Return to Play After Shoulder Surgery in National Football League Athletes”

Mentor: Dr. Brent Ponce

L-3. Ashley Bentley – MS4

“Roadmap for Arthroscopic Release of the Suprascapular Nerve at the Transverse Scapular Ligament”

Mentor: Dr. Brent Ponce

L-4. Ben Bush, MS4*

“Comparison of Surgical Approaches to Tumors of the Oropharynx”

Mentor: Dr. Scott Magnuson

L-5. Sara Foppe, MS2

“Shorter Stay and Similar Complication Rate with Limited Laminotomy for Selective Dorsal Rhizotomy: A Comparison Study”

Mentor: Dr. John Wellons, III

L-6. Benjamin Raines, MS2

“Long Term Outcomes After Ulnar Collateral Ligament Reconstruction in Competitive Baseball Players: A Minimum of 10 Years Follow-Up”

Mentor: Dr. James Andrews

L-7. Shilpa Reddy, MS4

“Incidence of Postoperative Outer Layer Foveal Defect Following Idiopathic Macular Hole Repair”

Mentor: Dr. John Mason, III

L-8. Daniel Reid, MS2

“Development of Novel HIF Activating Compounds for Musculoskeletal Application”

Mentor: Dr. Shawn Gilbert

L-9. Charles Salisbury, MS2

“Arcuate Retinotomy for the Repair of Large Macular Holes”

Mentor: Dr. Nathan Littlejohn

L-10. Thomas Sellers, MS2

“Weight Gain Following the Surgical Treatment for Blount Disease”

Mentor: Dr. Joseph Khoury

Poster Presentations

Group M

M-1. Kym Do, MS2

“Do Stool Form and Frequency Correlate with Colonic Transit in Adults with Fecal Incontinence?”

Mentor: Dr. Alayne Markland

M-2. Ian Campbell, MS4

“The History of the Fiberoptic Endoscope”

Mentor: Dr. Hughes Evans

M-3. Lindsey Glueckert, MS2*

“Impact of Insurance Status on Post-Liver Transplant 5-Year Survival”

Mentors: Dr. Derek Du Bay

M-4. Maxwell Thompson, MS2

“Risk Factors Associated with Reoperation due to Hemorrhage Following Liver Transplantation”

Mentor: Dr. Derek DuBay

Abangan, Alexandra Leigh (Alex)

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Dr. Andrew Edwards

Co-Authors Matthew Gentry

Title Quality of CPR Performed During In-Hospital Cardiac Arrest at University Hospital, University of Alabama at Birmingham

Abstract

Background: There is a relative paucity of studies analyzing In-hospital CPR quality, despite reported return of circulation of only 30% for witnessed arrests within the hospital. Previous studies analyzing quality variables such as no flow fraction (NFF) and compression rate, published prior to CPR guideline changes in 2005, generally demonstrated rates much lower than recommended by the AHA. Objective: To determine the quality of CPR performed during in-hospital cardiac arrests using objective CPR quality variables and matching this data to national registry of CPR (NRCPR) data for outcome, demographic, and other pertinent data. Methods: Retrospective data was collected from Lifepak20 monitors located throughout the hospital from 1/10/2011-3/9/2011 and analyzed using Physio-Control software and manual review to determine rate of compressions and CPR ratio during each cardiac arrest. Supplementary data, including outcome and demographics, were obtained from the NRCPR database. Results: 22 viable files with corresponding events documented in the NRCPR database were identified. Return of spontaneous circulation (ROSC) was seen in 54.5% of patients; however 97.7% of patients died prior to discharge. Patients who had ROSC had a higher CPR ratio: 86% vs. 76%, and a higher compression rate: 131 vs. 128 compressions/minute. There was no significant difference between the first five minutes and total CPR time with regard to compression rate or CPR ratio. 96% of patients received CPR with greater than 100 compressions/minute, and over 25% of patients received compressions at a rate over 140 per minute. Conclusions: Although small sample size limited the generalizability of the data, at UAB hospital both the CPR ratio and the compression rate seem to be greatly higher than previously published data. Given the results from this small study, there appears to be a need for a larger database which could have therapeutic implications for the manner in which CPR is performed.

Albertson, Asher Jefferson (Asher)**Project Length** Long**Prior Research Experience** Yes**Funding Source** NIH Medical Scientist Training Program Grant**Advisor** Dr. John Hablitz**Co-Authors****Title** HCN Channels Modulate Synaptic Transmission onto Layer V Basket Cells**Abstract**

Hyperpolarization activated non-specific cation (HCN) channels pass an inward, cationic current (I_h) upon membrane hyperpolarization. The actions of HCN channels have been well characterized within the dendrites of excitatory hippocampal and cortical pyramidal neurons. At this location, I_h active at resting membrane potentials filters incoming excitatory inputs, reduces their ability to summate, and decreases the intrinsic excitability of the membrane. These actions together reduce cellular and network excitability. Perhaps unsurprisingly, HCN channels are almost universally reduced in models of epilepsy. The actions of HCN channels in interneurons have not been extensively investigated. Interneurons lack the long, linearly oriented dendrites along which HCN channel function has been investigated. It is our hypothesis that I_h modulates the intrinsic and input-processing properties of interneurons differently than pyramidal neurons. Differential or opposing effects of HCN channel disruption in excitatory and inhibitory cell types may contribute to epileptic pathology. To examine this, we performed whole-cell patch clamp recordings from fast-spiking, layer-five basket cells in acute slices from rat neocortex. We examined action potential trains using depolarizing current pulses. Excitatory post-synaptic potentials (EPSPs) were evoked using extracellular stimulation in the presence of inhibitory blockade. Experiments were performed before and after I_h inhibition with the HCN channel inhibitor ZD-7288. We observed very low levels of I_h in neocortical basket cells. Despite this HCN channel inhibition significantly decreased the amplitude of evoked EPSPs. Additionally, HCN channel inhibition decreased interneuron's ability to maintain firing during prolonged spike trains. ZD-7288 also decreased action potential frequency during spike trains. Unlike pyramidal neurons, loss of I_h did not increase summation of multiple EPSPs evoked at 25Hz. Together, these data suggest that in contrast to excitatory neurons, loss of I_h may decrease the excitability of inhibitory neurons.

Allen, Heather Elizabeth (Heather)**Project Length** Intermediate**Prior Research Experience** Yes**Funding Source****Advisor** David Standaert**Co-Authors** H.E. Allen, A.S. Harms, D.G. Standaert**Title** Complement activation in response to overexpression of alpha-synuclein in the substantia nigra**Abstract**

Parkinson disease (PD) is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), resulting in tremor, rigidity, bradykinesia and postural instability in 3-5% of people above age 65. Several studies have suggested that chronic inflammation is important for PD neurodegeneration. For example, regular users of non-steroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen, have a reduced risk of developing sporadic PD, and a genetic variation in a noncoding region of HLA-DR, an antigen-presenting protein, is associated with the development of late-onset PD. Although IgG and several complement components throughout the cascade (C1q, C4, C3, C7 and C9) are present in post-mortem brain in PD, few studies have addressed whether complement is functionally relevant to the disease process. Previously, we have shown that targeted overexpression of alpha-synuclein (a-syn) in the SNpc of mice driven by an adeno-associated virus (AAV) vector recapitulates the reactive microgliosis observed in human PD and leads to a 30% reduction in the total number of dopaminergic neurons 6 months post-injection. Therefore, we examined whether targeted a-syn overexpression in the SNpc could directly lead to complement activation. We detected changes in complement component expression and localization by quantitative PCR and immunohistochemistry. Results from these studies indicate that overexpression of alpha-synuclein induces upregulation of C3 and other complement components, suggesting a potential mechanism of neurodegeneration relevant to PD. Support provided by the Parkinson's Association of Alabama.

Allen, Laura Ansley (Laura)

Project Length	Short
Prior Research Experience	Yes
Funding Source	HSF Community and Rural Health Fellowship
Advisor	Dr. John Wellons, III
Co-Authors	Laura A. Allen, BE, Nicole A. Safiano, Michael I. Falola, MD, MPH, Camille E. Broome, MPH, Chevis N. Shannon, MBA, MPH, DrPH, John C. Wellons, III, MD
Title	Predictors and Outcomes of Surgical Intervention for Birth-Related Brachial Plexus Palsy

Abstract

Introduction: Risk factors for birth related brachial plexus palsy (BRBPP) have been well reported, but few studies address risk factors specific for children requiring surgical intervention. The intention of this study was to identify maternal, infant, and socioeconomic status (SES) risk factors and examine functional outcomes at a single center between 1999 and 2010.

Methods: A retrospective chart review was conducted to determine the nature of injury, type of procedure, and functional outcomes. 208 infants were identified with BRBPP that presented for neurosurgical care as infants. Of those, 36 (17%) received neurosurgical intervention and had at least 9 months follow up. Descriptive statistics and exploratory analysis were performed using SAS 9.2.

Results: Patients undergoing surgery were more likely to have a history of grade II or III macrosomia (>4500 grams) compared to those who did not undergo surgery (p=0.002). Gender, race, insurance status, income markers, maternal age, gestational diabetes, shoulder dystocia, and use of vacuum/forceps at birth, were not different between the two groups. Of those undergoing surgery, 18 procedures were done to improve shoulder function and 35 procedures were done to improve elbow flexion. Of those with adequate initial and post-operative Mallet Scores, 9/14 (64%) improved in shoulder abduction and 13/20 (65%) improved in hand-to-mouth function (p=NS).

Conclusion: Of the maternal, infant, and SES factors, only grade II or III macrosomia was associated with operative over non-operative BRBPP. Surgical intervention appears to improve functional outcomes, but the natural history of unimproved non-operated infants in this population is unknown and challenging to analyze.

Bates, Alana Louise (Alana)

Project Length Short
Prior Research Experience Yes
Funding Source HSF Community and Rural Health Fellowship
Advisor Dr. Walter H Johnson

Co-Authors

Title Determining Body Mass Index Trends in Young Adult Survivors of Congenital Heart Disease

Abstract

Background: Exponentially rising numbers of congenital heart disease (CHD) patients survive into adulthood. There is limited data on the impact of the obesity epidemic in this population.

Objectives: We hypothesized that CHD patients would have higher BMIs than those without CHD because of potentially decreased exercise tolerance.

Materials and Methods: We retrospectively studied 19-24 year old patients of the Alabama Congenital Heart Disease Center (ACHDC) with at least one great (GC) or moderate complexity (MC) heart defect, comparing BMI to young adults without CHD using the Behavior Risk Factor Surveillance System (BRFSS). Inclusion criteria included (1) current age 19-24 y, (2) ≥ 1 of 23 CHD diagnoses considered moderate or severe, and (3) medical visit at ACHDC within the past 2 years.

Results: We studied 219 patients: GC 130, and MC 89, with overall mean BMI 25.94 (mean age 252.28 mo). Of the GC group, mean BMI 25.26 (mean age 254.33 mo); the MC group had mean BMI 26.97 (mean age 249.29 mo). Differences in mean BMI were not statistically significant between groups (Mann-Whitney test, $P = 0.0682$). Of our patients, 55.71% were normal (BMI <25), 19.63% overweight ($25 \leq \text{BMI} < 30$), and 24.66% obese (BMI ≥ 30). Compared to BRFSS (2005 Alabama-specific normal data for this age range; 47.3% normal BMI, 28.6% overweight, and 24.2% obese), we observed greater normal, less overweight, and nearly identical percentages of obese patients.

Conclusions: Our patients' BMI's did not appear different from that of other young adults in Alabama. We conclude that our CHD patients overall likely have health and exercise tolerance that is sufficient to avoid obesity rates in excess of the normal population.

Bentley, Kathryn Ashley (Ashley)

Project Length Short

Prior Research Experience No

Funding Source

Advisor Dr. Brent Ponce

Co-Authors Ponce B A, Savage A J, Larrison M, McGwin G

Title Roadmap for Arthroscopic Release of the Suprascapular Nerve at the Transverse Scapular Ligament

Abstract

Background: Suprascapular neuropathy is becoming increasingly recognized as a source of shoulder pain and weakness. Arthroscopic techniques for release of the nerve at the suprascapular notch have been recently described. However, this technique is technically demanding and has been recommended to be performed only by surgeons with advanced arthroscopic skills.

Purpose: The purpose of our study is to better define the arthroscopic anatomy and landmarks for exposing and releasing the suprascapular nerve at the level of the transverse scapular ligament.

Methods: 10 matched pairs (20 shoulders) of fresh human cadaveric shoulder underwent arthroscopic release of the suprascapular nerve at the transverse scapular ligament by a surgical technique previously described. During arthroscopic release, the distances from the posterior, anterolateral, and suprascapular nerve portals to the origin of the TSL were recorded. Following arthroscopic TSL release, open dissection of the shoulders was then performed and the distance from the SSN portal at the origin of the transverse ligament to both the suprascapular artery and nerve was measured.

Results: Arthroscopic portal distances to the TSL were: posterolateral – 8.8mm (range:7.0-10.4), anterolateral 8.9mm (range:7.0-10.3) and suprascapular nerve portal – 4.9mm (range:3.7-6.5). No significant differences were noted in extremity, age or gender. In all cases we were able to expose the lateral origin of the transverse scapular ligament (TSL) without injury to the suprascapular artery or nerve. In all specimens the artery passed superior to the TSL and the nerve inferior, and in all specimens the artery was noted to be more lateral than the nerve.

Conclusion: Arthroscopic suprascapular nerve release can be performed safely and effectively as long as the surgeon has an intimate understanding of the arthroscopic anatomy of this region. This study helps to clarify distances required for exposing the transverse scapular ligament.

Bentley, Kathryn Ashley (Ashley)

Project Length Intermediate

Prior Research Experience No

Funding Source

Advisor Dr. Brent Ponce

Co-Authors Ponce B AFleisig G, Cain L A, Dugas J, Andrews J

Title Return to Play after Shoulder Surgery in National Football League Athletes

Abstract

Introduction: Nearly half of the athletes at the National Football League (NFL) combine have a history of shoulder injuries. However, no study has defined the spectrum of shoulder injuries in the NFL requiring surgery and analyzed the factors impacting return to play (RTP).

Purpose: To describe the spectrum of injury, determine the RTP rate after surgery and to determine the important factors in predicting RTP.

Methods: Fifty-five NFL athletes receiving shoulder surgery were evaluated. Data were collected through operative notes and player data from www.NFL.com. Only athletes who were active NFL players at the time of injury were evaluated. Chi-square and t-tests were used to compare demographic and player characteristics according to RTP status ($p < 0.05$).

Results: The most common diagnosis was instability/labral tear (73%) followed by injury to the rotator cuff (47%). The average number of procedures performed was 2.8 and only 13% ($n=7$) athletes had a single procedure performed. The most frequently performed procedure was a Bankhart repair (18%). Thirty-eight percent of surgical cases occurred in the month of January. Seventy-four percent were defensive players ($n=42$), and the most common position was lineman ($n=45$). Seventy-eight percent (43) of athletes returned to game play, at an average of 9.1 (range 1-36) months after surgery. Average age for the group that did RTP was 30 years versus 28 for the group that did not return ($p=0.01$). The group that did not RTP was drafted an average of three rounds later ($p=0.001$) and played an average of 2.0 more seasons before surgery ($p=0.06$) than the RTP group. Absolute number of games before surgery and number of procedures performed were not associated with RTP.

Conclusion: Return to play rate after shoulder surgery in the NFL is quite high with most players having surgery in the off season. Older players were less likely to return. The majority of athletes had multiple procedures and had a mixed spectrum of disease not isolated to instability or rotator cuff pathology.

Billue, Katherine Lynn (Katie)

Project Length Intermediate

Prior Research Experience No

Funding Source

Advisor Carlos Estrada MD, MS

Co-Authors Monika M. Safford MD, Amanda H. Salanitro MD, MS, MSPH, Thomas K. Houston MD, MPH, William Curry MD, Yongin Kim MS, Jeroan J. Allison MD, MSc

Title A Web-based Diabetes Intervention for Physician: A Cluster-randomized Effectiveness Trial. A closer look at Medication Intensification in Rural Primary Care Practices.

Abstract

Objective: Determine the effectiveness of a wide-reach, low-intensity intervention aimed at provider education to improve management for patients with diabetes mellitus.

Design: Effectiveness cluster-randomized trial with baseline and follow-up cross-sections of patients with diabetes in each participating physician's practice.

Setting: Eleven US Southeastern states, 2006-2008.

Participants: Rural primary care physicians (n=205).

Intervention: Implementation trial of a Web-based multi-component intervention including interactive problem-based continuing medical education (CME), state-of-the-art performance feedback, quality improvement tools, and resources (guidelines; office-based efficiency tools for the busy practitioner; brief, culturally-relevant counseling tools).

Outcome Measures: Primary: medication intensification, a dose increase of an existing medication or addition of a new class of medication for glucose, blood pressure, and lipids control on any of the three most recent office visits. Secondary: medication intensification by strata of glucose, blood pressure, or lipid control.

Results: Of 364 physicians attempting to register, 102 were randomized to the intervention and 103 to the control arms; 95% had in-office access to the Internet; 95 physicians provided baseline and follow-up data on 2,127 patients. For A1c control, medication intensification increased in both groups (intervention, pre- 26.4% vs. post- 32.6%, p= 0.02; control, pre- 24.8% vs. post- 31.1%, p = 0.03); and confirmed in the adjusted analysis (intervention, adjusted odds ratio [AOR] 1.37; 95% confidence interval [CI] 1.06, 1.76; control, AOR 1.41 [95% CI 1.06, 1.89]); however, we observed no incremental benefit solely due to the intervention (group-by-time interaction, p = 0.82). Among patients with the worst glucose control (A1c >9%), intensification increased in both groups (intervention, pre- 35% vs. post- 63%, p= 0.002; control, pre- 36% vs. post- 61%, p = 0.008).

Conclusions: A wide-reach, low-intensity, Web-based intervention had no incremental effect on medication intensification for control of glucose, blood pressure, or lipids for patients with diabetes of physicians practicing in rural Southeast US.

Bishop, Amber Nichole (Amber)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Marjorie Lee White
Co-Authors	J. Lynn Zinkan, Nancy Tofil
Title	Pediatric Medical and Trauma Resuscitation Teamwork Survey

Abstract

Purpose of Study: To use an online survey to investigate knowledge and attitudes about key features of teamwork and communication by members of the response teams for medical and trauma resuscitations at Children's of Alabama.

Methods Used: A 15 item survey was developed to collect demographic information, experience with resuscitations and knowledge of and frequency of application of key teamwork principles. Four open-ended questions offered the opportunity to make suggestions for improving resuscitations. The survey was administered via Survey Monkey™ to physicians, nurses, clinical assistants, unit clerks, respiratory therapists, critical care pharmacists, radiology technologies, social workers, chaplains and other members of the healthcare team. This study was approved by the IRB at the University of Alabama at Birmingham.

Summary of Results: 206 people were invited to participate in the survey and 100 responded to the entire survey, resulting in a 48% response rate. Respondents were 38% nurses, 28% physicians, 15% pharmacists, 6% chaplains, 5% nurse practitioners, 4% radiology technicians, 3% unit clerks and 1% clinical assistants. Only 12% of respondents were familiar with basic communication strategies such as closed-loop communication, standardized handoffs, debriefs, the two-challenge rule and team huddles. Survey respondents noted that the team leader often performs procedures and that patient assessments are only rarely done in a protocol-driven way. Multiple other data points were collected involving comfort level and effectiveness of communication. In addition, multiple suggestions were made to improve team performance in the narrative data.

Conclusions: Teamwork is increasingly being seen as crucial for providing quality patient care. This survey of pediatric emergency care team members demonstrates significant knowledge and perception gaps. Future directions planned include the implementation of a TeamSTEPPS based curriculum, simulation activities focused on teamwork and a follow-up survey to assess improvement.

Bishop, Robin Joy (Robin)

Project Length

Prior Research Experience No

Funding Source Departmental or Mentor funds

Advisor Tom English, PhD.

Co-Authors Robin Bishop and Tom English, PhD.

Title Predictors of Infant Mortality in Alabama Counties

Abstract

Background: With a shortage in primary care in the United States, access to quality healthcare is a concern. One measure of healthcare effectiveness is the infant mortality rate. Alabama as a state ranks 48th in infant mortality and 62 of its 67 counties were named Primary Care Health Professional Shortage Areas. Studies have found correlations between primary care supply and health care indicators, including infant mortality. The objective of this study was to test whether this relationship holds true at the county level within Alabama.

Design and Methods: Data was obtained from publically available Selected Health Status Indicators maintained by the Alabama Department of Health and Alabama Rural Health Association. The main independent variable was primary care supply. Dependent variables included infant mortality rate, percentage of low birth weight infants, and inadequate prenatal care, along with several socioeconomic variables. Data was analyzed using Pearson's correlation coefficients. Counties were used as the unit of analysis.

Results: Although bivariate correlation showed several significant relationships among socioeconomic factors, primary care supply was not significantly correlated with any of the health quality measures including: inadequate prenatal care (-0.144), low birth weight (0.04), or infant mortality (.119).

Conclusions: This study failed to show a direct relationship between primary care supply, infant mortality, and low birth weight. However, this may be because only one year's worth of data was used and the incidence of infant mortality was low. In addition, in 46% of the counties, more than 98% of the births occurred outside the county of maternal residence. This study shows that there are many components with complex and interconnecting relationships that influence rates of infant mortality. In addition it calls into question the usefulness of data analysis at the county level.

Black, Jonathan Andrew (Jonathan)

Project Length Intermediate
Prior Research Experience No
Funding Source Departmental or Mentor funds
Advisor Vera Bittner

Co-Authors

Title Impact of Obesity on Outcomes in Cardiac Rehabilitation

Abstract

Background: More than two-thirds of patients with coronary heart disease (CHD) are overweight or obese and obesity is the most common cardiovascular risk factor in patients who have suffered a myocardial infarction. Cardiac rehabilitation/secondary prevention programs (CR) include education, counseling, exercise training, and behavior modification interventions.

Purpose: This study was designed to better understand the impact of obesity on CR outcomes.

Hypothesis: 1. Obese patients will be less likely to complete CR. 2. Obese patients who complete CR will improve cardiovascular risk factors and lifestyle measures, but not to the same degree as non-obese patients.

Methods: Data were collected from a CR program based in an academic medical center that provides comprehensive secondary prevention services. Patients were stratified into obese group (N=754; BMI \geq 30 kg/m²) and non-obese group (N=793). Baseline characteristics and CR outcomes were compared using t-testing and chi-square testing as appropriate.

Results: Obese patients are less likely to complete CR than non-obese patients: 51.1% vs 61.1%, respectively, $p=0.04$. Obese patients had greater risk factor and comorbidity burden at entry than non-obese patients. For many metrics, obese patients who complete CR improve as much as non-obese patients (hemoglobin A1C, systolic BP, 6 min walk distance, MCS and PCS component scores of SF 36). In some areas obese patients improve more than non-obese patients: BMI decreased 0.9kg/m² compared to 0.3kg/m² ($p<0.001$); triglycerides decreased 45.1 and 20.1mg/dL ($p=0.01$); diet score decreased 15.3 and 10.5 ($p=0.003$); diastolic blood pressure dropped 2.6 and 1.6mmHg ($p=0.03$)

Conclusion: Obese patients are less likely to complete CR, but those who complete CR benefit as much as non-obese patients. Future studies need to explore the reason for differential dropout so that CR programs can be tailored to better address the needs of obese patients and improve the health and quality of life of this patient population.

Blosser, Emily Greenwood (Emily)

Project Length Long
Prior Research Experience Yes
Funding Source Departmental or Mentor funds
Advisor David A. Randolph, MD, PhD

Co-Authors

Title Maternal Antibiotics Increase Risk of Klebsiella Late-Onset Sepsis in Neonatal Mice

Abstract

Late-onset bacterial sepsis (LOS) is a leading cause of morbidity and mortality among premature infants in the United States. Infections with Gram-negative bacteria, such as *Klebsiella pneumoniae*, occurring when bacteria translocate across premature gut epithelium into the bloodstream, can be particularly severe. Preterm infants in the neonatal intensive care unit undergo intense antibiotic regimens due to high risk of infection. Paradoxically, prolonged exposure of preterm infants to empiric antibiotic therapy early in the hospital stay is associated with increased risk of intestinal infection and death after adjustment for covariates.

Bacterial translocation rates across the gut epithelium are determined by complex interactions between the host's commensal microbiota and immune system, and pathogens. Commensal microbes are believed to confer protection from bacterial translocation by competing with pathogens for space and resources, and by inducing gut immune system development directly. We have developed a physiologic model of neonatal LOS in which 5 day-old, conventionally-housed, C57BJ/6 mouse pups are intragastrically inoculated with pathogenic *K. pneumoniae*. As in humans, resistance is age-dependent with young pups being highly susceptible and adults being resistant ($p < 0.01$). Resistance is also dependent on an intact adaptive immune system, as 100% of Rag^{-/-} pups, which lack B and T cells, succumb ($p < 0.01$). Using this model, we sought to test the hypothesis that maternal antibiotics increase risk of LOS in pups, and that fecal transplant in pups is sufficient to reverse the effects of maternal antibiotics. Here we show that antibiotics (administered to mother from late pregnancy until pups' challenge) do confer increased risk of LOS in pups ($p < 0.01$). Polymerase chain reaction for *K. pneumoniae* in stool samples indicates that clearance is delayed in surviving pups of antibiotic-treated dams compared to pups of untreated dams ($p < 0.01$). Fecal transplant appears to partially ameliorate the effects of maternal antibiotics in pups, and should therefore be further explored as a potential preventative practice ($p < 0.04$). While further studies are needed to determine if increased risk derives from a decrease in the number or variety of commensal organisms present after antibiotic treatment, these findings provide new insights into the etiology of neonatal LOS.

Bray, Alexander Wendell (Alexander)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Richard J. Whitley
Co-Authors	Justin Roth, Gregory Friedman, Katherine Lanford, Yancey Gillespie
Title	Characterization of the Susceptibility of Pediatric Medulloblastomas to Neuroattenuated HSV Infection

Abstract

The current standard of therapy for medulloblastoma, the most common pediatric brain malignancy, possesses only a 50% cure rate in five years. In addition, it carries with it the high risk of significant neurological and cognitive sequelae associated with the use of radiotherapy on the still developing pediatric brain. Herpes Simplex Virus attenuated via deletion of the g34.5 neurovirulence gene has repeatedly demonstrated effective oncolytic activity against glioma, another brain malignancy, both in vitro against glioma derived cell lines and in vivo against glioma tumors xenotransplanted into nude athymic mice. It has also proven safe in several Phase I clinical trials further adding credence to its promise as a novel therapeutic. In this study, we examined the ability of this Dg34.5 Herpes Simplex Virus to similarly infect, replicate, and ultimately destroy two different pediatric medulloblastoma cells in vitro. These cells were derived from patient tumors and maintained in vivo by passaging through athymic nude mice before being harvested, cultured, and infected with attenuated HSV at several MOIs. The cells were then examined at various time-points post infection to measure viral replication and HSV induced cytotoxicity. Measured cytotoxicity to the virus differed greatly between the two medulloblastoma lines tested, ranging from as low as 40.89% to as high as 92.13% of cells, and similar differences were also observed when viral replication was measured. Altogether, the high susceptibility noted in the one cell line indicates that medulloblastomas do not possess any inherent resistance to the oncolytic activity of the virus. However, it does appear that certain individual medulloblastoma tumors, such as the second one tested here, may prove refractory to viral oncolysis. Depending on its extent, this resistance within the tumor population could seriously limit the use of neuroattenuated HSV as a novel therapeutic for pediatric medulloblastoma.

Breland, David Matthew (Matt)

Project Length	Short
Prior Research Experience	No
Funding Source	Diabetes Research and Training Center
Advisor	Jayleen Grams, MD, PhD
Co-Authors	M Kakade, MPH*, J S Richman, MD, PhD*, R H Clements, MD§, R Stahl, MD*, J Grams, MD, PhD* §Department of Surgery, Vanderbilt University, *Department of Surgery, University of Alabama at Birmingham
Title	Impact of Follow-up on Clinical Outcomes after Laparoscopic Roux-en-Y Gastric Bypass

Abstract

Laparoscopic Roux-en-Y gastric bypass (LRYGB) has been demonstrated to be an effective and durable treatment for morbid obesity. Postoperative follow-up has been shown to predict patient success at weight loss following LRYGB. However, up to 17-40% of patients do not follow up at one year without prompting by their surgeon. We hypothesized that follow-up compliance would predict success at weight loss and resolution or improvement of obesity-associated medical problems following LRYGB. A retrospective chart review was conducted on 529 patients who underwent LRYGB at UAB from 2004-2008. The patients were divided based on compliance with the recommended follow-up protocol, with A signifying <50% attendance and B signifying ≥50% attendance at follow-up visits within the first two postoperative years. Data collected included patient demographics, preoperative and postoperative weight, body mass index (BMI), and presence of obesity-associated comorbidities including T2DM, obstructive sleep apnea (OSA), and hyperlipidemia (HLD). Multivariate analysis was performed with %EWL as the outcome of interest. There were significant differences between A and B groups with respect to age and sex. There were no other significant differences. After adjusting for age, sex, preoperative BMI, race, and % compliance, A had a lower %EWL than B at one year follow-up (mean 68% vs. 71%, $p=0.278$). At two years, A had greater %EWL than B (77% vs. 74%, $p=0.472$). After two years, there were significant differences in resolution or improvement of comorbidities between A and B for HLD (81% vs. 95%, $p=0.020$) and OSA (94% vs. 99%, $p=0.046$), but not for T2DM (100% vs. 100%). Thus, compliance with the postoperative follow-up protocol was associated with greater %EWL at one year but not at two years. There were significant differences in the resolution or improvement of HLD and OSA, but compliance with follow-up protocols did not affect resolution or improvement of T2DM.

Brito, Amanda Leigh (Amanda)

Project Length Short
Prior Research Experience Yes
Funding Source HSF Community and Rural Health Fellowship
Advisor Marilyn Crain, MD
Co-Authors

Title Mucoid *Streptococcus pneumoniae* in Cystic Fibrosis

Abstract

Background: Cystic fibrosis (CF) is a genetic disorder resulting in progressive deterioration of lung function associated with recurrent bacterial infections. The transition from nonmucoid to mucoid *Pseudomonas aeruginosa* (PA) hastens this decline. Prospective collection of SP from Children's Hospital (CH) Birmingham, AL, beginning in 2002 revealed a surprising number of SP isolates from CF sputum; many were mucoid. We examined the relationship between SP infection and clinical status in CF patients.

Methods: The CH electronic medical records of 280 patients enrolled in the CH CF clinic between 01/01/2008 and 05/31/2010 were examined for demographic and clinical factors. Age, sex, race/ethnicity, CF genotype, admissions for CF exacerbations, body mass index (BMI), sputum cultures, pulmonary function tests (PFT), recent infections, and antibiotic therapy were recorded.

Results: Overall 88.9% of CF patients were white; 46.4% female, the median age was 11 years (range <1yr - 24 yrs), and 2.5% died. 23.9% grew SP: 58% once, 30% twice, 7% thrice, with fewer having four and five SP cultures. Patients with SP were 94% white, 37.3% female, had a median age of 8 yrs, and 1.5% died during the study period. Patients without SP were 87.3% white, 49.3% female, had a median age of 12 yrs and 2.8% died. The median BMI in patients with and without SP was 15.72 and 16.94, respectively. Mean and median PFTs follow: with SP 70.15% and 71.8% respectively and without SP 71% and 67.8% respectively.

Conclusions: Our data showed that CF patients with SP were more frequently white, male, and younger than patients without SP, with a lower frequency of death. Further analysis of data will clarify the relationship between SP and other bacteria including PA. The observation of two species of mucoid bacteria in the CF lung raises the possibility that mechanisms selecting for mucoidy may be similar.

Brosius, Stephanie Nicole (Stephanie)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. John Shacka
Co-Authors	Burton Mader, Peter Leiu
Title	Generation of LAMP-1 knockdown and overexpression cell lines for study of ASYN clearance

Abstract

Parkinson's disease (PD) is a neurodegenerative disorder affecting dopaminergic neurons in the substantia nigra and produces symptoms of tremor, bradykinesia, rigidity and poor balance. One of the hallmarks of the disease is the presence of α -synuclein (ASYN) containing Lewy bodies. While the mechanism of ASYN toxicity is unknown, previous research has shown that the autophagy-lysosome pathway (ALP), a key pathway in intracellular degradation and recycling, is altered in PD, thus contributing to the accumulation of ASYN. As part of the ALP, lysosome-associated membrane protein-1 (LAMP-1) is a membrane glycoprotein that aids in lysosome motility and regulates fusion with endosomes and autophagosomes. LAMP-1 is up-regulated during lysosomal biogenesis and prior studies have indicated that knockdown of LAMP-1 augments cell death as a result of agents inducing lysosomal dysfunction. However, whether manipulation of LAMP-1 regulates ASYN accumulation has not been determined. We hypothesize that over-expression of LAMP-1 enhances neuronal survival and clearance of toxic ASYN species, whereas LAMP-1 knockdown will exacerbate ASYN accumulation and neuronal cell death. In preparation for further experimentation, the human LAMP-1 gene was amplified, inserted into a pTA vector and then transformed into *Escherichia coli*. DNA was then extracted and the target sequence was inserted into the PCMV6 vector, which was then used to transfect human cell lines including SH-SY5Y neuroblastoma cells and HEK 293 cells. Over-expression of LAMP-1 was validated in both cell lines as compared to vector control. In addition, SH-SY5Y cells were introduced with either siRNA specific for LAMP-1 or a scrambled control via Amaxa™ nucleofection. Transient knockdown of LAMP-1 was established as compared to control 72h post-nucleofection. Development and optimization of these cell lines will allow us to critically evaluate the role of LAMP-1 in regulating ASYN clearance and associated neurotoxicity.

Brossier, Nicole Marie (Nikki)

Project Length Long
Prior Research Experience Yes
Funding Source Departmental or Mentor funds
Advisor Steven L. Carroll, MD, PhD
Co-Authors Stephanie J. Byer, Stephanie N. Brosius
Title Role of Ras Isoforms in Malignant Peripheral Nerve Sheath Tumors

Abstract

We hypothesized that multiple neurofibromin-regulated small G-proteins from the classic Ras (H, N, and K-Ras) and R-Ras (R-Ras, R-Ras2, and M-Ras) subfamilies promote the proliferation and migration of malignant peripheral nerve sheath tumor (MPNST) cells. We found that H-Ras, N-Ras, and R-Ras2 proteins were uniformly expressed in 8 MPNST lines; their expression of K-Ras2b and R-Ras was variable, while M-Ras protein was not detected in these lines. RT-PCR analyses demonstrated that the guanine nucleotide exchange factors necessary to activate these Ras proteins were also present. Raf-1 RBD affinity assays confirmed that all Ras proteins expressed in MPNST lines were constitutively activated. We then introduced a dominant negative (DN) H-Ras mutant into MPNST cells to inhibit the activation of the classic Ras isoforms; DN R-Ras was similarly used to inhibit the activation of the R-Ras subfamily isoforms. DN H-Ras and DN R-Ras were both found to inhibit MPNST mitogenesis, while only DN R-Ras inhibited migration and only DN H-Ras inhibited survival under nutrient-deprived conditions. Consistent with these differential effects, unique changes to the phosphoproteome were observed by mass spectrometry downstream of DN H-Ras versus DN R-Ras. We conclude that both classic Ras and R-Ras subfamily members contribute to MPNST pathogenesis. Inhibition of multiple Ras isoforms will therefore likely be required to achieve an optimal therapeutic effect. Funded by R01 CA122804 and F30 NS063626.

Burke, Mata Rodopoulos (Mata)**Project Length** Short**Prior Research Experience** Yes**Funding Source****Advisor** Charles Landen**Co-Authors** Adam Steg**Title** Gamma-secretase Inhibitors Increase Sensitivity to LDE225, a Smoothed antagonist, in Chemoresistant Ovarian Cancer Cells in Vitro**Abstract**

Background: Cancer stem cells (CSCs) are a specialized subpopulation of cancer cells that have been implicated in the development of recurrent, chemoresistant tumors in multiple malignancies. Previous studies have demonstrated that the unique tumorigenic properties of these cells are dependent on expression of the Notch and Hedgehog signaling pathways. However, monotherapy with Hedgehog and Notch inhibitors has resulted in only modest effects in vitro.

Objective: This study examines the effect of combination therapy with a notch-targeting gamma secretase inhibitor (compound E-GSI) and hedgehog-targeting smoothed inhibitor (LDE225, Novartis) in chemoresistant ovarian cancer cells and investigates possible mechanisms of synergy between these drugs.

Methods: SKOV3TRip2 (taxane-resistant) and A2780cp20 (cisplatin-resistant) cells were treated with increasing concentrations of GSI alone and in combination with variable concentrations of LDE225. Cell viability was determined using an MTT assay, and dose-response curves were generated for each treatment condition. SKOV3TRip2 cells were also transfected with control siRNA or siRNA constructs against individual members of the Notch and Hedgehog pathways. RNA was isolated using Trizol reagent and cDNA was synthesized. Taqman quantitative PCR was used to determine gene expression in treated/transfected cells by the comparative C_T method.

Results: Combination therapy with GSI and LDE225 showed a synergistic effect in SKOV3TRip2 cells, but not in A2780cp20 cells. Knockdown of Jagged1 (a Notch ligand expressed in SKOV3TR but not A2780cp20) in SKOV3TRip2 cells resulted in a decrease in Hedgehog members *Gli2* and *Patched* mRNA. Furthermore, SKOV3TRip2 cells treated with GSI showed a decrease in *Gli2* and *Patched* expression. However, when SKOV3TRip2 cells were subjected to Jagged1 knockdown and treated with increasing concentrations of LDE225, no synergy was observed.

Conclusions: The results of this study demonstrate that there is a synergistic effect between LDE225 and GSI. Through these effects and verified transcriptional modification of *Gli2*/*Patched*, we have discovered a previously unrecognized crosstalk between the Notch and Hedgehog pathways that appears to be independent of Jagged1.

Bush, Benjamin Daniel (Ben)

Project Length	Short
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	J. Scott Magnuson
Co-Authors	Frederick JW, Sweeny L, Carroll WR, Rosenthal EL
Title	Comparison of Surgical Approaches to Tumors of the Oropharynx

Abstract

Educational Objective: At the conclusion of this presentation, the participants should be able to better compare oncological and functional outcomes between the mandibulotomy and transcervical approach for resection of oropharyngeal tumors.

Objectives: Compare the outcomes of patients with squamous cell carcinoma of the oropharynx who underwent resection with mandibulotomy compared to a transcervical resection without mandibulotomy.

Study Design: Retrospective review.

Methods: A retrospective review of patients (n=69) undergoing tumor resection of the oropharynx was performed at a tertiary care facility from March 2003 to December 2010. Oncological and postoperative complication outcomes of the patients who underwent mandibulotomy were compared to those who underwent transcervical approach.

Results: In the study population, 54% underwent mandibulotomy (n=37; mean age of 59) and 46% underwent a transcervical approach (n=32; mean age of 57). A trend towards more complications requiring surgical intervention in the mandibulotomy group (35%; n=13) compared to transcervical approach (22%; n=7; p=0.12) was observed. Mandibulotomy patients required an average of 0.75 additional surgeries to manage complications, whereas transcervical patients required 0.25 surgeries (p=0.05). The most common complication in the mandibulotomy group was bone exposure with 19% (n=7) at the site of the osteotomy. Positive margin status was similar between the two cohorts with 22% (n=8) of the mandibulotomy patients and 28% (n=9) of the transcervical patients (p=0.54). There was no statistical difference in the disease free survival, overall survival, hospital stay, or PEG tube retention time.

Conclusions: Oncologic outcomes were similar in the two groups but a trend toward a higher rate of postoperative complications in patients undergoing mandibulotomy was seen. This suggests the transcervical approach may be more advantageous than mandibulotomy for head and neck oncologic surgery.

Calix, Juan Jose (Juan)

Project Length Long

Prior Research Experience Yes

Funding Source

Advisor Moon H. Nahm

Co-Authors JJ Calix, MB Oliver, L Sherwood, BW Beall, MH Nahm

Title Ambiguous serotypes within serogroups 9 and 11 of *Streptococcus pneumoniae* are mediated by differential disruption of the O-acetyltransferase *wcjE*

Abstract

Background: *Streptococcus pneumoniae* expresses at least 93 structurally distinct polysaccharide (PS) capsular serotypes. Inactivation of the O-acetyltransferase *wcjE* in the capsule synthesis (*cps*) loci of serotypes 9V and 11A results in serotypes 9A and 11E, respectively. Diverse *wcjE*-null mutations have been described, but the effects of these mutations on capsular antigenicity have not been broadly examined.

Methods: We detected reactivity of anti-capsular monoclonal antibodies (mAbs) or conventional factor sera (Fs) to multiple serotype 9V, 9A, 11A and 11E strains using a novel flow cytometric serotyping assay (FCSA). FCSA can quantify the amount of capsular antigen expression on individual cells.

Results: 9V and 11A strains strongly reacted with Hyp9VG2 and Hyp11AG2 mAbs, respectively, while *wcjE*::Janus cassette (JSC) recombinants (Δ *wcjE*) and most clinical 9A (n=7) and 11E (n=7) isolates showed no reaction. Unexpectedly, five clinical isolates initially serotyped as 9A or 11E displayed moderate reactivity with mAbs specific for *wcjE*-dependent epitopes, and were designated 9A α (n=3) or 11E α (n=2). 9A α strains reacted weakly with the 9V-specific Fs 9g, according to FCSA, and one 9A α strain was mildly agglutinated by Fs 9g. Capsule expression was comparable in all strains according to reactivity with antibodies against *wcjE*-independent PS epitopes. *cps* loci sequences from representative 11E and 11E α or 9A and 9A α strains only differed in the nature of the mutation to *wcjE*. Recombinational replacement of JSC in 9V Δ *wcjE* with *wcjE* alleles from two 9A α strains conferred moderate Hyp9VG2 and Fs 9g reactivity, while replacement of JSC with an analogous allele from a 9A strain did not.

Conclusion: Incomplete inactivation of *wcjE* may result in strains expressing partially O-acetylated capsules. This phenomenon yields antigenically “ambiguous” strains that could potentially be mis-serotyped as *wcjE*-wild type serotypes and challenges whether such serotypes can be clearly defined using conventional immunologic and genetic methods.

Campbell, Ian Sheppard (Ian)

Project Length Intermediate

Prior Research Experience No

Funding Source

Advisor Hughes Evans

Co-Authors

Title The History of the Fiberoptic Endoscope

Abstract

Using primary source material from Lister Hill Library and the UAB historical archives, I researched the history of the fiberoptic endoscope. Developed in 1957 by gastroenterologist and former UAB professor Basil Hirschowitz, the fiberoptic endoscope was a revolutionary piece of medical technology, an innovation that transformed the practice of gastroenterology. In my paper, I provide a biographical sketch of Dr. Hirschowitz, focusing on his role in the development of the fiberscope. Furthermore, I attempt to locate the fiberscope in terms of its cultural significance within the American gastroenterology community.

Cezayirli, Phillip Cem (Phillip)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	L. Burt Nabors, M.D., Asim K. Bag, M.D.
Co-Authors	Asim K. Bag, M.D., L. Burt Nabors, M.D.
Title	Glioblastoma Multiforme Patient Prognosis: Can Change in Peritumoral Cerebral Blood Flow Predict Survival?

Abstract

Background: Perfusion MRI may be used to determine cerebral blood volume (CBV), a semiquantitative measurement of angiogenesis routinely used in the diagnosis and monitoring of glioblastoma multiforme (GBM) patients. GBM tumors have poorly defined margins and invade well beyond the enhancing area into a peritumoral zone. Cerebral blood flow (CBF), another parameter derived from perfusion MRI, reflects amount of blood flow per unit brain tissue per unit time. CBV—an indirect quantification of degree of neoangiogenesis—correlates well with survival of GBM patients. We propose that CBF should also correlate with survival.

Purpose: The purpose of this study was to determine if CBF correlated with survival.

Methods: Using IB Neuro software (Imaging Biometrics, LLC), we generated voxel-by-voxel CBF maps from the perfusion MRI and then performed region-of-interest based CBF analysis of the tumor and peritumoral zone before and after treatment with an antiangiogenic drug (AAD) (Cilengitide). We defined peritumoral zone as the FLAIR signal abnormality outside the enhancing tumor. The change in CBF was then correlated with overall survival by proportional hazards regression.

Results: We reviewed 112 patients from a multi-center Phase I/II trial of Cilengitide (EMD 121974). Seventeen patients met optimum quality scan criteria and were included in the analysis—excluded patients either lacked or had suboptimal imaging. Although pretherapy CBF (tumoral and peritumoral) does not correlate with survival, we found that both percent and absolute change in the peritumoral CBF (max, median, and mean) with AAD treatment correlates with survival (p values all <0.05 and lowest hazard ratio 0.299). Intratumoral CBF or change of CBF did not correlate with survival.

Conclusions: The use of peritumoral CBF change is prognostic for survival time. A larger study with strict imaging parameters and quality control measures should attempt to validate our initial findings.

Chestnut, Michael David (Michael)

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Brad Woodworth M.D.

Co-Authors Angela Blount, MD Carmel McNicholas, PhD Shaoyan Zhang, PhD Daniel Skinner, B.S. Michael Chestnut, B.S. Eric J. Sorscher, MD Bradford A. Woodworth, MD

Title Resveratrol enhances airway surface liquid depth by increasing CFTR channel open probability

Abstract

Objective/Hypothesis: Using Cl⁻ secretagogues to improve mucociliary transport in sinus disease represents a novel therapeutic strategy. Previous investigations indicate the polyphenolic molecule resveratrol promotes CFTR-mediated Cl⁻ transport. The objectives of the present study were to investigate resveratrol's effects on channel open probability (Po) and determine whether this translates to hydration of airway surface liquid (ASL).

Study Design: *In vitro* study.

Methods: Well-characterized primary murine nasal septal epithelial (MNSE) cells and HEK293 cells heterologously expressing CFTR were investigated using the patch clamp technique to obtain single channel recordings under non-phosphorylating conditions. Effects on ASL depth (in μM) were measured using confocal laser scanning microscopy.

Results: In inside-out patches from apical membranes of MNSE cells, in the absence of ATP and PKA, resveratrol stimulated a ~9 pS chloride channel consistent with CFTR. This observation was confirmed in HEK293 cells heterologously expressing CFTR where resveratrol application increased CFTR_{INH-172}-sensitive channel activity. Activity resulted in a significant increase in ASL depth (7.1±0.43 vs. 5.1 ± 0.23, control) confirming that resveratrol hydrates the ASL in sinonasal epithelium.

Conclusions: These findings indicate resveratrol is a potent Cl⁻ secretagogue that hydrates ASL in sinonasal epithelium by increasing channel Po. Clinical trials utilizing resveratrol as a therapeutic intervention to increase mucociliary transport and ASL hydration in sinus disease are planned.

Cochran, Michael Andrew (Drew)

Project Length Intermediate
Prior Research Experience Yes
Funding Source Departmental or Mentor funds
Advisor Sadis Matalon, PhD

Co-Authors

Title Increased Superoxide Dismutase Activity in Endothelial Cells Treated With Liposomes

Abstract

Superoxide dismutase (SOD) is an enzyme that catalyzes the conversion of superoxide anion to hydrogen peroxide, protecting cells from damaging oxidative reactions. Three human forms of SOD have been identified, two of which require copper and zinc, and one, which requires manganese. CuZn-SOD is active in the cytosol, while Mn-SOD is active in the mitochondria. SOD delivered to cells may aide in protection from oxidative stress, chlorine toxicity, or reperfusion injury. In this project we created liposome formulations containing either CuZn-SOD or Mn-SOD at a concentration of 3,000 units/ml. H441 cells (human lung adenocarcinoma epithelial cells) and capillary endothelial cells were treated with liposomes consisting of 1,2 dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), cholesterol and 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) in a 35:17:1 molar ratio, respectively, extruded through a 100-nm membrane filter. After 18 hours, the liposomes were removed, the cells were washed and SOD activity was measured using a xanthine/xanthine oxidase spectrophotometric assay. In H441 cells, there were no significant differences of measured SOD activity between media controls and cells treated with liposomes containing either SOD. However, compared to media controls, there was increased SOD activity in endothelial cells treated with liposomes containing both CuZn-SOD and Mn-SOD ($p=0.03$). Endothelial cells treated with CuZn-SOD liposomes also had an increased amount of SOD activity than cells treated with CuZn-SOD solution ($p=0.03$). There were no significant differences in endothelial cells treated with Mn-SOD solution and Mn-SOD liposomes. There also were no significant differences in activity between endothelial cells treated with CuZn-SOD and Mn-SOD liposomes ($p=0.06$). We conclude that extruded liposomes consisting of DPPC, cholesterol and DOTAP at 35:17:1 molar ratio, containing CuZn-SOD or Mn-SOD, is a potential vehicle for delivering SOD to cells. Follow up work is warranted and should assess the extent of anti-oxidative protection offered to endothelial cells following treatment with the liposome formulation.

Corrick, Ryan Marshall (Ryan)**Project Length** Long**Prior Research Experience** Yes**Funding Source****Advisor** Joseph L. Messina, Ph.D**Co-Authors** Li Li, Ph.D.**Title** Acute Hepatic Growth Hormone Resistance Following Injury**Abstract**

Acute growth hormone (GH) resistance is frequently observed following severe injury. Because GH action is important for wound healing and maintenance of lean body mass, growth hormone resistance may complicate recovery from injury. In order to study the effects of injury on growth hormone signaling, we subjected 12-week old male mice to soft-tissue trauma combined with hemorrhage. All procedures were conducted under continuous isoflurane anesthesia. Hemorrhage was accomplished by withdrawal of sufficient blood from the femoral artery catheters to reduce mean arterial pressure to 35-40 mmHg. GH or vehicle was administered intravenously after 30, 60, or 90 min of hemorrhage, and livers were collected 10 min later. Additional mice were anesthetized, subjected to soft-tissue trauma and arterial catheterization, and injected with growth hormone or vehicle to control for the effects of surgical procedures. These "trauma alone" controls exhibited modest reductions in hepatic GH signaling compared to uninjured mice. However, severe decreases in GH signaling were measured after 30, 60, or 90 min of hemorrhage compared to controls. SDS-PAGE-Western analysis indicated a ~10 kDa decrease in molecular weight of the growth hormone receptor (GHR) following hemorrhage. We are unsure whether this decrease is due to a proteolytic event or a post-translational modification of GHR. However, such low molecular-weight GHR was detected as early as 30 min following onset of hemorrhage, corresponding with severely impaired GH signaling, and persisted even after fluid resuscitation and 60 min of recovery (TH210'). In contrast to full-length GHR, low molecular-weight GHR was not tyrosine-phosphorylated in response to GH stimulation. These results suggest that the combination of injury and hemorrhage results in the rapid development of hepatic GH resistance, which may be due to changes to the GHR.

Cuddapah, Vishnu Anand (Vishnu)

Project Length Long
Prior Research Experience Yes
Funding Source
Advisor Harald Sontheimer
Co-Authors

Title Kinase activation of CIC-3 chloride channels accelerates cytoplasmic condensation during mitotic cell rounding in human glioma cells

Abstract

“Mitotic cell rounding” describes the rounding of mammalian cells before dividing into 2 daughter cells. This shape change is facilitated by a coordination of cytoskeletal contraction and cytoplasmic shrinking secondary to changes in osmotic pressure. While considerable research has elucidated mechanisms of cytoskeletal contraction, little is known about how osmotic gradients control cytoplasmic shrinking during cell division. CIC-3, a voltage-gated chloride channel, is highly expressed by glioma cells and plays a critical role in regulating shape and volume changes in response to osmotic pressures. Therefore, we hypothesized that CIC-3 facilitates cytoplasmic condensation and cell division in dividing glioma cells by allowing extrusion of osmotically-active Cl⁻ via CIC-3. Given that in human glioma cells CIC-3 activity is regulated by CaMKII, a calcium-sensitive kinase, we also hypothesized that CaMKII activates CIC-3 to promote cytoplasmic condensation and glioma cell division. To address these hypotheses, we used a combination of timelapse microscopy, immunocytochemistry, genetic knockdown, and biophysical measurements. Using these techniques, we find that in human glioma cells, mitotic cytoplasmic condensation involves the activation of CIC-3 by CaMKII. CIC-3 and CaMKII colocalize to the plasma membrane in dividing cells, and auto-activated CaMKII is particularly abundant in dividing cells. Dividing cells have elevated Cl⁻ currents, which were completely inhibited by a specific CaMKII inhibitor. Knockdown of endogenous CIC-3 protein expression using short-hairpin RNA eliminated CaMKII-dependent Cl⁻ currents in dividing cells and impeded cytoplasmic condensation. Additionally, inhibition of CIC-3 or CaMKII reduced glioma cell proliferation and promoted the formation of flattened cells that do not undergo cytoplasmic condensation. These data indicate that CaMKII activates CIC-3 during mitotic cell rounding, leading to Cl⁻ efflux and cytoplasmic condensation. These results are clinically significant, because inhibition of CIC-3 impedes glioma cell proliferation and may improve clinical outcomes for the treatment of glioblastoma multiforme, the most lethal type of gliomas.

Deep, Nicholas Larry (Nicholas)

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Farrell O. Mendelsohn M.D.

Co-Authors Daniel S. Atherton

Title Micro-anatomy of the Renal Sympathetic Nervous System: a Human Postmortem Histologic Study

Abstract

Hypertension remains an epidemic uncontrolled with pharmacologic therapies. A novel catheter inserted into the renal artery has been shown to lower blood pressure by ablating the renal sympathetic nerves with radiofrequency energy delivered through the arterial wall. We report a histologic study describing the anatomic substrate for this technique, specifically the renal sympathetic nervous system. Histological sections from proximal, middle, and distal renal artery segments from 9 renal arteries (6 human autopsies) were analyzed. Nerves were manually counted and their distance from the lumen-intima interface was measured using a micrometer. The nerves were then categorized by location into 0.5mm-wide “rings” that were arranged circumferentially around the renal artery lumen. Of all nerves detected, 1.0% was in the 0-0.5mm ring, 48.3% were in the 0.5-1.0mm ring, 25.6% were in the 1.0-1.5mm ring, 15.5% were in the 1.5-2.0mm ring, and 9.5% were in the 2.0-2.5mm ring. Beyond 0.5mm, the proportion of nerves tended to decrease as the distance from the lumen increased. 90.5% of all nerves in this study existed within 2.0mm of the renal artery lumen. Additionally, the number of nerves tended to increase along the length of the artery from proximal to distal segments (proximal=216; middle=323; distal=417). In conclusion, our analysis indicates that a great proportion of renal sympathetic nerves have close proximity to the lumen-intima interface and should thus be accessible via renal artery interventional approaches such as catheter ablation. This data provides important anatomic information for the development of ablation and other type devices for renal sympathetic denervation.

DeMedicis, Jeffrey Vincent Collier (Jeff)

Project Length Intermediate

Prior Research Experience No

Funding Source

Advisor Cynthia J. Brown, MD, MSPH

Co-Authors

Title Physical Therapy in the Hospital: Importance of Functional Assessment

Abstract

Background: To address the need for out of bed mobility, physicians often rely on physical therapy to combat decreased mobility and its associated morbidity in the hospital setting. Understanding the characteristics that include or exclude patients from physical therapy will identify those patient populations at greatest risk.

Objectives: To determine the proportion of patients referred to physical therapy (PT) during hospitalization; and to compare characteristics of those who received and did not receive PT.

Methods: Among a cohort of hospitalized veterans, age ≥ 65 years, enrolled in a randomized clinical trial to examine the impact of a hospital walking program on out of bed mobility, we determined the proportion that received a PT referral and compared characteristics of those who did and did not have a PT referral.

Results: 97 participants (mean age 74 years, 97% men, 82.5% white and 17.5% black) had a median length of stay of 3 days. Two weeks prior to admission greater than 60% were independent in all activities of daily living, however by hospital admission this proportion had decreased to 46%. Thirty-five (36%) participants were referred to PT, and there was no significant difference in referrals based on walking program group assignment. Participants referred to PT were older (76.6 vs. 72.52 years), had more limited community mobility (Life-Space Assessment score 43.1 vs. 58.14), dependent in at least one ADL 2 weeks prior to admission (57% vs. 28%) and on admission (74% vs. 42%) when compared to those not referred to PT. Over half of the patients who experienced preadmission functional decline in their ADLs did not receive PT.

Conclusions: A significant number of patients who might benefit from physical therapy did not received PT referrals. Assessment of preadmission functional status by physicians may help identify patients who would benefit from physical therapy during hospitalization.

Den Beste, Kyle Andrew (Kyle)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Sarah Wise, MD
Co-Authors	Elizabeth Hoddeson, MD, Asma Nusrat, MD, Charles Parkos, MD
Title	Epithelial Permeability Alterations in an Air-Liquid Interface Model of Allergic Fungal Rhinosinusitis

Abstract

Chronic rhinosinusitis is a common debilitating condition characterized by mucosal edema, nasal discharge, and facial pain of greater than 12 weeks duration. The cause of the disease is poorly understood, though over-expression of Th2 cytokines has been observed in a subtype of chronic rhinosinusitis known as allergic fungal rhinosinusitis (AFRS). The aim of this study was to compare epithelial permeability and tight junction (TJ) protein expression amongst primary sinonasal cells cultured from patients with AFRS and non-inflammatory controls. We hypothesized that epithelial permeability would be increased and TJ integrity decreased in the AFRS cultures when compared to control.

Primary cells were isolated from nasal mucosa during sinus surgery and categorized into two groups: non-inflammatory control and AFRS. Each group of cells was grown to confluence on permeable supports and transitioned to an air-liquid interface (ALI) to accurately replicate the native environment in respiratory epithelium. Trans-epithelial resistance (TER) was measured with a horizontal Ussing chamber to characterize the functional permeability of each cell type to passive ion exchange. After TER recordings were complete, cells were processed for Western blot and immunofluorescence labeling, followed by confocal microscopy. After a minimum of ten samples were measured and processed from each group, we observed a 40% mean decrease in TER in AFRS cells compared to control. The resistance deficits observed in AFRS correlated with decreased expression of the TJ proteins occludin and junction adhesion molecule-A, and increased expression of a leaky TJ protein claudin-2. To our knowledge, this is the first study associating altered barrier function and intercellular junction protein alterations *in vitro* in cell samples isolated from AFRS patients. Given that these cells were not incubated with inflammatory cytokines *in vitro*, it must be assumed that the AFRS phenotype represents a retained modification in protein expression from the *in vivo* phenotype.

DiToro, Daniel Francis (Daniel)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Casey Weaver
Co-Authors	Colleen Winstead
Title	Role of TCR Specificity in CD4 T Cell Differentiation

Abstract

Infectious organisms demonstrate a stunningly diverse array of cellular and molecular pathogenicities. Adaptive immunity compensates for this by providing a plastic and lasting response tailored to the invading pathogen. CD4 T cells are an essential component of adaptive immunity that function by modifying the behavior of other cellular actors. There are several distinct subsets of mature CD4 T cells, each uniquely suited to drive a functionally distinct arm of the immune response. Thus the selective differentiation of CD4 T cells following antigen presentation is essential for an appropriate and effective adaptive immune response. The mechanisms by which antigen-presenting cells guide this process have received significant attention. But the role of factors intrinsic to naïve CD4 T cells, including T Cell Receptor (TCR) antigen specificity, remains murky. TCR's bind antigen with variable avidity. This avidity has been shown to correlate with the strength of downstream signaling. Given the central role of TCR stimulation in CD4 T cell differentiation, it is possible that TCR antigen specificity and avidity influence this process. This has been difficult to investigate given the lack of multiple TCR-transgenic mice for a given infectious system. To circumvent this problem we engineered *Listeria monocytogenes* (LM) to express peptides specific for multiple TCR-transgenic mouse strains. Using adoptive transfers of physiologically relevant numbers of CD4 T cells, we have assessed the activation and differentiation of multiple transgenic lines in the same infectious environment. We found that transgenic CD4's appear to preferentially follow specific differentiation pathways relative to the endogenous response as early as 48 hours following infection. In addition, using peptide tetramers harboring antigen specific for the TCR-transgenic cells, we showed that endogenous CD4's that bind the same antigen demonstrate a similar phenotype. This data suggests that TCR antigen specificity or avidity may play a significant role in CD4 differentiation.

Dizon, Brian Leonard (Brian)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	John F Kearney
Co-Authors	Nicholas W Kin
Title	Neonatal Exposure To Bacterial Carbohydrate Antigens Exerts Long-Lasting Effects On Clonal B Cell Responses

Abstract

It is unclear how exposure to antigens to the developing immune system early in life influences subsequent antibody responses to the same antigens in adulthood. We developed a flow cytometric method to detect, quantify, and phenotype B cell populations reactive to N-acetyl-D-glucosamine (GlcNAc) or phosphorylcholine (PC) expressed on the cell wall polysaccharides of Group A Streptococci (GAS) and *Streptococcus pneumoniae*, respectively. Comparative analysis of mice immunized with GAS or treated with PBS at 3 days of age revealed differences in adult frequencies and numbers of antigen-specific Id⁺ B cells in absence of re-challenge. Similarly, analysis of the PC-specific B cells in mice exposed to *S. pneumoniae* at 3 days old demonstrated loss of a protective clonotype TEPC15. Neonatal exposure to these organisms boosted the response to secondary immunization in adulthood and the production of antibodies with idiotype (Id⁺) profiles distinct from those of control mice; however, the mice died quickly from infection with virulent GAS. Finally, GlcNAc-specific antibodies generated by neonatal exposure at 3 days of age exhibited impaired ability to promote opsonophagocytosis. These data show that neonatal vaccination with carbohydrate antigens associated with GAS and *S. pneumoniae* impacts the clonal composition of the antigen-specific B cell repertoire, resulting in the loss of protection against virulent bacteria. These findings define a developmental window in neonatal life during which bacterial carbohydrate antigen exposure exerts long-lasting deleterious effects on humoral responses to the same bacteria in adulthood. These observations have important ramifications for the design and implementation of carbohydrate antigen-based vaccines eliciting protective antibodies in neonates.

Do, Kym Ngoc (Kym)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Alayne Markland
Co-Authors	Patricia S. Goode, Kathryn L. Burgio, David T. Redden
Title	Do Stool Form and Frequency Correlate with Colonic Transit in Adults with Fecal Incontinence?

Abstract

Background: Despite a lack of evidence, stool form and stool frequency based on bowel diaries are often used as clinical surrogates for colonic transit time (CTT) in patients. Stool form and CTT correlates with constipation, but data do not exist for adults with fecal incontinence (FI).

Question: The aim of this study was to assess the correlation between stool characteristics (form and frequency) and CTT in adults with FI.

Methods: From an ongoing randomized controlled trial of treatment to improve stool consistency in adults with weekly FI, 37 participants provided baseline self-reported 7-day bowel diary data (stool form and frequency) and CTT evaluation (Modified Metcalf methodology using radio-opaque markers). Two independent raters, one expert and one novice, reviewed the CTT evaluations for concordance. In the bowel diary, participants recorded their daily bowel movements and FI episodes and rated the stool consistency for each using the validated Bristol Stool Form Scale (BSFS). The BSFS has 7 visual and written descriptors for stool form, ranging from 1-hard to 7-watery. Interclass correlations (ICC) were calculated between the two reviewers for the concordance of the CTT measurements (in hours). Stool form and frequency were correlated with CTT using Spearman's rank correlation.

Results: Of the 37 participants, 30% were women (11/37) with a mean age of 61±7 years; 24% were African-American. Participants had 2.6 ±1.7 bowel movements per day with a mean stool consistency of 4.5±1.2. The mean CTT was 28.0±15.3 hours. The ICC for the raters was 0.96. Weak correlations were found between stool form and CTT (Spearman's rho = 0.34, p=0.05) and between stool form and stool frequency (Spearman's rho = 0.36, p=0.04). However, stool frequency and CTT were not correlated.

Conclusions: Stool form and CTT were weakly correlated in adults with FI. Stool frequency was a poor surrogate for CTT.

Douglas, Samuel Lessley Ardis (Samuel)

Project Length Short
Prior Research Experience Yes
Funding Source NIH T35 Short Term Training Grant
Advisor Walter H. Johnson, Jr., MD
Co-Authors

Title Echocardiographic Assessment Of Aortic Size And Morphometry In A Population Of Children With And Without Congenital Heart Disease Or Connective Tissue Disease

Abstract

Background: The misdiagnosis of Marfan Syndrome (MFS) can lead to unfounded psychosocial burden and should be minimized as much as possible. *Purpose:* The specific goals of our retrospective study were: 1). Compare the normal values described in previous studies with those at UAB, 2). Establish normal values for the diameter of nontraditional aortic measurements, and 3). Determine more reliable–criteria for the diagnosis of Marfan Syndrome (MFS). *Methods:* The data was collected from previously obtained digital echocardiograms and included the measurements of the aorta at 9 distinct locations along the aorta (i.e. the aortic annulus (ANN), Sinus of Valsalva(SOV), Sinoatrial ridge(SAR), ascending aorta at the right pulmonary artery(AAO@RPA), distal ascending aorta(DAO), transverse arch (TArch), proximal and mid-thoracic descending aorta(PTDAO, MTDAO), and proximal abdominal descending aorta(AbdmAo)). We acquired aortic measurements in 142 normal patients, 28 patients with a confirmed genetic mutation/deletion of the FBN1 gene, and 30 patients with clinical diagnosis of a connective tissue disease. Data was normalized against BSA and analyzed using SPSS. *Results:* Using linear regression analysis, we acquired formulae for each location on the aorta, thus allowing the prediction of the normal diameter based on Body Surface Area, and further allowing the creation of clinically applicable nomograms. *Conclusion:* The formulae we derived from our data sets has allowed us to calculate z scores (number of standard deviations differing from the expected mean diameter) for each patient at each of the 9 distinct locations on the aorta. The average z score at the SOV for the normal patients and the patients with confirmed MFS was 0.01 ± 0.99 and 2.58 ± 2.33 , respectively. We speculate that an improved normal database of aortic dimensions, including more standardized locations within the aorta than traditional measurements, may allow for greater sensitivity and specificity in the echocardiographic evaluation of patients with MFS or a related aortic disorder.

Dover, Laura Lynne (Laura)

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Dr. Elizabeth Jaffee, Sydney Kimmel Comprehensive Care Center at Johns Hopkins

Co-Authors Laura Dover, Bridget Kennan, Todd Armstrong, Elizabeth Jaffee

Title Lymphocyte Activation Gene-3 Modulation Potentiates Immunogenesis of GM-CSF-Secreting Whole-cell Cancer Vaccines in HER-2/neu Tolerized Mice

Abstract

Tumor-specific immune tolerance limits the effectiveness of tumor vaccines across a variety of cancers. In addition to the inherent conundrum of tumor proteins existing as altered self-proteins, cancer immunotherapy must face additional immune-evading tactics employed by cancers both locally and systemically. Markedly in the HER-2/*neu* breast cancer model, an up-regulated T_{Reg} population acts to suppress self-reactive T cells, which include the *neu*-specific CD8⁺ T cells necessary for tumor clearance. Although immune-modulating doses of chemotherapeutics and TCR transgenic adoptive transfers have proven effective at overriding T_{Reg} immunosuppression in a minority of *neu*-tolerant mice, other avenues to combat immune-evading mechanisms must be explored to ensure efficacy of cancer vaccines in a broader patient population. One such avenue is modulation of the lymphocyte activation gene-3 protein (LAG-3 or CD223), which is expressed on a number of lymphocytes where it serves various immunosuppressive roles. Here we looked at the effects over 55 days of parallel vaccine therapies in traditional *neu*-N mice compared with their *neu*-N x LAG-3^{-/-} counterparts. We have shown that, when injected with even 50-fold the amount of tumor cells, LAG-3^{-/-} *neu*-tolerant mice are able to clear tumors more efficiently than those of the standard *neu*-N line. Subsequent *in vitro* experiments and DEAD assays show that LAG-3^{-/-} dendritic cells (DCs) have significantly increased capabilities to induce *neu*-specific CD8⁺ T cell proliferation three and five days post-vaccination. Our results suggest that, in the absence of LAG-3, effector T cells specific for the *neu*-epitope face less challenges of anergy, at least in part due to enhanced DC stimulation, and thus clear tumors more readily. In conclusion, LAG-3 manipulation and its role in adjuvant cancer vaccine therapy merits further investigation, as it adds efficacy without inducing significant autoimmunity—attributes which have yet to be found to coincide with the modulation of any other immune checkpoint.

Edmiston, Anna Michelle (Anna)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Candace L. Floyd, Ph.D.
Co-Authors	Anna M. Edmiston, Sarah M. Kezar, Don E. McCormick, Candace L. Floyd, Ph.D.
Title	Functional and Psychological Recovery following Spinal Cord Injury: Systematically evaluating the effects of exercise rehabilitation in a rat model

Abstract

Spinal cord injury (SCI) typically results in functional impairment, and approximately 30% of persons with SCI suffer from depression. Depression is often treated with serotonergic antidepressants, but recent trials have shown exercise to be more effective than antidepressants in alleviating depression. Exercise improves functional recovery and reduces depression in SCI patients; however, the mechanisms for these effects are difficult to evaluate in the heterogeneous clinical population and remain poorly understood. In this study, we used a clinically-relevant rat model of SCI to systematically evaluate the effect of post-SCI exercise rehabilitation on locomotor function, bladder function, neuropathic pain, and depression. Ten adult male rats received an equivalent contusion SCI and then were randomly assigned to receive either swimming rehabilitation (swim training and shallow water walking 4 days/week for 4 weeks) or no rehabilitation. Hind limb locomotion was evaluated weekly post-SCI using the Basso, Beattie, Bresnahan (BBB) scale, the Louisville Swim Scale (LSS), and kinematic analysis. We found that the rehabilitation group had improved hind limb locomotion as compared to the control group in all three assessments. We assessed bladder function by days to micturition. Von Frey filaments were used to measure allodynia. No significant differences in allodynia or bladder control were observed between groups. Depression was measured using the Porsolt test, and we found that rats in the rehabilitation group had increased immobility time versus the control group. Although increased immobility time indicates increased depression in able-bodied rats, animals with greater swimming ability exhibited greater immobility time which may obfuscate the interpretation in paraplegic animals. Taken together, these data suggest that exercise rehabilitation improved functional recovery and increased immobility time in a rat model of SCI. Future studies will evaluate additional measures of psychological health and potential cellular substrates associated with these exercise-induced effects. Supported by W81XWH-10-1-0839 and AAP RREMS fellowship.

Farrington, Woodrow Jackson, II (Woody)

Project Length Short
Prior Research Experience Yes
Funding Source Departmental or Mentor funds
Advisor Dr. William Jordan

Co-Authors

Title A Retrospective Analysis of Aortic Remodeling Following TEVAR in Acute and Chronic Dissection

Abstract

Objective: To determine the changes in aortic luminal diameter for patients with acute and chronic aortic dissection.

Methods: Patients treated for type B aortic dissection were identified from a prospectively maintained registry. Health systems charts, medical correspondence and computed tomography (CT) imaging were reviewed. Measurements for true lumen (TL) and false lumen diameters were recorded at the first transverse section directly inferior to the aortic arch. Maximum diameter (MD) was recorded at the point of maximal dilation regardless of position. Data were analyzed for up to 720 days following endovascular intervention.

Results: Of 52 patients treated with TEVAR for AD, pre and post op CT was available for analysis and comparison in 30 patients. Of these patients, follow up imaging was analyzed up to 720 days. Fourteen patients (47%) were treated within 14 days of dissection (acute), while 16 patients (53%) were treated beyond this period (chronic). Indications for treatment were malperfusion (5), expansion (10), pain (8), and uncontrolled hypertension (7). For all patients at 2 years, MD decreased by a mean of 2.1 mm while TL increased by a mean of 12.7 mm. Overall, 19 patients (63%) had a decrease in MD and 26 patients (87%) had an increase in TL. Subgroup analysis revealed the following: For those treated in the acute period, MD decreased an average of 1.8 mm while TL increased an average of 9.8 mm. For those treated for chronic dissection, MD decreased an average of 4.1 mm while TL increased an average of 15 mm.

Conclusion: TEVAR shows stabilization and positive remodeling of both acute and chronic type B aortic dissection by both decreasing the MD and increasing the TL.

Feist, Richard Minton, Jr. (Reese)

Project Length Intermediate
Prior Research Experience Yes
Funding Source NIH T35 Short Term Training Grant
Advisor Clyde Guidry
Co-Authors Jeffery L. King, Robert Morris, C. Douglas Witherspoon
Title Müller Cells and Retinal Pigment Epithelium Contribute to the Myofibroblast Population in Proliferative Vitreoretinopathy

Abstract

Proliferative vitreoretinopathy (PVR) membrane formation is the leading cause of failure following retinal detachment repair. These membranes contain myofibroblast-like cells expressing α smooth muscle actin (α SMA), and generate tractional forces upon the retina that cause re-detachment. Origins of the extracellular matrix and myofibroblasts in these membranes are unknown, but Müller cells, the predominant glia in retina, and retinal pigment epithelia (RPE) are capable of undergoing phenotypic transformation in culture to assume myofibroblastic characteristics. To identify whether these cells contribute to membrane formation *in vivo*, human PVR membranes were probed using indirect immunohistochemistry. Distribution of a glial marker, glial fibrillary acidic protein (GFAP), and an epithelial marker cytokeratin (CK) 18 were examined in relation to collagens I and II. Freshly isolated porcine Müller cells and RPE were also maintained in continuous culture for 1 month and evaluated for collagen I and II expression by RT-PCR. PVR membranes were probed with GFAP, CK18 or the late stage epithelial marker CK19, in conjunction with α SMA to identify the cellular origin of the myofibroblast population. Samples were also probed for GFAP and CK19 to determine the specificity of this late stage epithelial marker. Collagen I was detected in all samples, and was expressed in conjunction with cells expressing GFAP or CK18. RT-PCR showed expression of collagen I in the cell cultures, indicating both cell types are a likely source *in vivo*. Cells expressing GFAP, CK18 and CK19 were also positive for α SMA, indicating that glia and RPE contribute to the myofibroblast population. Therefore, Müller cells and RPE participate in the pathogenesis of PVR, both as a source of myofibroblasts and in the formation of extracellular matrix.

Figge, David Anthony (David)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	David Sweatt
Co-Authors	Day J.J., Childs, D., Kibe, M., & Sweatt, J.D.
Title	Chronic cocaine administration causes epigenetic alterations within the nucleus accumbens

Abstract

Following the administration of psychostimulants, such as amphetamine and cocaine, many of the brain's reward and memory forming areas, such as the nucleus accumbens (NAc), exhibit significant neuroplastic changes. It has been shown that these changes are vital to the formation of drug associated memories and behavioral adaptations. However, the exact molecular mechanisms underpinning these long-term neuroadaptations following drug use have not yet been fully determined. It has been well documented that epigenetic alterations, including DNA methylation and histone modifications, are of pivotal importance in the regulation of transcriptional activity and specifically in the brain for the formation and consolidation of long term fear associated memories. It is through these mechanisms, that we propose following chronic cocaine administration there will be significant epigenetic changes in the NAc correlating to cocaine induced behavioral phenotypes. Here, we examined epigenetic changes within the NAc following repeated cocaine experience using direct bisulfite sequencing and methylated DNA immunoprecipitation (MeDIP) for DNA methylation changes or western blot for alterations in histone modifications. Rats received repeated injections of either cocaine (20 mg/kg; i.p.) or vehicle (saline), and tissue from the NAc was removed following locomotor assessment. Either DNA or protein was purified and quantitatively analyzed for changes due to chronic cocaine administration. DNA was either analyzed using bisulfite sequencing or subjected to MeDIP to assess methylation levels within promoter regions of key plasticity genes that are known to be altered by cocaine experience, including *Arc*, *Zif268*, *Creb*, and *Reelin*. Histone changes were determined by quantitative immunoblots. Our preliminary results reveal a repeated cocaine experience produced robust epigenetic alterations, and these changes correlated with the degree of cocaine sensitization observed in cocaine-treated animals. Together, these results suggest that epigenetic regulation maybe of pivotal importance in the control of transcriptional machinery in response to chronic cocaine.

Flaniken, Ian Zahner (Ian)

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Frederick D. Goldman

Co-Authors Erik R. Westin

Title Assessing the Role of DNA Damage Response in a Human Disease Model

Abstract

Telomere length regulates replicative lifespan of cells and their subsequent entry into senescence or apoptosis. The genetic disease dyskeratosis congenita (DC) is caused by short telomeres that arise due to mutations in components of telomerase (*TERT*, *TERC*, and *DKC1*), the enzyme complex that synthesizes telomere repeats to chromosomal termini. Short telomeres are a key trait of DC, which also features the clinical triad of mucosal leukoplakia, abnormal skin pigmentation, and nail dystrophy, in addition to premature aging and bone marrow failure. Thus, DC is a useful disease model for examining the effects of telomere shortening on cellular proliferation and the molecular pathways that induce senescence. Furthermore, treatment of bone marrow failure in DC patients with stem cell transplantation is complicated by poor tolerance to myeloablative conditioning regimens utilizing radiation and chemotherapy. Here, we demonstrate the negative effects of severe telomere attrition on the proliferation of T lymphocytes in cell culture using cells acquired from two related DC patients with a mutation in *TERC*. This impaired proliferation in DC lymphocytes is further compounded by an increased sensitivity to γ -irradiation, in a dose dependent manner, compared to control cells. We propose that this heightened sensitivity to DNA damage in telomere-insufficient cells is due to the activation of p53, a powerful tumor suppressor responsible for entry into senescence/apoptosis in response to telomere attrition and/or DNA damage. Further studies investigating p53 activation in DC and control cells exposed to radiation are currently in progress.

Foppe, Sara Elizabeth (Sara)

Project Length Short

Prior Research Experience No

Funding Source

Advisor Dr. John Clifton Wellons, III

Co-Authors CN Shannon, MI Falola, JC Wellons, WJ Oakes

Title Shorter Stay and Similar Complication Rate with Limited Laminotomy for Selective Dorsal Rhizotomy; A Comparison Study

Abstract

Introduction: Historically, selective dorsal rhizotomy (SDR) has utilized an extensive multilevel laminotomy technique. In recent years, limited laminotomy has been adopted to minimize exposure of the cauda equina. The purpose of this study was to compare traditional inpatient cost-surrogate endpoints between procedures.

Methods: A retrospective review was conducted on 127 cerebral palsy patients who underwent SDR at a pediatric acute care facility between the years 1993 and 2011. Of the 127 patients, 72 (57%) underwent limited laminotomy and 55 (43%) underwent extensive laminotomy. In addition to standard demographics and pre- and postoperative functional status, OR time, complication rates, ICU time, and inpatient hospitalization time were examined.

Results: The mean age at operation was 4.3 years for the entire cohort, similar across both groups. No statistical difference was found when looking at preoperative or change in ambulatory status, OR time, or complication rates between groups. Mean post-operative days spent in the ICU for limited and extensive laminotomy patients were 1 and 1.7, respectively ($p=0.001$). Mean hospital stay was 2.7 days for limited laminotomy and 4.4 days for extensive laminotomy ($p < 0.001$).

Conclusions: A limited laminotomy for SDR leads to a shorter hospital stay and reduced amount of time in the ICU compared to extensive laminotomy in similar patients. OR time, complication rates, preoperative ambulatory status, and change in ambulatory status were similar. This data will be useful in formal comparative cost analysis of the two procedures.

Frederick, John William (John)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Eben Rosenthal
Co-Authors	Larissa Sweeny, Yoland Hartman, Eben Rosenthal
Title	Anti-CD147 Inhibits Proliferation by Down Regulation of EGFR in Cutaneous Squamous Cell Carcinoma

Abstract

Educational Objective: At the conclusion of this presentation, the participants should be able to have a better understanding of CD147 and its role in cutaneous squamous cell carcinoma.

Objectives: Investigate the molecular pathway behind anti-CD147 treatment in cutaneous squamous cell carcinoma (cSCC).

Study Design: Pre-clinical investigation.

Methods: Cutaneous squamous cell carcinoma cell lines, Colo-16, SRB-1, and SRB-12, were treated with a range of chimeric anti-CD147 mAb (0, 50, 100, 200 µg/mL) doses or transduced with a small interfering RNA (siRNA) against CD-147. In vitro cell proliferation, migration, and protein expression was then quantified.

Results: In response to anti-CD147 mAb treatment, there was a significant decrease in proliferation, with an average of 78% of control (P-value for Colo-16, SRB-1, and SRB-12: 0.06, 0.06, 0.003). The wound assay demonstrated a decrease in cell migration, averaging a 43% reduction in closure when compared to untreated (P-value for Colo-16, SRB-1, and SRB-12: < 0.001). Colo-16 cells silenced for CD147 expression demonstrated similar reduction in proliferation and delay wound closure. In vitro phenotype in response to anti-CD147 therapy resulted in reduction in EGFR expression. A significant decrease in EGFR expression by immunofluorescence and western analysis was observed in response to loss of CD147 signaling, which was mirrored by a decrease in downstream expression of BAD and AKT.

Conclusions: Loss of CD147 function results in a suppression of the malignant phenotype in vitro which may be a result of decreased EGFR expression and AKT pathway activation.

Gaston, David Curtis (David)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Jacqueline N. Parker, Ph.D., Richard J. Whitley, MD
Co-Authors	Carl I. Odom, Jacqueline N. Parker, Ph.D., Richard J. Whitley, MD
Title	A conditionally-replicating oHSV vector dually encoding IL-15 and IL-15 receptor alpha for malignant glioma therapy

Abstract

Conditionally replication-competent oncolytic herpes simplex type-1 viral vectors (oHSV) are promising therapeutic agents for malignant glioma. Preliminary microarray data from a Phase Ib clinical trial of the oHSV G207 revealed increased transcript levels of interleukin (IL)-15 and all receptors necessary for optimal IL-15 signaling in patients surviving at least 6 months post-G207 therapy. Also increased were transcript levels indicating the presence of actively cytotoxic CD8⁺ T cells and natural killer (NK) cells, immune effectors stimulated by IL-15. We hypothesize that IL-15 propagates CD8⁺ T and NK cell anti-glioma immune responses, thus contributing to tumor clearance in concert with lytic oHSV replication. To investigate this hypothesis, oHSV vectors expressing the murine (m)IL-15 gene in the U_L3/U_L4 intergenic region with or without the mL-15Ralpha gene in the diploid gamma_1 34.5 regions were constructed. These vectors demonstrated no change in replicative ability compared to parental vectors, indicating the genetic insertions did not impair oncolytic ability. The vector encoding mL-15 alone produced a low level of mL-15, whereas mL-15 production was substantially improved in the vector dually encoding mL-15/IL-15Ralpha as detected by protein immunoblot. This vector also produced and secreted the physiologically relevant complex of mL-15 bound to mL-15Ralpha as detected by an ELISA specific for the mL-15/IL-15Ralpha complex. The neurotoxicity of both vectors was demonstrated to be greater than 1x10⁷ plaque forming units, which is comparable to other engineered oHSV vectors. Continuing *in vitro* investigation seeks to determine the bioactivity of oHSV produced mL-15/IL-15Rα in CD8⁺ T and NK cell activation assays. *In vivo* studies investigating the stimulation of bystander immune-mediated tumor clearance by oHSV-produced mL-15/IL-15Rα in murine models of malignant glioma are underway. Results of these studies may warrant engineering of oHSV vectors expressing human IL-15/IL-15Rα for possible investigation in clinical trials for malignant glioma.

Glueckert, Lindsey Noel (Lindsey)

Project Length	Short
Prior Research Experience	Yes
Funding Source	HSF Community and Rural Health Fellowship
Advisor	Derek A. DuBay MD
Co-Authors	David Redden PhD, Maxwell Thompson MS2, Devin E. Eckhoff MD
Title	Impact of Insurance Status on Post Liver Transplant 5-Year Survival

Abstract

Introduction: Patient insurance status has been demonstrated to predict survival for several disease processes. Our study objective was to measure the impact of insurance status on post-liver transplant (LTx) 5-year survival. We hypothesize public and non-insured patients have decreased LTx survival compared to privately insured patients.

Methods: We conducted a retrospective study of liver transplants performed at The University of Alabama at Birmingham from 1999-2010 (n=970). Insurance cohorts were classified as private, Medicare, Medicaid, and non-insured. Kaplan-Maier curves were constructed and Log-Rank tests used to measure LTx survival. Univariate and multivariable Cox regression analyses were performed to control for confounding variables.

Results: The Log-Rank tests comparing the Kaplan-Maier survival estimates demonstrated significant differences between the insurance status strata (p=0.003). Compared to private insurance, crude unadjusted survival estimates were worse in Medicare (p=0.008) and non-insured patients (p=0.005), whereas no significant differences were observed in Medicaid patients (p=0.5). After adjusting for potential confounding variables including patient demographics, co-morbidities and surrogate markers of socioeconomic status, the non-insured remained associated with worse LTx survival (HR 4.05, 95% CI 1.85-8.83) while a non-significant trend towards worse survival was observed in Medicare (HR 1.52, 95% CI 0.96-2.40).

Recipient median household income was additionally analyzed to test if insurance status is merely a surrogate marker of income. Recipient household income was not associated with LTx survival on univariate analysis (p=0.4) or when controlling for insurance status (HR 0.99, 95% CI 0.90-1.09).

Discussion: The poorer LTx survival of Medicare and non-insured patients compared to Medicaid and privately insured patients suggest factors other than demographic, socioeconomic, and co-morbidities may be associated with increased mortality. Impact of insurance status on allograft rejection and consequences of insurance change will be discussed in secondary analyses. Further studies are required to determine other factors responsible for differences in survival observed across these cohorts.

Gribben, Valerie Janet (Valerie)

Project Length Intermediate
Prior Research Experience Yes
Funding Source
Advisor Hughes Evans, MD
Co-Authors

Title Illness and Injury in Mary de Morgan's Fairy Tales

Abstract

Under the guidance of Hughes Evans, MD, my Scholarly Activity focuses on authoress Mary de Morgan (1850-1907), whose family was at the epicenter of scientific and artistic circles in Victorian England. Though often overlooked in studies of her illustrious family, Mary de Morgan wrote three collections of intriguing fairy tales.

My Scholarly Activity delves into Mary de Morgan's fascination with science and health, a topic that has never been investigated. Close readings of her tales showed how the themes of illness and injury pervade almost all of her stories. For example, in "Siegfrid and Handa," a village is punished for its selfishness with an epidemic of fever, and in "Through the Fire," a "crippled" boy is made well by a magic belt from the fairies. This Spring, I visited London, where I was able to work with the de Morgan family papers, which included personal letters and unpublished manuscripts. In the most poignant of her fairy tales, Mary de Morgan's characters perish from wasting illnesses that rob them of beauty and health, and the most affecting evidence of Mary's interest in medicine were letters written by Mary's sister, Christiana de Morgan, to Mary over the course of two years as Christiana began to experience the ravaging effects of the tuberculosis. Unfortunately, Christiana was not the only de Morgan to die of tuberculosis—her brothers George and Edward were similarly stricken, as was her sister Alice. Mary herself would die of TB in 1907, after she moved to Egypt in a final effort to save her health.

The results of this SA not only herald the re-discover the voice of Mary de Morgan, but also present her tales in a new and fascinating light: an intriguing union between the fanciful realm of fairy tales and the grim realities of the Victorian medical world.

Guzman Karlsson, Mikael Carl Gustav (Mikael)

Project Length Short
Prior Research Experience Yes
Funding Source Departmental or Mentor funds
Advisor Farah D. Lubin
Co-Authors

Title Assessing G9a-p65/RelA Interactions during Memory Consolidation via *in situ* PLA

Abstract

Epigenetic mechanisms have long been associated with cell differentiation and development. However, recent studies have also implicated epigenetic mechanisms in several brain regions including the hippocampus involved in various types of learning and long-term behavioral changes in the adult. Typically, epigenetic mechanisms consist of DNA methylation and post-translational modifications of histones. Previous research from our lab suggests that histone methylation is a major epigenetic mechanism that is dynamically regulated in the hippocampus during the consolidation of contextual fear memories. Specifically, dimethylation of histone H3 at lysine 9 (H3K9me2), a modification associated with transcriptional silencing, was found to be dynamically up-regulated in the hippocampus during memory consolidation. Although it is known that the histone methyltransferase complex G9a/GLP is responsible for H3K9me2, the upstream mechanism by which G9a/GLP is activated is still unclear. *In vitro* studies suggest that methylation of the p65/RelA subunit of the nuclear factor kappa B (NF- κ B) by mono-methyltransferases such as the SET domain containing 6 (SETD6) may mediate the recruitment of the G9a/GLP complex to gene promoters. However, whether or not the NF- κ B transcription factor, which itself has been shown to be important in memory consolidation, interacts with the G9a/GLP complex *in vivo* has yet to be investigated. Our central hypothesis is that learning induced changes in H3K9me2 methylation are dependent on the interaction between G9a and p65/RelA. In order to examine such protein-protein interactions in a cell-type specific manner, we applied the *in situ* proximity ligation assay (PLA) technology to rat hippocampal tissue one hour after contextual fear conditioning. Preliminary data suggest operational feasibility of the *in situ* PLA technology in regards to detecting and quantifying G9a-RelA interactions in neurons. Together, these studies begin to define the role of NF- κ B in the initiation of G9a/GLP-H3K9me2 activity in the hippocampus during memory consolidation.

Hadley, Jennifer Ann (Jennifer)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Adrienne Lahti, MD
Co-Authors	Mark Bolding, David White
Title	Imaging Biomarkers for the Prediction of Treatment Response in Schizophrenia

Abstract

Response to antipsychotic drugs in schizophrenia is not homogeneous. When treated with an antipsychotic drug, only 5-10% of patients with SZ experience a full remission; 66% of the remaining patients go on to experience a partial remission, and 33% are considered “treatment resistant”. The length of time required for the development of treatment response to antipsychotic drugs (at least 6 weeks) suggests that a mechanism of ongoing neuronal plasticity underlies the response to antipsychotic drug treatment. We have set out to characterize the effects of antipsychotic drug on functional connectivity (the correlation of activity within and between cognitive networks) in persons with schizophrenia using both fMRI and ¹⁵O-PET.

Our previous imaging studies have made significant progress by identifying several brain regions that show consistent changes in regional cerebral blood flow in response to antipsychotic drug use and are part of a neuronal network known to be modulated by dopamine. These regions consisted of the ventral striatum/nucleus accumbens (VS), the hippocampus (Hip), and the medial frontal cortex (MFC). We hypothesized that there would be differences in connectivity between these regions at three time points in antipsychotic drug treatment: (1) in the medication-free baseline state, (2) after 1 week of treatment, and (3) after 6 weeks of treatment.

We found that the functional connectivity between MFC and VS significantly increased at week 1, and then significantly decreased from week 1 to week 6. The functional connectivity between MFC and Hip significantly decreased at week 1 and week 6 relative to baseline. Critically, the strength of the functional connectivity between the MFC and Hip after 1 week of treatment was predictive of treatment response. This pattern of changes may represent an important biomarker for indexing treatment response. The regulation by APDs of the balance between prefrontal and limbic inputs to the striatum may be crucial to restoring adaptive behavior.

Hardin, David Michael (David)

Project Length Short

Prior Research Experience Yes

Funding Source HSF Community and Rural Health Fellowship

Advisor Dr. John Wheat, MD

Co-Authors

Title Rural Alabama: Observations of Diversity in Medical Practices and Health Care Challenges

Abstract

Approximately twenty percent of Americans live in areas deemed to be rural, and each region of rural America is unique in different ways. The structure of the health care system and manner in which health care is utilized by the local population vary widely across rural America. Furthermore, the challenges facing health care in rural setting are equally varied in each community.

While rural health care systems are varied and diverse in many areas, economic difficulty is a characteristic of health care that all rural providers have in common. Hospitals and private practices who serve rural populations have traditionally struggled with limited local economies, difficulty recruiting health care professionals, inadequate transportation over long distances, and many other issues relating to the quality and accessibility of health care (Nemet, 2000). While the broad economic concerns seem to be uniform throughout rural health care, the reasons for these difficulties are much more region-specific and require more thorough investigation at a local level.

Moreover, these access and economic issues have greatly hampered efforts to implement and sustain quality improvement measures in rural health care settings. While best-practices, operations management, and quality assurance techniques have achieved success in many urban settings, rural health care tends to lag behind quality improvement initiatives and implementation of new technology.

These themes were studied and new challenges were identified through a series of interviews involving physicians who served rural populations of Alabama. The areas of Greensboro, Camden, Muscle Shoals, and Tuscaloosa, Alabama each painted unique pictures of healthcare needs in rural populations and how those needs are addressed locally and statewide. Additionally, key disparities were observed between the Black Belt regions and rural areas of Northwest Alabama.

Hines, Kathryn Charlton (Katy)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Amanda Soong, MD
Co-Authors	Amanda Soong, MD
Title	Grandparent Caregivers' Knowledge Deficit Regarding Child Safety and Development

Abstract

Background: In today's society, an increasing number of children are being raised in households headed by a grandparent or other older adult caregiver. However, there is minimal literature available addressing the knowledge grandparent caregivers have regarding current theories of child development, safety, and health needs.

Objective: To evaluate basic knowledge local grandparent and older adult caregivers have regarding child safety topics.

Methods: We attended four local grandparent support group meetings, at which time meeting participants were each asked to complete a child safety survey. The survey included 14 multiple-choice questions.

Results: Forty-nine surveys were collected. The average survey score was 42.1% (5.9 of 14 correct answers). Questions most often answered incorrectly were those addressing the following topics (percentage of correct responses in parentheses): usefulness of walkers in helping infants learn to walk (24.5%), proper ages for infants to start eating baby food (20.4%) and drinking water (20.4%), hot water safety (8.2%), and daily screen time for children less than two years (18.4%) and greater than two years of age (4.1%). Questions regarding the safest position for a baby to sleep and crib safety received a greater number of correct responses, though recommendations regarding these topics received greater scrutiny during discussion with survey participants.

Conclusions: This study indicates that local grandparent and older adult caregivers have a knowledge deficit regarding child safety topics. These survey results can be used to tailor local pediatricians' anticipatory guidance to this caregiver population.

Honasoge, Avinash Vinayak (Avinash)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Harald Sontheimer
Co-Authors	
Title	Proton Concentration Modulates the Rate of Glioma Invasion via a pH-sensitive K ⁺ Conductance

Abstract

Gliomas are both the most common and the most aggressive primary brain cancer in humans, causing significant comorbidities and loss of life despite the best current treatments. In particular, gliomas have two striking properties: enhanced migration through the surrounding brain tissue and marked pH heterogeneity. The former is facilitated by heightened extrusion mechanisms for K⁺ and Cl⁻ with obligatory water release, allowing glioma cells to squeeze through tight intracranial spaces; the latter is due to a combination of factors including increased lactic acid production (due to hypoxia) and increased extracellular acidification (via various exchangers and pumps). Here, we tie these two properties together by demonstrating a pH-modulated K⁺ conductance in human glioma cells. The underlying K⁺ currents are quinine- and ruthenium red-sensitive, have a reversal potential near that of K⁺, and are reversibly abolished by acidic pH (6.0). There is an approximately 30% decrease in whole-cell current density (from 5.18±0.60 to 3.74±0.56 pA/pF at +40 mV) when pH changes from 7.4 to 6.0. These currents are insensitive to blockers of big-, intermediate-, and small-conductance Ca²⁺-activated potassium channels (previously implicated in glioma cell physiology), as well as to low [Ca²⁺]_i. Migration assays show a marked attenuation of motility in acidic media, consistent with the hypothesis that these pH-sensitive K⁺ currents participate in cell migration but require alkaline pH to be activated. Hence we show evidence for a hitherto unrecognized K⁺ conductance in glioma cells with properties that exploit the unique pH environment around these tumors.

Hull, Travis David (Travis)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Anupum Agarwal, MD
Co-Authors	James George, PhD and Subhashini Bolisetty, PhD
Title	Cardiomyocyte-Specific Heme-Oxygenase-1 Overexpression in Cardiac Transplantation

Abstract

Background: Heme oxygenase-1 (HO-1) is an enzyme that catalyzes the oxidative breakdown of heme into carbon monoxide, biliverdin, and iron. Additionally, cytoprotective and immunoregulatory functions of HO-1 have recently been described. Allograft vascular disease (AVD) is the most common cause of graft loss and death in cardiac transplant patients that survive beyond one year. Protection against AVD has been observed in models of allograft rejection in which HO-1 was globally induced by pharmacologic treatment of graft recipients, while HO-1 inhibition decreases survival. Information regarding the mechanisms of graft protection by HO-1 and how these observations can be exploited therapeutically remain to be elucidated.

Hypothesis: We hypothesize that HO-1 induction mediates cytoprotection in a biphasic manner. Expression within the parenchyma of the donor heart provides initial, local protection against ischemia/reperfusion injury while expression within host hematopoietically-derived cells provides immunomodulatory protection through inhibition of graft-infiltration by inflammatory cells.

Methods/Results: A mouse heterotopic heart transplantation model was utilized in conjunction with a novel transgenic mouse containing a floxed b-gal-stop-codon cassette with HO-1 downstream of the stop codon, thereby allowing inducible overexpression of HO-1 in cardiac myocytes via the cre-lox system. These mice were bred with a transgenic mouse containing a tamoxifen-inducible myosin heavy chain promoter driving cre recombinase expression to generate myocardial specific HO-1 overexpressing mice. The double transgenic mice were administered tamoxifen for 5 days to activate the transgenic MHC promoter, which resulted in overexpression of HO-1, specifically in cardiac myocytes. Immunohistochemical staining was performed on heart sections obtained from HO-1 overexpressing donors and wild-type donor controls to demonstrate that HO-1 immunomodulates graft-infiltration by inflammatory cells.

Conclusion: These preliminary data suggest that the HO-1 system plays a role in regulating the immune processes that lead to AVD.

Jackson, Justin Myron (Justin)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Sadis Matalon, Ph.D.
Co-Authors	Emily Ness, Ahmed Lazrak, Sadis Matalon
Title	Effects of Inter Alpha Trypsin Inhibitor on Amiloride Sensitive Epithelial Sodium Channels (ENaC)

Abstract

Inter Alpha Trypsin Inhibitor (IaI) is an endogenous human plasma serine proteases inhibitor. Epithelial Sodium Channel (ENaC) is a tetrameric ion channel formed by the association of three subunits α , β , and γ . ENaC activity at the apical membrane of epithelial cells is regulated by the proteolysis of its subunits and the ubiquitination and removal from the membrane by endocytosis. Herein we express ENaC subunits in *Xenopus* oocytes and measure channels activity using electrophysiology methods, and subsequently generate a current/voltage relationship (IV curve). Since ENaC activity is regulated by membrane bound proteases, the incubation of oocytes expressing ENaC with IaI should decrease the number of active channels at the membrane and hence the sodium current recorded. We hypothesize that IaI inhibits the membrane bound proteases that are needed for ENaC activation. These experiments will be conducted using oocytes harvested from the *Xenopus laevis* frogs. The oocytes will be injected with cRNA for human ENaC subunits (α , β , and γ). We expect human ENaC to express in these oocytes, and via electrophysiological methods, we will measure the amiloride sensitive current (i.e. current before and after addition of amiloride) in control oocytes and those incubated with IaI (0.1mg/ml) for one hour. The control group will consist of oocytes that are injected with water only, or oocytes that are injected with cRNA human ENaC only. The control group will be compared to the experimental group, which will consist of the oocytes that are injected with cRNA human ENaC and then incubated with IaI for one hour. These studies have clinical relevance because we know that certain lung diseases, such as cystic fibrosis, have increased ENaC activity that contributes to its pathology. These studies might provide us with alternative ways to down regulate ENaC activity and alleviating the CF symptoms. Preliminary results show that oocytes incubated with IaI do have decreased current when compared to the control group. Other investigations are still pending.

Jarboe, John Stewart (John)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Chris Willey MD, PhD
Co-Authors	Joshua C. Anderson, Christine W. Duarte, Tapan Mehta, Somaira Nowsheen, Patricia H. Hicks, Alexander C. Whitley, Timothy D. Rohrbach, James A. Bonner, G. Yancey Gillespie, Eddy S. Yang
Title	MARCKS is a Novel Prognostic Factor for Tumors with Un-methylated MGMT Status among the Proneural Subtype of Glioblastoma Multiforme

Abstract

BACKGROUND: Distinct molecular pathways drive glioblastoma growth and therapeutic response. Classification of these tumors into molecular subtypes will lead to improved treatment stratification and the identification of novel therapeutic targets. Global kinase activity assessment (kinomic profiling) of human glioblastoma tumor specimens can be used to identify novel growth regulatory pathways. Using this approach, we identified myristoylated alanine rich c-kinase substrate (MARCKS), an important mediator of phospholipid signaling, as a potential glioblastoma signaling molecule. We aimed to establish the role of MARCKS in the regulation of glioblastoma growth, prognosis and treatment response.

METHODS: We analyzed human glioblastoma xenografts and cell lines for MARCKS expression, growth characteristics, and kinomic profiling. We investigated the growth and radiation treatment effect of MARCKS expression in glioblastoma cells. We confirmed these findings with the outcome data of 192 glioblastoma patients.

RESULTS: Kinomic evaluation of human glioblastoma xenografts with known radiation sensitivity identified MARCKS as a potential regulator of tumor growth and therapy response. MARCKS protein expression was inversely correlated with glioblastoma proliferation and intracranial xenograft growth rates. Importantly, age-adjusted MARCKS gene expression inversely correlated with overall survival in glioblastoma patients. Specifically, patients with high MARCKS expressing tumors of the Proneural molecular subtype had significantly increased survival rates. This effect was most pronounced in tumors with unmethylated O⁶-methylguanine DNA methyltransferase (*MGMT*) promoters, a traditionally poor prognostic factor. Genetic silencing of MARCKS promoted glioblastoma proliferation and radiation resistance, while MARCKS overexpression greatly reduced glioblastoma growth potential.

CONCLUSION: MARCKS levels impact glioblastoma growth and radiation sensitivity. High MARCKS expressing glioblastoma tumors are associated with improved survival, particularly with unmethylated *MGMT* promoters. These findings suggest the use of MARCKS as a novel target and biomarker for prognosis in the Proneural subtype of glioblastoma.

Johnson, Erica Monique (Erica)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Sadis Matalon, PhD.
Co-Authors	Sadis Matalon, Lan Chen
Title	"Effects of Respiratory Syncytial Virus (RSV) and Chlorine Exposure on ENaC Activity"

Abstract

For my scholarly activity project I decided to test the effects of both chlorine and RSV infection on human pulmonary epithelial cells. The significance of RSV is demonstrated by its impact on the child and adult population. It is the leading cause of bronchiolitis in children causing the majority of hospitalizations in children less than two. Also, the viral infection may lead to significant morbidity and mortality in immunosuppressed adults and most likely underdiagnosed for respiratory infections in healthy adults. The goal of my project was also aimed at observing the effects of chlorine on lung epithelium- a continuation of my summer research project from MS1. I have previously described the damage to lung cells by an increase in ROS and decrease in antioxidants, but with this project I targeted the mechanism at the cellular level to include the amiloride-sensitive epithelium sodium channel (ENaC). I aimed to prove that both RSV and chlorine exposure synergistically decrease ENaC activity and lead to decreased alveolar fluid clearance therefore resulting in the symptoms of ARDS, pulmonary edema, and respiratory compromise that are associated with their exposure. Also this project would aim at proving the idea that when children are infected with RSV at younger age, their lungs may be more susceptible to damage even with minute incidental or deliberate exposure to chlorine gases, and this damage could cause significant respiratory distress through the fore mentioned mechanism. In testing my above hypothesis I learned to perform cell isolation, cell culture, and use the Ussing chamber instrument to measure the short circuit currents for the ENaC channel.

From my research thus far I have concluded that when working with H441 cells (human-like adenocarcinoma clara cells) and exposing them to RSV that 24hours post-infection there was a statistical significant decrease in ENaC activity and the current it could produce. The decreased current translates into decreased function of the channel to perform clearing of alveolar fluid. When assessing the cells post RSV infection AND chlorine exposure post-24hours there was a decrease in ENaC activity and function in the RSV + Cl₂ groups when compared to air-controls or chlorine only groups.

Since my hypothesis was proving true in human adenocarcinoma cells, I wanted to perform this experiment on cells more similar to in vivo healthy human pulmonary epithelium. I chose rat primary alveolar type II cells to experiment with. While working with these cells I concluded that there was a statistically significant decrease in ENaC function and activity in RSV + Cl₂ exposed groups when compared to their air-control, RSV only, or chlorine only counterparts.

Johnson, Erica Monique (Erica)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Sadis Matalon, PhD.
Co-Authors	Sadis Matalon, Lan Chen
Title	"Effects of Respiratory Syncytal Virus (RSV) and Chlorine Exposure on Pulmonary Epithelium"

Abstract

For my scholarly activity project I decided to test the effects of both chlorine and RSV infection on human pulmonary epithelial cells. The significance of RSV is demonstrated by its impact on the child and adult population. It is the leading cause of bronchiolitis in children causing the majority of hospitalizations in children less than two yrs. Also, the viral infection may lead to significant morbidity and mortality in immunosuppressed adults and is likely underdiagnosed for respiratory infections in healthy adults. The goal of my project was also aimed at observing the effects of chlorine on lung epithelium- a continuation of my summer research project from MS1. I have previously described the damage to lung cells by an increase in ROS and decrease in antioxidants, but with this project I targeted the mechanism at the cellular level to include the amiloride-sensitive epithelium sodium channel (ENaC). I aimed to prove that both RSV and chlorine exposure synergistically decrease ENaC activity and lead to decreased alveolar fluid clearance, therefore resulting in the symptoms of respiratory distress that are associated with their exposure. Also this project would aim at proving the idea that when children are infected with RSV at younger age, their lungs may be more susceptible to damage even with minute incidental or deliberate exposure to chlorine gases, and this damage could cause significant respiratory compromise through the fore mentioned mechanism. In testing my above hypothesis I learned to perform cell isolation, cell culture, and use the Ussing chamber instrument to measure the short circuit currents for the ENaC channel.

I wanted to perform this experiment on cells similar to in vivo healthy human pulmonary epithelium; therefore, after confirming preliminary results in human adenocarcinoma (H441) cells, I chose rat primary alveolar type II cells to work with. While working with these cells I concluded that there was a statistically significant decrease in ENaC function and activity in RSV + Cl₂ exposed groups when compared to their air-control, RSV only, or chlorine only counterparts. The decreased current translates into decreased function of the channel to perform clearing of alveolar fluid.

Kakati, Donny Debajyoti (Donny)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Martin Young
Co-Authors	Vick DiCarlo and Kortland Hudson
Title	Direct Regulation of Myocardial Glycogen Metabolism by the Cardiomyocyte Circadian Clock

Abstract

Myocardial processes ranging from transcription to contractile function vary based on time of day. Increased myocardial energetic demand during the active/awake period is paralleled by changes in glucose metabolism. During periods of increased cardiac performance, intracellular glycogen levels act as a significant fuel source. Myocardial glycogen levels oscillate in a time-of-day-dependent manner in the heart. However, little is known regarding mechanisms mediating time-of-day-dependent variations in myocardial glycogen turnover. Circadian clocks have emerged as critical modulators of time-of-day-dependent cellular functions. We hypothesized that the cardiomyocyte circadian clock mediates time-of-day-dependent oscillations in myocardial glycogen levels. To investigate whether the cardiomyocyte circadian clock modulates myocardial glycogen levels over the course of the day, a genetic mouse model in which this molecular mechanism is disrupted (i.e., cardiomyocyte-specific BMAL1 knockout [CBK] mice) was utilized. All mice were housed in under 12h:12h light:dark cycle conditions. Myocardial glycogen levels were measured in rat and mouse hearts using a spectrophotometric assay. A two-step process consisting of hydrolysis of glycogen to make glucose followed by assay for free glucose utilizing both glycolysis as well as the pentose-phosphate pathway was utilized. Results show that glycogen levels exhibit a time-of-day-dependent oscillation in normal rat hearts, peaking at the dark-to-light (awake-to-sleep) phase transition. During the dark (active) phase, both female and male CBK mouse hearts also exhibited significantly greater glycogen levels relative to wild-type littermate hearts. In contrast, no significant differences were observed in myocardial glycogen levels between wild-type and CBK mice during the light (sleep) phase. These results show that the cardiomyocyte circadian clock regulates myocardial glycogen levels in a time-of-day-dependent, gender-independent, manner. Future studies will be necessary to further elucidate the molecular and genetic links between the cardiomyocyte circadian clock and myocardial glycogen levels.

Kapadia, Akash A. (Akash)

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Fadi G. Hage M.D.

Co-Authors Meagan Bowling M.D., Yiu-Fai Chen, Ph.D, Alexander Szalai, Ph.D, Suzanne Oparil M.D.

Title Estrogen inhibits CRP-induced inflammation in mouse macrophages in an estrogen-receptor dependent manner

Abstract

Previous work in our laboratory has shown that C-reactive protein (CRP) is a pathogenic mediator of cardiovascular disease. In an acute vascular injury model, CRP exacerbates vascular remodeling by interacting with FcγRI on the surface of macrophages and administration of 17β-estradiol (E2) abolishes the CRP effect. To test the hypothesis that E2 regulates CRP-induced inflammation in resident/recruited macrophages in the vessel wall in an estrogen receptor (ER)-dependent manner, bone marrow was harvested from C57BL/6 mice and grown in culture with M-CSF. After 7 days, the cells were >90% positive for the macrophage marker F4/80, and were treated with E2 (10⁻⁷M), E2+non-selective ER antagonist ICI (10⁻⁶M), ER-α agonist PPT (10⁻⁷M), ER-β agonist DPN (10⁻⁷M) or vehicle for 24 hours, then incubated with CRP (50 mcg/ml) or vehicle for 4hrs. RNA was extracted and analyzed using real-time reverse transcription-polymerase chain reaction (RT-PCR) to measure the expression of inflammatory mediators. CRP resulted in the increased expression of Chemokine (C-C motif) ligand 4 (CCL4) by 50-fold (52±7 vs. vehicle, p<0.05). Pre-treatment with E2 attenuated the response to CRP by one half (26±2 vs. 52±7, p<0.05). Treatment with ICI completely suppressed the inhibitory effect of E2. PPT reproduced the effects of E2 by attenuating CRP-induced mRNA expression of CCL4 (29±2 vs. 52±7, p<0.05) while DPN had no effect (51±4 vs. 52±7, p NS). In conclusion, CRP-treatment of bone-marrow derived mouse macrophages induces increased expression of CCL4; E2 pre-treatment, via an ER-α dependent mechanism, attenuates the inflammatory response to CRP in mouse macrophages, which may help explain the vasoprotective effect of E2 against CRP-induced vascular remodeling in vivo.

Karim, Samina Sayeeda (Samina)

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Dr. Lawrence S. Lamb

Co-Authors Yun Su

Title *CMV Infection Enhances Immune Evasion of Glioma-derived Cell Lines to In Vitro Expanded/Activated V δ 1+ T Cells via Down-regulation of NKG2D Ligands*

Abstract

Human cytomegalovirus (CMV) is a β -herpes virus that has a lifelong viral presence with life-threatening symptoms in immunocompromised hosts, while asymptomatic in immunocompetent hosts. Published evidence suggests that $\gamma\delta$ T cells play a role in protection against CMV infection in immunosuppressed patients as evidenced by their expansion in CMV-infected organ transplant patients and subsequent resolution of viremia. Malignant glioma tumors often show the presence of CMV genetic material and proteins, and evidence exists that the presence of CMV may be associated with initiation and/or progression of glioblastoma multiforme (GBM). To investigate the role of CMV infection on glioblastoma cell lines, we examined the response of ex vivo V δ 1+ $\gamma\delta$ T cells on unmanipulated and CMV-infected established GBM cell lines and cell lines developed from primary tumors. Artificial CMV infection was necessary as GBM cell lines lose CMV residues shortly after ex vivo propagation in culture or as xenografts. Results showed that the V δ 1+ T cells exhibited specific cytotoxicity towards CMV infected but not towards uninfected fibroblasts regardless of the CMV serologic status of the donated allogeneic feeder cells. Expanded/activated V δ 1+ T cells also killed U251, U87, and U373 GBM cell lines and two primary tumor explants. We also found that V δ 1+ cells targeted both CMV-infected and unmanipulated U251 cells but showed a significant decrease in cytotoxicity to CMV-infected U251 cells. Flow cytometry analysis of CMV-infected cell lines revealed down-regulation of the NKG2D ligands ULBP-1, ULBP-2, ULBP-3, and ULBP-4 as well as MICA/B in CMV-infected cells. These studies show that acute CMV infection enhanced the resistance of U251 and U373 GBM cell lines to innate recognition and cytotoxicity and may contribute to the poor immunogenicity of GBM.

Kebbel, Frederick Albert, V (Eric)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Bradford Woodworth, M.D.
Co-Authors	Daniel Skinner, B.S.; Shaoyan Zhang, Ph.D
Title	CFTR Modulation by the Tobacco Smoke Toxin Acrolein

Abstract

Objectives: Evidence indicates that decreased mucociliary clearance (MCC) is a major contributing feature to chronic rhinosinusitis. Tobacco-smoke exposure is thought to inhibit transepithelial Cl⁻ secretion – a major determinant of airway surface liquid hydration and MCC. The objective of the current study was to evaluate the effects of acrolein exposure (a major tobacco smoke toxin) on vectorial Cl⁻ transport through the major apical anion channel CFTR in sinonasal epithelium.

Methods: Primary murine nasal septal (MNSE, wild type and transgenic CFTR^{-/-}) and human sinonasal epithelial (HSNE) cultures were exposed to acrolein in Ussing chambers and effects on Cl⁻ secretion investigated using pharmacologic manipulation. Cellular cAMP signaling and cytotoxicity were also investigated.

Results: Acrolein stimulated Cl⁻ secretion (ΔI_{SC} – change in short-circuit current in $\mu A/cm^2$) at physiologic concentrations (100 μM , 15.8 +/- 2.2 vs. 2.4 +/- 0.8(control); $p < 0.0001$), suppressed forskolin-stimulated Cl⁻ transport at 300 μM (13.3 +/- 1.2 vs. 19.9 +/- 1.0; $p < 0.01$), and completely abolished all transport at 500 μM (-1.1 +/- 1.6). Stimulated Cl⁻ secretion was solely reliant upon the presence of CFTR (confirmed in transgenic CFTR^{-/-} MNSE), but independent of cAMP signaling. Inhibition at higher concentrations was not secondary to cellular cytotoxicity.

Conclusions: The present study demonstrated that acrolein has complex, but direct interactions with the major apical Cl⁻ channel CFTR. Robust inhibition of Cl⁻ transport at higher concentrations indicates a potential contribution of this toxin to decreased mucociliary transport in individuals with chronic tobacco smoke exposure.

Killian, Mary Elaine (Ellie)

Project Length Short

Prior Research Experience No

Funding Source

Advisor Helen Krontiras, MD

Co-Authors De los Santos J, Forero-Torres A, Krontiras H

Title Receptor concordance in triple-negative breast cancer (TNBC) recurrences.

Abstract

The phenotype of TNBC is defined by absence of estrogen (ER) and progesterone receptors (PR) and lack of amplification of the HER2 oncogene. It is an aggressive form of breast cancer, and despite sensitivity to contemporary chemotherapy, TNBC have a poorer prognosis than other phenotypes. This study examines the concordance of receptor status in recurrences among patients with TNBC.

After obtaining IRB approval, we identified patients with TNBC treated at the University of Alabama at Birmingham between 1998 and 2010. Patient and tumor characteristics and disease status were recorded. Patients with ER, PR, or HER2 (3+) positivity on immunohistochemistry (IHC), or HER2 amplification by fluorescence in situ hybridization were excluded. Data regarding the receptor status of the recurrence, if known, was documented.

Five hundred and two women with TNBC were diagnosed at our institution between 1998 and 2010. Of these, 95/502 (19%) had recurrences. Twenty-seven (28%) were local, 18 (19%) were regional, 35 (37%) were distant, and 15 (16%) were local-regional and distant. These women were between 33 to 84 years of age. Of the women with a recurrence, 78/95 (82%) had a biopsy confirming breast cancer recurrence. Of those biopsied, 33/78 (42%) had receptor studies performed, and of these, 30 included data for estrogen, progesterone and HER2 receptors. The remaining 3 had only IHC for estrogen receptors performed. Twenty-two/thirty (73%) had concordance on biopsy with initial TNBC status, whereas 8/30 (27%) women developed a pathologically discordant recurrence.

In this single institution study of TNBC patients, approximately one quarter of patients developed a pathologically discordant distant recurrence noted at biopsy. It is unclear whether patients experiencing a pathologically discordant recurrence differ in prognosis from those with concordant recurrences. Further study is necessary to evaluate this and determine whether routine biopsy based on pathologic discordance rates and outcomes are warranted.

Kim, David J. (David)

Project Length	Short
Prior Research Experience	No
Funding Source	HSF Community and Rural Health Fellowship
Advisor	James Willig
Co-Authors	Andy Westfall
Title	Multimorbidity Patterns in HIV+ Patients: The Role of Obesity in Chronic Disease Clustering

Abstract

Background: Antiretroviral therapy (ART) has transformed HIV from a once lethal disease to a chronic condition with prolonged life expectancy. Associated with this increase in life expectancy is an increase in multimorbidity (occurrence ≥ 2 chronic conditions) and obesity. However, the interaction between obesity and multimorbidity in HIV-infected individuals has not been studied.

Objectives: To assess the prevalence of multimorbidity and investigate the role of obesity in shaping multimorbidity patterns in HIV-infected individuals.

Design: Retrospective, cross-sectional cohort study of patients receiving care at the UAB 1917 HIV/AIDS Clinic (1917 Clinic) who received treatment from July 1 2010 to June 30 2011.

Methods: The 1917 Clinic Cohort electronic medical record was used to explore multimorbidity patterns in 1844 patients. Multimorbidity patterns were identified by tetrachoric factor analysis. Associations between BMI and multimorbidity were evaluated using Poisson regression.

Results: The observed prevalence of multimorbidity was 77% (1413/1844). Prevalence increased with each BMI category from underweight (64%) to obese (79%). Tetrachoric factor analysis yielded a three factor multimorbidity solution as follows: Factor 1 - hypertension, gout, diabetes mellitus, chronic kidney disease, Factor 2 - dyslipidemia, chronic ulcer disease, osteoarthritis, cardiac and mood disorders, and Factor 3 - Hepatitis C and tobacco, alcohol, and substance abuse. Obese patients had a higher prevalence of Factor 1 and 2 than normal weight patients (61% and 74% compared to 33% and 72%, respectively). Prevalence of Factor 3 was lower for obese patients than normal weight patients (46% compared to 65%, respectively). Overlap among the three factors increased with each BMI category.

Conclusions: Obesity is associated with greater multimorbidity in HIV infected individuals. In order to provide appropriate care, clinical practice guidelines for HIV will need to adapt to the dynamically changing needs of people living with HIV-AIDS.

Klinger, Andrew P (Andrew)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center
Advisor	Orlando Gutierrez and Emmy K Bell
Co-Authors	Suzanne S. Choquette, Betty Darnell, Emmy K. Bell, Orlando M. Gutierrez
Title	Contribution of Food Additives to Daily Sodium and Phosphorus Intake in Diets Rich in Processed Foods

Abstract

Control of sodium and phosphorus intake is critical to the management of chronic kidney disease (CKD) patients. Sodium and phosphorus contents in typical westernized diets far exceed current recommendations for daily intake, in part because of preservatives added to processed and fast foods. However, the relative contribution of additives to total daily sodium and phosphorus intake is unclear. To examine this, separate menus for a low-additive diet and an additive-enhanced diet were developed by the metabolic kitchen of the Clinical Research Unit. The low-additive menu consisted of four different days of meals based on the USDA RDA of approximately 1800 kcal, 1000 mg calcium, and 900 mg of phosphorus per day. The additive-enhanced menu was designed to provide identical energy, calcium, and phosphorus intake per day but using processed foods. Each day's worth of food from each menu collected and analyzed for total energy and micronutrient content. The caloric, protein, carbohydrate, and fat contents of the two diets were similar, with only minor differences noted in some but not all days. Similarly, minor variations in calcium and potassium contents were noted in some, but not all, of the menu days. In contrast, total sodium content was consistently higher each day of the additive-enhanced menu as compared to the low-additive menu, with the magnitude of the difference ranging from 703 to 1,750 mg of sodium. Similarly, total phosphorus content was significantly higher each day of the additive-enhanced menu as compared to the low-additive menu, with the magnitude of the difference ranging from 483 to 790 mg of phosphorus/day. Food additives in processed foods substantially increase the content of phosphorus and sodium in meals designed to be low in both. The addition of these additives could have clinical implications the management of sodium and phosphorus homeostasis in patients who require controlled diets.

Kulkarni, Abhay Krishnaji (Abhay)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Richard Lopez
Co-Authors	Hyung-Gyoon Kim
Title	Therapeutic Antitumor Activity of Allogeneic Gamma Delta T-cells

Abstract

Gamma Delta (gd) T-cells are a unique subtype of immune cells that have specific functions within a host including the ability to destroy tumor cells. Additionally, the number of functional gd-T-cells in cancer patients is significantly decreased compared to that of healthy individuals. This provides the rationale for pursuing allogeneic gd-T-cell transplant to increase a patient's store of functional gd-T-cells and reduce tumor burden.

Current gd-T-cell transfer techniques require bone marrow transplants, which limit the number of donors due to human leukocyte antigen (HLA) matching. A novel strategy to use gd-T-cells therapeutically is to transfer these cells from donors, irrespective of their HLA matching, while providing the recipients with transient lymphodepletion to avoid immediate rejection of gd-T-cells. It is hypothesized that a treatment of transient lymphodepletion followed by gd-T-cell transfer will produce a significant decrease in the overall tumor burden, even in mismatched recipients.

To test this hypothesis, three groups of BALB/c (H2Kd) mice were given syngeneic 4T1LUC tumor cells (H2Kd). One group did not receive any treatment. Another group received initial lymphodepletion as treatment. The final group was treated by lymphodepletion followed by the adoptive transfer of allogeneic gd-T-cells obtained from healthy, fully mismatched C57BL/6 (H2Kb) mice. Tumor burdens for all three of these groups were measured at three separate time points.

At each of these time points there was significantly less tumor burden in mice that received either treatment compared to mice with no treatment. However, there was no significant difference in tumor burden between mice that received only lymphodepletion versus mice that were lymphodepleted with gd-T-cell infusions. These results indicate that combined lymphodepleted plus gd-T-cell infusion treatment does have anti-tumor outcomes; however, in these studies, statistically different effects of the fully HLA mismatched gd-T-cells at the administered level were not noticeable.

Kundukulam, Joseph Anto (Joseph)

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Dr. Brent Ponce, MD

Co-Authors Dr. Gerald McGwin, PhD; Dr. Anthony Narducci, MD; Dr. Marshall Crowther, MD

Title Rotator Cuff Crepitance: Can Cuff Tears be Felt?

Abstract

INTRODUCTION The specificity and sensitivity of rotator cuff exams range widely depending on technique and author. One factor that may explain the low accuracy with examination tests is the role of patient participation which may be limited by pain or secondary gain. An examination technique that is less dependent upon patient effort may be useful.

PURPOSE To assess the sensitivity and specificity of direct palpation of the rotator cuff and the presence of crepitance in identifying rotator cuff tears

METHODS Sixty-six consecutive patients presenting with shoulder pain were prospectively enrolled. In addition to the crepitance test, multiple established rotator cuff examination tests were performed along with a standardized history survey. The cuff examination tests included: impingement, drop arm, empty or full can, painful arc, internal and external rotation lag signs, bear-hug, and belly-press. Following the physical exam, patients received additional imaging with MRI or ultrasound when indicated. Imaging studies were interpreted by musculoskeletal radiologists blinded to the examination findings. Chi-square tests and analysis of variance were used to compare patient and physical exam characteristics with respect to the presence and type of rotator cuff tears.

RESULTS The crepitance test had a sensitivity of 89% and a specificity of 46% for identifying rotator cuff tears. When looking at full thickness tears and high grade partial tears the sensitivity was 77% and the specificity was 81%. The sensitivity and specificity for the detection of low grade partial tears and no tears was 77% and 73%, respectively. Crepitance was present more often and more associated with full thickness tears of the rotator cuff as opposed to low or high grade partial thickness tears ($p < 0.001$). In instances of no tear of the rotator cuff, crepitance was less likely to be present. Of the elements in the patient history, only a higher patient age was strongly associated with a tear ($p < 0.001$). There were also no other physical exam findings that were strongly associated with rotator cuff pathology.

CONCLUSION Palpation of rotator cuff crepitance is a highly sensitive test that may assist in the detection of rotator cuff tears.

Laan, Danuel Jan (Danuel)

Project Length Short
Prior Research Experience Yes
Funding Source CaRES Program
Advisor Dr. Gary Piazza
Co-Authors

Title Novel compounds which inhibit Epidermal Growth Factor dependent cancer growth

Abstract

The epidermal growth factor receptor (EGFR) is frequently overexpressed in many cancers and is therefore an attractive target for treatment. Selective inhibitors of the intracellular, tyrosine kinase, domain of EGFR used clinically such as gefitinib (Iressa) reduce tumor growth and limit toxicity to normal adult tissue. Unfortunately, this class of antineoplastic agents has not achieved the clinical efficacy which was predicted. Thus, the goal of this study was to identify novel EGFR inhibitors with improved potency. Structure activity relationships of a series of related experimental compounds were determined by immunohistochemistry and proliferation assays to evaluate their ability to inhibit EGFR activation and EGFR dependent cell growth, respectively. The effects of said molecules were evaluated on both an EGF dependent cell line (KB-HeLa variant) and an EGF independent cell line (MDA-MB231, mammary carcinoma). Six highly active and potent compounds with IC50 values ranging from 1.8 to 12.2 nM were identified and found to be appreciably more potent than gefitinib with an IC50 of 32.7 nM. The three most active compounds were also assayed for their ability to inhibit EGFR autophosphorylation in a cell-free system, and rank order of potency was maintained among the compounds. However, in cell-free assay, only one of the compounds was more potent than gefitinib. Together, these results suggest that at least two compounds were identified to be at least as potent as gefitinib while apparently having improved access to the intracellular domain of EGFR.

Lewis, Travis Benjamin (Travis)

Project Length Long

Prior Research Experience Yes

Funding Source

Advisor David G. Standaert, David T. Curiel

Co-Authors Joel N. Glasgow, Anya M. Glandon, David T. Curiel, David G. Standaert

Title Transduction of Dopamine Neurons by Adenoviral Vectors is Modulated by CAR Expression: Rationale for Tropism Modified Vectors in PD Gene Therapy

Abstract

Background: Gene-based therapy is a new paradigm for the treatment of Parkinson disease (PD) and offers considerable promise for precise targeting and the flexibility to impact multiple pathobiological processes for which small molecule agents are not available. Some success has been achieved utilizing adeno-associated virus for this approach, but it is likely that the characteristics of this vector system will ultimately create barriers to progress in clinical therapy. The adenovirus (Ad) vector overcomes limitations in payload size and targeting. Cellular tropism of Ad serotype 5 (Ad5)-based vectors is regulated by binding of the Ad attachment protein (fiber protein) to its cognate cellular receptor, the coxsackie and adenovirus receptor (CAR). Many clinically relevant tissues are refractory to Ad5 infection due to negligible CAR levels, but can successfully be targeted by tropism-modified, CAR-independent forms of Ad.

Objective: To evaluate the role of CAR protein in transduction of dopamine (DA) neurons in mice *in vivo*.

Methods: Ad5 was delivered to the substantia nigra (SN) both in wild type (wt) animals and those genetically engineered to express exogenous CAR. Cellular tropism was assessed by confocal immunohistochemical (IHC) analysis in the SN and striatal terminals. Endogenous CAR levels were assessed in the SN by western blot and IHC.

Results: We have found that in wt animals, Ad5 results in robust transgene expression in astrocytes and other non-neuronal cells, but poor transduction of DA neurons. In contrast, Ad5 delivery to CAR transgenic animals results in transduction of SNc neurons and expression of transduced protein in their striatal terminals. Using western blot analysis, we found that there is a relative paucity of CAR expression in the ventral midbrain of wild type animals, but much higher levels are present in the transgenic animals. Interestingly, the hCAR transgene is concentrated in post-synaptic terminals in the SN.

Conclusion: These findings demonstrate that CAR is important for the transduction of wild type DA neurons by Ad5, and provide a rationale for the development of tropism-modified, CAR-independent Ad-vectors for use in gene therapy of human PD.

Lockhart, Jonathan Russell (Jon)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Tim M. Townes
Co-Authors	Dewang Zhou
Title	FOKLF1: A New Target for Sickle Cell Disease and β-thalassemia Therapy

Abstract

Sickle cell disease (SCD) and beta-thalassemia are devastating diseases affecting millions worldwide that greatly need effective treatments. It is well established that these diseases result from defects in the beta-globin gene, which encodes a component of adult hemoglobin. The diseases do not manifest until an individual switches from producing gamma-globin (fetal form) to the pathological beta-globin. Specific developmental transcription factors are responsible for switching from gamma-globin to beta-globin gene expression by inhibiting or enhancing interaction with the powerful Locus Control Region. We have previously shown that BCL11A represses gamma-globin expression in erythroid progenitors. KLF1 is a transcription factor that regulates BCL11A and globin gene expression. Our lab has demonstrated that when KLF1 is knocked down, BCL11A expression is reduced and the ratio of gamma- to beta-globin gene expression is increased. These findings suggest that KLF1 directly activates beta-globin gene expression while indirectly inhibiting gamma-globin gene expression via BCL11A. We have recently isolated a protein that interacts with KLF1 and activates beta-globin expression in adult definitive progenitors; we have named this protein Friend of KLF1 (FOKLF1). We hypothesize that characterization of this previously unstudied protein may lead to new strategies for the treatment of hemoglobinopathies. Interestingly, silencing of FOKLF1 expression significantly increases the ratio of human gamma- to beta-globin gene expression. Sequence analysis of FOKLF1 has shown that the protein contains an ATPase Associated with diverse cellular Activities (AAA+) domain. Mutation of a highly conserved catalytic residue in other members of this protein family decreases nucleotide hydrolysis by several orders of magnitude. We have also identified a Really Interesting New Gene (RING) finger domain that contains highly conserved residues that may serve as targets for domain inactivation by site directed mutagenesis. This study suggests that FOKLF1 may be a potential therapeutic target for the treatment of SCD and beta-thalassemia.

Luke, Elizabeth Waud (Elizabeth)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center
Advisor	Monika M. Safford, MD
Co-Authors	Marquita Lewis, MS; Susan Andreae; Christopher Gamboa, MPH
Title	Perceptions of the Effects of a Peer-Delivered Diabetes Intervention on Healthy Eating Habits of the Peer's Families

Abstract

Over the past ten years, rates of obesity and weight gain within the United States have grown rapidly. The community-based ENCOURAGE diabetes trial tested the effectiveness of a peer-delivered intervention designed to optimize diabetes self-care. The intervention was theory-driven and based on principles of empowerment. Peers were trained over two days in motivational interviewing skills and diabetes self-care basics, including healthy eating, the importance of physical activity, and stress reduction. Using these skills, they worked with 5-12 participants over 10 months to encourage better diabetes self-care. The conceptual underpinnings of the intervention suggest that peer support provided by a trained Peer to participants in the study would naturally influence the health behaviors of the Peer's own family. To explore these potential wider effects of the ENCOURAGE intervention, this study examined the reported impact of participating as an ENCOURAGE Peer on healthy eating in the Peer's own family. Semi-structured interviews were used to query each Peer about attempts made to implement healthy eating habits within their own families. This study tested in a preliminary fashion the hypothesis that participating in a peer support intervention results in attempts to improve eating habits within the Peer's family. A majority of Peers reported that being a Peer affected their family in a favorable manner, and overall reported that healthy eating habits had changed "very much" among their family members with whom they had encouraged to adopt healthy eating habits. If confirmed, these preliminary findings suggest that peer support interventions that include healthy eating may have effects that reach beyond the intended population, and suggest that these "bystander" intervention effects could be harnessed to increase the impact of peer support interventions. Further research in other Peer-intervention studies could provide additional insights on the impact of trained Peer supporters on the health of their family members.

Ma, Elizabeth Yean (Elizabeth)

Project Length Short

Prior Research Experience Yes

Funding Source NIH Medical Scientist Training Program Grant

Advisor Stephen Barnes

Co-Authors Ray Moore

Title Monomeric and Oligomeric Catechin and Epicatechin in Commercial Grapeseed Extract Dietary Supplements

Abstract

Grapes have been an integral part of our diet since the Neolithic ages, and have been used in folk medicine to treat many diseases, including cancer, cholera, and constipation. Recent investigation has led to the discovery of proanthocyanidins – oligomers (OPCs) of flavanols, (-) catechin, and (-) epicatechin – in grape seeds, a byproduct of the wine-making industry. Grape seed extracts (GSE) exhibit powerful anti-oxidant activity, and have been shown to prevent memory loss in rat models of menopause and to regulate brain proteins associated with Alzheimer’s disease.

The goal of the present study was to determine whether commercially available dietary supplements that nominally provide 100 mg of OPC’s actually contain what they proclaim.

METHODS: GSE (0.1-0.7g) were dispersed into water (100ml) by stirring for 1 hour and centrifuged to remove insoluble materials. Water extracts (10ml) were extracted twice with 2.5 volumes of ethyl acetate, which were then evaporated to dryness and reconstituted in 10ml of water. All samples were diluted 100-fold in water, with apigenin as an internal standard, and analyzed by reverse-phase-LC-electrospray ionization mass spectrometry (LC-ESI-MS) for monomeric catechin, epicatechin, and OPC’s. These were compared to samples from an enriched OPC preparation from Kikkoman.

RESULTS: Kikkoman’s Gravinol-S GSE preparation contained higher amounts of catechin and epicatechin compared to the commercial products. GNC was found to contain a higher concentration of monomers than NW, despite the fact that NW pills were almost 1.5-2 times greater in mass.

CONCLUSIONS: Commercial products often claim to have a standardized amount of OPC’s per pill, but this may not actually be the case, as shown by the variance between the products of two different companies: GNC and NW. However, further testing would be required to determine the amount of dimers, trimers, and other OPC’s contained in each pill before any accurate conclusion can be reached.

Martin, Rachel Ethridge (Rachel)

Project Length Intermediate

Prior Research Experience No

Funding Source

Advisor Marjorie Lee White, MD, MPPM, MEd

Co-Authors Shawn Gilbert, MD; Scott Doyle, MD; Amber Q. Youngblood, RN; Lynn Zinkan, RN, MPH; Nancy M. Tofil, MD, MEd

Title High-Fidelity Simulations for Orthopedic Residents: Medical Complications and Systems Challenges

Abstract

Introduction: High fidelity simulation is being used more often to train health care providers. Surgical specialties use task trainers to teach operative management but rarely do they practice medical complications. Orthopedic residents handle many medical complications during postoperative care, but this skill that is often acquired sporadically in uncontrolled environments. The simulated setting is an ideal place to practice complications in a standardized manner. Our hypothesis is that orthopedic residents will accept, enjoy and find value in high-fidelity simulation as well as feel more capable of responding to postoperative medical complications after standardized experiences.

Methods: Starting in January 2009, during their pediatric orthopedic rotation all orthopedic residents attend a 2 hour simulation session. They are presented with two cases focusing on medical complications of pediatric orthopedic care. The residents complete an assessment, diagnostic testing and access help via hospital-specific protocols. The scenarios are followed by a video-enhanced debriefing session. Following the simulation, learners complete an evaluation of the experience.

Results: To date, 27 orthopedic residents have participated in groups of 2-3 in the orthopedic simulation course. All participants found the course either extremely helpful or very helpful in improving their patient care skills. All participants felt that their participation in the simulation exercise would improve their performance when dealing with medical complications in the actual clinic setting. The resident learning themes were increased knowledge of physiology and understanding systems within the Children's Hospital.

Conclusions: We believe that this is a novel curriculum designed to educate orthopedic residents about medical complications of postoperative pediatric patients as well as orient residents to institution-specific resources. With further investigation we hope to develop ways to track these residents' performance in the clinical setting and demonstrate the transferability of simulated learning to the realm of patient care.

McAnnally, John-Ryan Griffin (John-Ryan)

Project Length Intermediate
Prior Research Experience Yes
Funding Source Departmental or Mentor funds
Advisor Henry E. Wang, MD, MS

Co-Authors

Title National Estimates of Mortality from Sepsis and Septic Shock in the Era of Early Goal-Directed Therapy

Abstract

BACKGROUND Sepsis is a time sensitive condition that carries a high mortality rate. Recent advances in treatment modalities and protocols are thought to improve mortality from sepsis and septic shock. We hypothesized that improved sepsis care would result in an observable decrease in sepsis deaths nationally. The objective of this study was to characterize recent temporal trends in sepsis mortality in the United States (US).

METHODS We conducted a time-series analysis of deaths attributable to sepsis using the Centers for Disease Control and Prevention Compressed Mortality File, a repository of all deaths in the US, each linked to an *International Classification of Disease, ninth revision* (ICD-9) code. We included all deaths of persons of any age during the years 1999-2007. We calculated age-adjusted death rates for sepsis using previously described ICD-9-based definitions. We analyzed temporal trends in sepsis deaths generally and across race and age. We tested for the presence of trends with time-series adjusted Pearson's product-moment correlation.

RESULTS National sepsis deaths decreased (48.1 per 100,000 to 39.1 per 100,000, $p < 0.000$) during the study period (1999-2007). Downward trends in sepsis deaths were observed for neonates (29 to 20.5, $p < 0.000$), age 1-14 (1.6 to 1.2, $p = 0.009$), age 15-34 (5.9 to 3.5, $p < 0.000$), age 75-84 (278 to 245, $p = 0.036$), and age > 85 (1065 to 750, $p < 0.000$). Downward trends in age-adjusted sepsis deaths were observed for American Indian (53.7 to 37.4, $p = 0.016$), Asian (32.6 to 25.6, $p < 0.000$), Black (86.3 to 67.9, $p < 0.000$), and White (43.8 to 36.6, $p = 0.002$) races. Sepsis death rates for middle-aged Americans (age 35-74) did not change significantly over the study period. No upward trends were identified for any population.

CONCLUSION Sepsis death rates are declining in the United States across all races and most ages. The elderly may gain the greatest benefit from recent sepsis management practices, while the middle-aged may derive little added benefit. These patterns of mortality provide key insight into the sepsis disease process and may inform research and management decisions in the future.

McCabe, Patrick Kai-Ming (Patrick)

Project Length	Short
Prior Research Experience	No
Funding Source	American Federation for Aging Research MSTAR Fellowship
Advisor	Dr. Patricia Goode, Dr. Rojymon Jacob, Dr. David Redden
Co-Authors	Janet Colli, Erik Busby, Tracey Wilson, Alayne Markland
Title	Bladder, Bowel, and Sexual Dysfunction Symptoms One to Five Years after Intensity-Modulated Radiation Therapy for Prostate Cancer

Abstract

Background: After conventional radiation therapy for prostate cancer, 15% of men report urinary symptoms, 10% note bowel symptoms, both of which include incontinence, urgency, and frequency, and 50% report sexual dysfunction.

Question: The study identifies the prevalence of urinary, bowel and sexual symptoms in men who have undergone intensity-modulated radiation therapy (IMRT) for prostate cancer at UAB.

Methods: 298 men who had undergone IMRT for prostate cancer between Jan. 1, 2005 and Jan. 1, 2010 were invited to participate. They were mailed an IRB-approved Questionnaire Packet which comprised a solicitation letter, consent form, and the Expanded Prostate Cancer Index Composite (EPIC-26), a validated symptom and quality of life questionnaire.

Results: Thus far, 33 men have responded, fourteen white, ten African-American, one Asian, and eight unknown. 48.5% reported urine leakage daily or weekly and 21.2% more than once daily; 27 of 30 respondents indicated the burden due to leakage was no, very small, or a small problem. 82.8% of 29 respondents cited the burden of nocturia and 80% of 30 respondents the burden of daytime urinary frequency was at most a small problem, a rating that also applied to 84.8% and 89.7% of 33 respondents regarding burden of bowel urgency and loss of stool control respectively.

63.6% of 33 men rated ability to gain an erection in the last four weeks as poor or worse. 75% had an erection less than half of the times desired. 66.7% of 30 men said ability to achieve orgasm was poor or worse. Overall, 71.9% of 32 men rated their sexual function as poor or worse.

Conclusions: Sexual dysfunction and urinary incontinence are prevalent among men treated using IMRT for prostate cancer. RT techniques should be further improved to reduce side-effects. Patients with side-effects need continued monitoring and symptom management.

McCluskey, Suzanne Michelle (Suzanne)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Sonya Heath, M.D.
Co-Authors	Katharine Bar, M.D.
Title	Challenges and missed opportunities in the diagnosis of acute HIV

Abstract

HYPOTHESIS: The incidence of HIV in the United States has remained unchanged for the past decade despite many advances in the field. We hypothesize that acute HIV is an important driver of the current epidemic, in part due to its protean manifestations, challenge of timely diagnosis, and associated high viral loads. **METHODS:** We analyzed a cohort of acute HIV patients who presented to the 1917 clinic from 1999 to 2011 for demographics, social history, symptoms, and laboratory data. From these data, we identified a subset of patients with atypical presentations of acute HIV. In addition, we determined the interval between a patient's estimated date of infection and the date of diagnosis, and the number of healthcare visits during that period. For patients not diagnosed with HIV on their first visit, an alternative diagnosis was recorded. **RESULTS:** Of 58 patients in our cohort, seven were identified as having atypical presentations of acute HIV. Forty-eight patients were symptomatic, 38 of whom sought medical care for symptoms. Only nine patients were diagnosed with acute HIV at their first healthcare visit. Most other patients were diagnosed on their second or third visit, though one patient was not diagnosed until the sixth visit. Pharyngitis, mononucleosis, and upper respiratory infection were the most common alternative diagnoses. Patients identified prior to seroconversion had significantly higher viral loads than patients identified later in the course of infection. **CONCLUSIONS:** Acute HIV may present atypically and is often missed at a patient's first presentation to the healthcare system. These missed diagnoses correspond to a high degree of infectivity supporting our hypothesis of acute HIV as a driver of the current epidemic. Despite recommendations for universal opt-out HIV screening, there is still a need for additional education to physicians in primary and acute care settings about seronegative patients and acute HIV.

McQueen, Katie Lauren McLemore (Katie)

Project Length Short
Prior Research Experience Yes
Funding Source NIH T35 Short Term Training Grant
Advisor Michelle Olsen, Ph.D.
Co-Authors

Title Expression and Regulation of Astrocytic Proteins during the Development of Rats

Abstract

Two essential functions of astrocytes throughout the central nervous system are to buffer extracellular K⁺ and glutamate following periods of neuronal activity. These functions are mediated by two astrocyte-specific proteins: the inwardly rectifying potassium channel, Kir4.1, and glutamate transporter, GLT-1. Together, these two proteins function to dampen neuronal excitability. Despite the importance of these two astrocytic proteins for normal brain function, little is known regarding their regulation. The purpose of this research is to examine the developmental expression patterns of Kir4.1 and GLT-1 in different brain regions in the rat by quantitative PCR and Western blotting. The data obtained from this study will be applied to future studies that examine the roles of the proteins in normal brain function and in pathological conditions where expression levels of both of these proteins are reduced.

Our studies focused on developmental changes in the cortex and the hippocampus. Tissue was examined from several age groups: newborns, 1-week, 2 weeks, 4-weeks, and 3 months. Western blot data reveal that Kir4.1 and GLT-1 are significantly upregulated from birth to postnatal day 28. No further increase in protein levels was observed after this time point. Quantitative PCR demonstrated a near 10-fold increase in transcript levels of Kir4.1 (*KCNJ10*) and GLT-1 (*SLCC1A2*) from birth to postnatal day 28. No significant increases occur between the 4-weeks and 3-month time point in either protein expression or transcript levels of either Kir4.1 or GLT-1.

The data indicates that the developmental up-regulation of both Kir4.1 and GLT-1 is controlled at the transcriptional level. Future studies in the laboratory are aimed at determining if epigenetic mechanisms, such as DNA methylation patterns, account for increased transcription during development. Understanding the regulation of these genes during development may elucidate common mechanisms that lead to altered transcription rates in brain injury and neurodevelopmental disorders.

Meadows, Jarrod Phillip (Jarrod)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	John Hablitz and David Sweatt
Co-Authors	
Title	Epigenetic Control of Homeostatic Plasticity

Abstract

The electrical architecture of the brain is highly complex and changing. Neural circuits must be able to maintain a precise balance between excitation and inhibition in order to maintain proper informational integrity. Neurons must also have the ability to refine synapses in an activity-dependent manner. Both of these basic properties are important in higher-order functions, such as memory storage. In addition to plasticity at individual synapses, neurons also have the ability to regulate their total synaptic inputs. A specific example of this ability is synaptic scaling, in which neurons adjust their excitatory inputs up or down in response to network activity. This phenomenon has been shown to be dependent on Ca^{2+} flux at the postsynaptic cell, altering calcium/calmodulin-dependent protein kinase IV (CaMKIV) activity. This leads to an alteration of protein synthesis, finally resulting in the insertion or removal of AMPA receptors in a multiplicative manner across all synapses. We hypothesize that the changes in CaMKIV activity lead to an increase/decrease in postsynaptic AMPA receptors via epigenetic mechanisms. We will test this hypothesis using electrophysiological and molecular techniques in dissociated cultures of pyramidal neurons. We predict that we will be able to manipulate synaptic scaling with the use of DNA methyltransferase and/or histone deacetylase inhibitors.

Merino, Aimee Marie (Aimee)

Project Length Long
Prior Research Experience Yes
Funding Source NIH Medical Scientist Training Program Grant
Advisor Richard A. Kaslow

Co-Authors

Title HLA-B Signal Peptide and Common Motifs in Heterosexual HIV-1 Acquisition

Abstract

Background: Human leukocyte antigen (HLA) molecules interact with natural killer (NK) cell receptors to mediate NK function. The *HLA-B* alleles encoding the Bw4 epitope reportedly have significant impact on HIV-1 infection. In another NK pathway, nonamer epitopes cleaved from the signal peptide of HLA-B molecules are bound to HLA-E and presented to lectin-like NKG2 receptors. However, virtually all HLA-Bw4 alleles carry threonine (Thr) at anchor position 2 (P2) of the nonamer, whereas Bw6 alleles carry either Thr or methionine (Met) at P2. That P2 residue difference influences HLA-E binding to its cognate NKG2 receptors. We examined associations of Bw4 and P2-Thr/Met with acquisition of HIV-1 infection and control of viral load (VL) in HIV-1 serodiscordant couples.

Methods: From 1995 to 2006, 566 couples were followed for at least nine months with quarterly counseling and testing. We tested associations of Bw4-P2 Thr, Bw6-P2 Thr, or Bw6-P2 Met in the presence and absence of KIR with HIV-1 acquisition by exposed seronegative partners and with VL in seropositive partners. Proportional hazards models of HIV-1 acquisition included index partner VL and genital ulcer or inflammation in either partner

Results: Acquisition of infection was accelerated in the presence of P2-Met (relative hazard, RH=1.79, $p < 0.0001$). Both Bw4 (always P2-Thr) and Bw6/P2-Thr were protective compared to P2-Met. We saw no association of P2-Met with VL. In contrast, the Bw4 epitope was associated with relatively lower VL in SC ($\beta = -0.25 \log_{10} \pm 0.11$, $p = 0.030$).

Conclusions: The association of P2-Met in the HLA-B signal peptide with accelerated HIV-1 acquisition was independent of the Bw4 epitope and may help explain protection by HLA-Bw4 observed elsewhere. Conversely Bw4, but not P2-Met, was associated with lowered VL in SC. Our results indicate that HLA-B alleles impact HIV-1 pathogenesis through diverse mechanisms.

Mgbemena, Okechukwu Nwakile (Okechukwu)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Paul Goepfert, M.D
Co-Authors	Anju Bansal, Ph.D
Title	HIV-1 cryptic epitopes induce a lower magnitude but similar functional avidity responses when compared to traditional epitopes

Abstract

Development of an effective CD8+ T cell-mediated HIV-1 vaccine has been a challenge mainly due to high genetic variability in the viral population. One strategy to combat this diversity is to broaden responses to a variety of epitopes thereby increasing the chance of recognition of the challenge virus. Cryptic epitopes (CE) are peptide sequences that arise from the Alternative Reading Frames (ARFs) of the HIV genome. For every gene, there are 5 potential ARFs: 2 in the sense and 3 in the antisense direction. We previously demonstrated that antisense CE specific responses can be detected during natural HIV infection. Herein, we compare the quality of CD8 T cells targeting cryptic epitopes (CE) to those that are specific to traditional epitopes (TE) (i.e. those encoded by functional viral proteins). We predicted forty HLA-B*5301 restricted CE (9-11mers) encoded by HIV-1 clade B proteome using the Epipred (Epitope prediction) program. The immunogenicity of these peptides was evaluated in 38 chronically HIV infected HLA-B*53 patients for CE specific T-cell responses using the interferon- γ (IFN- γ) based Enzyme-Linked Immunosorbent Spot (ELISpot) assay. The responder frequency for patients and individual peptides were 8/38 (21%) and 15/40 (38%) respectively. Five of B*5301 CE responses were further tested in an IFN- γ ELISpot assay to determine the peptide concentration that would induce 50% of the maximum response (i.e. functional avidity) and these were compared to traditional epitopes restricted by HLA-B*5301. The magnitude of responses to the selected cryptic epitopes was X compared to Y for traditional epitopes; however, the concentration of epitope needed to induce 50% of the maximum response was similar (X vs Y, respectively). Because functional avidity is a better predictor of an effective CD8 T cell response compared to magnitude, these results suggest that inducing cryptic epitopes in addition to traditional epitopes could be a useful HIV vaccine strategy.

Nichols, Joi Ashley (Joi)

Project Length	Short
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	Dr. Brian Sims
Co-Authors	Dr. Brian Sims; Cornelius Daniel; Aisha Watford
Title	Exposure of Neural Stem Cell to Bilirubin and Treatment with Theophylline

Abstract

Neonatal jaundice due to hyperbilirubinemia is a major issue in both premature and term newborns. The major consequence of hyperbilirubinemia is kernicterus, or acute bilirubin encephalopathy, due to the deposition of unconjugated bilirubin in brain tissue. The deposition of unconjugated bilirubin causes scarring which permanently damages neuronal cells. Current management in preventing bilirubin-induced neurotoxicity is phototherapy. The purpose of our research was to look at the neuroprotective effects of theophylline after induction of neurotoxicity. Prior to beginning our research, we hypothesized that increases in bilirubin concentration would cause an increase in cell death. Then subsequently, increasing the concentrations of theophylline would serve as neuroprotective agent and decrease cell death on neurotoxic stem cells. The methods included adding unconjugated bilirubin (UCB) at different concentrations to cultured cells to test UCB toxicity, followed by treatment with Theophylline. The next step involved measuring markers of apoptosis, such caspase-3 levels, with Western blot to determine the amount of cell death. Results showed that bilirubin is neurotoxic as well as supported the idea of theophylline providing neurotoxic stem cells with protection. To complete the research, future studies need to be done to determine additional concentrations of theophylline that consistently provide protection of neural stem cells, as well as perform immunohistochemistry to visualize bilirubin and Theophylline effects on cell tissue. Then, ultimately after understanding the full neuroprotective potential of theophylline, drug therapy to animals and later preterm infants may be completed.

Nwaobi, Sinifunanya Elvee (Sini)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Michelle Olsen
Co-Authors	Candace Floyd, Alex Gilbreath, Katie McQueen
Title	Alterations in astrocytic gene expression following pediatric traumatic brain injury

Abstract

Traumatic brain injury (TBI) affects over 1.7 million Americans each year, and is the leading cause of death and disability in young children in the United States. Astrocytes are the most numerous cells in the central nervous system and play a major role in both acute and long term response to injury. Two essential functions of astrocytes that are perturbed following CNS injury are: the ability to buffer extracellular K and glutamate. These functions are mediated by two astrocytic proteins, the inwardly rectifying potassium channel, Kir4.1, and the glutamate transporter, GLT-1. Astrocytes associated with injured tissue demonstrate a reduced capacity to regulate extracellular K and glutamate, suggesting a loss of functional GLT-1 and Kir4.1. In the adult spinal cord and brain, dysregulated K⁺ and glutamate homeostasis in the extracellular space leads to neuronal hyperexcitability, changes in synaptic physiology and plasticity. Furthermore, data from our lab and others demonstrate both proteins are developmentally regulated with the most significant increases in expression during early postnatal development.

Using a lateral fluid percussion injury model adapted for pediatric animals our data demonstrate reduced levels of both Kir4.1 and GLT-1 protein that correlate with astrocytic gliosis (increased GFAP expression). Preliminary studies demonstrate similar losses of protein and transcript levels using an *in vitro* injury model, suggesting transcriptional regulation. Furthermore, we show that the reduction in Kir4.1 transcripts can be rescued by DNA methylation inhibitors such as 5-aza (5-aza-2-deoxycytidine, an FDA approved cancer drug treatment). We hypothesize that DNA methylation may be a central mechanism in regulating astrocyte transcript levels and protein expression following injury. Future studies in the laboratory are aimed at elucidating if epigenetic mechanisms are responsible for altered transcription of Kir4.1 and GLT-1 following injury. This research has the potential to reveal novel therapeutic strategies for pediatric patients afflicted with traumatic CNS injury.

Parker, Walter Tyson (Walter)

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Dr. Marjorie Lee White and Dr. Nancy Tofil

Co-Authors Dawn Taylor-Peterson, Lynn Zinkan, Amber Youngblood

Title High-Fidelity Simulation as Part of Teen Trauma Prevention

Abstract

Background: The CDC reports motor vehicle collisions (MVC) as the number one cause of teen deaths in the United States. Despite a variety of current prevention efforts, teen drivers continue to have the highest rates of crashes, injuries, and fatalities of any age. The Trauma Prevention Program (TPP) at Children's of Alabama is a one-day education experience offered every other month for 10-20 adolescents "sentenced" to the program for offenses such as reckless driving, speeding and driving under the influence by a county district court judge. The program attempts to provide teens engaging in high-risk behavior with educational experiences aimed at influencing their decision-making the next time they are prone to engage in risky driving behaviors. In the past participants were brought to the trauma room and asked to imagine a trauma patient, but now the program includes the use of a SimMan (Laerdal, Wappinger Falls, NY) to perform a trauma simulation during the tour. Our hypothesis is that by adding a high fidelity simulation experience to the TPP, the dangers of reckless driving will have a higher impact on participants.

Methods: The TPP starts with participants in the trauma room as an Emergency Medical Services report initiates the simulation stating either that the patient is an unrestrained passenger travelling at high speeds or in a collision involving distracted driving. SimMan is then brought to the room with the trauma team performing all key actions including intubation, placement of a chest tube for a pneumothorax, insertion of a nasogastric tube, and urinary catheter placement. A four question, open-ended survey was completed by all participants. A qualitative data analysis of the questionnaire results was conducted using color-coding to identify different themes that emerged from responses given. 124 subjects participated from April 2009-April 2011. Average age was 17.3 +/- 0.9 years and 64% were males.

Results: When asked what driving behaviors participants would change after viewing the simulation, 40% reported they plan to drive more cautiously, with more awareness, and without distractions; 15% reported they plan to stop the use of cell phone or text messages while driving; and 21% reported they will wear seatbelts in the future. 20% of responses in one question and 16% in another commented on not wanting to put their parents or themselves through the pain and suffering of a MVC, and 33% commented on the importance of the healthcare team. When asked one thing in the simulation that made an impression, 46% reported not wanting to need the medical procedures such as urinary catheter or endotracheal tube.

Conclusions: The driving behaviors that the participants report wanting to change show understanding of important concepts that the program tries to convey such as driving without distractions, no texting while driving, and using seatbelts while driving. The reported themes of putting themselves in the situation and emphasis on the medical team and equipment may show that the participants are better able to imagine themselves in a trauma situation. Further research is needed to determine if this experience deters them from high risk driving.

Patel, Pratik Prafulchandra (Pratik)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Steven G. Lloyd
Co-Authors	Dr. Steven G. Lloyd
Title	Effects of background velocity error and breath-hold techniques on blood flow quantification using phase contrast MR imaging

Abstract

Context

Phase contrast MRI (PC-MRI) with breath-hold is often considered the “gold standard” for accurate and precise measurements of blood flow to assess intracardiac shunting and valvular regurgitation volume, but this method has several technical and patient-related factors that can lead to significant errors or problems comparing flows in different vessels.

Objective

To evaluate the influence of breath hold position on PC-MRI determined cardiac output (CO) to investigate the validity of determining valvular regurgitation volume and shunt ratios by MRI.

Design

In order to explore the breath hold position’s (and consequently, the intrathoracic pressure) impact on CO, nine normal healthy participants without evidence of cardiac disease were enrolled. ECG-gated, breath hold PC-MR images were acquired to measure flow in the ascending and the descending aorta at different intra thoracic pressures (ITP). Pressure was measured through a home-built water manometer with a U-shaped tube, with one end of the tube connected to the participant’s mouth via a mouthpiece. Participants adjusted pressure by contraction of inspiratory or expiratory effort of the diaphragm and chest wall muscles and were able to view the pressure manometer reading, in order to provide feedback on keeping pressure constant.

Main Outcome Measure

Flow/CO through the region of interest (ROI) in the aorta.

Results/Conclusions

Analysis of participant data shows no obvious correlation between ITP and CO (data to be shown in figure). There may be trends as it relates to ITP and CO for an individual; however, such trends cannot be generalized to the population.

Future Directions

Volunteer based-research is still an ongoing part of our project. We are still recruiting volunteers. Initial analysis has brought up some questions such as ITP with most reproducibility, ITP with highest CO. Hopefully, these questions will be answered as we move forward.

Patel, Shyam Arvind (Shyam)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Rizk El-Galley
Co-Authors	Timothy Stooksberry
Title	Efficiency of PSA-AV Score as a Predictor for a Positive Prostatic Biopsy when Compared to Age-Adjusted PSA and Non-adjusted PSA Methods

Abstract

Objective: The objective was to incorporate age, volume, and serum prostate specific antigen (PSA) level into one PSA-Age and Volume (PSA-AV) score in order to provide a better predictor for positive prostate biopsies.

Methods: The charts of patients who underwent a total of 1732 TRUS (Transrectal Ultrasound) biopsies were examined. Many variables were recorded such as race, age, prostate volume, and pre biopsy PSA levels. A PSA-AV score was calculated by multiplying the prostate volume with age divided by the pre biopsy PSA level. Data analyses of this score were performed and compared with two other predictors of prostate cancer. These two predictors were the PSA cutoff of 4 nI/mL and the age-adjusted PSA levels.

Results: Out of the 1732 total biopsies taken, 906 biopsies showed a positive result for prostatic adenocarcinoma. Stepwise analysis of the PSA-AV score in intervals of 400 showed an inverse relationship between PSA-AV score and prostatic adenocarcinoma detection rates. After analyzing possible PSA-AV cutoff values, a PSA-AV score of 700 showed to have the most clinical benefit in terms of sensitivity and specificity. At a PSA-AV score cutoff of 700, the sensitivity was 86.4%, and the specificity was 32.2%. Compared to the age-adjusted PSA cutoff, if one used a PSA-AV cutoff of 700, 83 additional biopsies would be taken, but 87 additional positive biopsies would be picked up. Additionally, using a PSA-AV cutoff of 700 resulted in 57 less biopsies with only 1 less positive biopsy being detect compared to using a PSA cutoff of 4.

Conclusions: Our results show that using a PSA-AV cutoff score of 700 has the most clinical benefit in terms of picking up positive biopsies or limiting unnecessary biopsies without sacrificing the other when compared to either the PSA cutoff of 4 or age-adjusted PSA methods.

Piazza, Nicholas Anthony (Nick)

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Isam-Eldin Eltoun MD

Co-Authors Bernard Gary, Heather Tinsley, PhD, William Grizzle, M.D, PhD, Gary Piazza, PhD, Isam-Eldin Eltoun, MD

Title Phosphodiesterase-5 (PDE-5) as a potential target and marker of lung cancer.

Abstract

Nonsteroidal anti-inflammatory drugs (NSAID) such as Sulindac sulfide (SS) display promising antineoplastic properties, but toxicities resulting from COX inhibition limit their clinical use. Although COX inhibition is responsible for the anti-inflammatory activity of SS, recent studies suggest that phosphodiesterase (PDE) 5 inhibition and activation of cyclic guanosine monophosphate (cGMP) signaling are closely associated with its ability to induce apoptosis of tumor cells. However, the underlying mechanisms responsible for apoptosis induction, factors that influence sensitivity of tumor cells to SS, and the importance of PDE5 for lung tumor cell growth have not been established. Here we show that SS and derivative compounds induce cell death in lung carcinoma cell lines A549 and H1299. Expression of PDE5 in these cell lines is supported by western blot study. Cells were dosed with SS and an experimental derivative (SRI28386) over 72 hours. Drug effects on cell growth and PDE activity were measured and the potency expressed as an IC₅₀ value, which is the concentration resulting in 50% inhibition when compared with the vehicle control. These findings provide evidence that SS induces apoptosis of lung tumor cells through a mechanism involving inhibition of PDE5. We conclude that PDE5 represents a novel molecular target for the discovery of safer and more efficacious drugs for lung cancer chemoprevention. To identify variable expression of PDE5 in different subcategories of lung cancer, a tissue array containing 102 core samples of varying lung carcinomas have been labeled with PDE5 and are being analyzed to identify types that may be susceptible to NSAID phosphodiesterase inhibition.

Pickens, Mekeisha Renae (MeKeisha)

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Marjorie Lee White, MD, MPPM, MEd

Co-Authors Nicole Jones, Marjorie Lee White, Nancy Tofil, Amber Youngblood, Lynn Zinkan, Mark Baker

Title Randomized trial comparing two mass casualty triage systems in simulated pediatric mass casualty incident

Abstract

Purpose of study: Several field triage systems have been developed to rapidly sort patients following a mass casualty incident (MCI). JumpSTART (Simple Triage and Rapid Transport) is a pediatric specific MCI triage system. SALT (sort, assess, lifesaving interventions, treat/transport) has been proposed as a new national standard for MCI triage for both adult and pediatric patients; however, it has not been tested in a pediatric population. We hypothesized that SALT would not be inferior to JumpSTART in triage accuracy, speed, or ease of use in a pediatric MCI. Methods: Paramedics were invited and randomly assigned to either SALT or JumpSTART study groups. Following randomization, subjects viewed a 15-minute PowerPoint lecture on either JumpSTART or SALT. Subjects were provided with a triage algorithm card for reference and were asked to assign triage categories to 10 pediatric patients in a simulated building collapse. The scenario consisted of 4 children in moulage and 6 high-fidelity medical simulation mannequins. Injuries and triage categories were based on a previously published MCI scenario. One investigator followed each subject to record time and triage assignment. All subjects completed a post-test survey and structured interview following the simulated disaster. Results: 43 total paramedics attended. 17 participants were assigned to the SALT group. Overall SALT triage accuracy was 66% +/- 15%, with an over-triage mean rate of 22% +/- 16%. SALT had a mean under-triage rate of 10% +/- 9%. 26 participants were assigned to the JumpSTART group. JumpSTART overall accuracy was 66% +/- 12%, with an over-triage mean of 23% +/- 16%. JumpSTART had a mean under-triage rate of 11.2% +/- 11%. Ease of use was not statistically different between the two systems (5 point Likert mean SALT=4.06, JumpSTART=3.88, p=0.528) Time taken to assign triage per patient was faster in the JumpSTART group (SALT = 34 sec +/- 23 sec, JumpSTART = 26 sec +/- 19sec, p<0.05). Conclusion: SALT does not appear to be inferior to JumpSTART in overall triage accuracy, over-triage or under-triage rates in a simulated pediatric MCI. Both systems were considered easy to use. However, JumpSTART was faster in time taken to assign triage designations.

Poholek, Catherine Helen (Katie)

Project Length Long
Prior Research Experience Yes
Funding Source NIH Medical Scientist Training Program Grant
Advisor Dr. Laurie E. Harrington
Co-Authors

Title The Role of Interleukin-21 in the Pathogenesis of Inflammatory Bowel Disease

Abstract

Upon encounter with antigen, CD4 T cells differentiate into subsets that each secrete a specific cocktail of cytokines and are each responsible for various aspects of the adaptive immune response. Th17 cells, while necessary for protecting the host against extracellular pathogens, have also been cast as pathogenic in the context of several autoimmune diseases, including Inflammatory Bowel Disease (IBD). Genome wide association studies (GWAS) have implicated interleukin (IL)-23 signaling, which is a key component of Th17 differentiation and expansion, as a potential candidate for the cause of IBD in humans, and many studies in murine models of colitis have shown Th17 cells to be partially responsible for inflammation and mucosal damage. Th17 cells produce several inflammatory cytokines, including IL-17, IL-21, IL-22, and IL-26. Although many of these cytokines may act in concert to induce inflammation in colitis, IL-21 is a very strong candidate for further scrutiny. IL-21 expression is increased in biopsies from patients with ulcerative colitis compared to healthy controls, and recent GWAS have shown an association between the locus containing IL-2/IL-21 and IBD. Using the CD45Rb^{hi} transfer model of colitis, we have shown that IL-21 is necessary for the full induction of disease. Our data show that the lack of disease seen in the absence of IL-21 is not due to an overall decrease in Th17 cells, nor to an increase in Foxp3⁺ T regulatory cells. These data highlight a previously unrecognized role for IL-21 in the pathogenesis of IBD.

Raines, Benjamin Todd (Benjamin)

Project Length Short
Prior Research Experience Yes
Funding Source Departmental or Mentor funds
Advisor

Co-Authors Daryl C. Osbahr, MD; E. Lyle Cain, Jr, MD; B. Todd Raines, MA, ATC; Dave Fortenbaugh, PhD; Jeffrey R. Dugas, MD; James R. Andrews, MD

Title Long Term Outcomes After Ulnar Collateral Ligament Reconstruction In Competitive Baseball Players: A Minimum Of 10 Years Follow-Up

Abstract

Purpose: To evaluate long-term baseball and post-baseball career outcomes of UCL reconstruction (UCLR) in baseball players.

Methods: 318 UCLR's were performed on competitive baseball players. Surgical data were collected prospectively, and patients were surveyed retrospectively using a questionnaire, Conway scale, and Disabilities of the Arm, Shoulder and Hand (DASH) scoring system, including work and sports modules, to determine baseball/post-baseball career outcomes ≥ 10 post surgery.

Results: 224 of 318 patients (70%) were contacted (average of 12.3 years post UCLR). Average ages at surgery and follow-up were 22 and 34.3 years, respectively. At follow-up, 93% were satisfied, with 3% reporting persistent elbow pain and 4% reporting limitations of elbow function during activities of daily living (ADL's). 92% were able to throw without elbow pain, and 98% still participated in throwing activities. 83% returned to the same or higher level of competition in <1 year (average of 3.6 years), with 86% retiring for reasons other than elbow. Many also had shoulder problems (34%) or surgery (25%) during their baseball career, typically resulting in retirement due to shoulder ($p < 0.001$). When assessing graft choice, concomitant injury procedures at time of UCLR, and post-operative transient ulnar neuropathy, there were no significant differences in return to play, competitive career longevity, and retirement etiology. Scores for DASH, work module, and sports module scoring systems were 0.68 ± 14.68 , 0.92 ± 6.40 , and 2.57 ± 11.11 , respectively. In addition, 59% worked in physically active jobs and 60% participated in baseball related activities.

Conclusion: Long-term follow-up of UCLR in baseball players indicates that most patients are satisfied, with few reports of persistent pain and limitation of elbow function during daily, work, and recreational activities. Most returned to the same or higher level of competition in <1 year, with acceptable career longevity and retirement for reasons other than elbow. Standardized disability and outcome scales indicate patients have excellent results when compared to the general population.

Reddy, Shilpa Gillella (Shilpa)

Project Length Short

Prior Research Experience No

Funding Source

Advisor John O. Mason, III

Co-Authors John O. Mason III, MD; Tracy L. Emond, MS; Dustin L. Pomerleau; Lindsey Wallace; Richard M. Feist, MD; Martin L. Thomley, MD; Michael A. Albert, Jr., MD; Benjamin W. Roberts, MD

Title Incidence of Postoperative Outer Layer Foveal Defect Following Idiopathic Macular Hole Repair

Abstract

Purpose: The incidence of outer layer foveal defect post pars plana vitrectomy and macular hole repair has been reported as high as 49%, though no significant postoperative effects on visual acuity have been noted. Our study seeks to investigate the incidence of outer layer foveal defects after macular hole surgery, and determine their effects on postoperative visual acuity.

Methods: A retrospective chart review was performed of all patients with an idiopathic macular hole who underwent pars plana vitrectomy with internal limiting membrane peeling with and without macular pucker from May 2008 to November 2010. Patients with previous vitreous surgery, comorbid retinal disease or failure of macular hole closure were excluded. Macular hole size, duration of symptoms, BCVA, and anatomical appearance on optical coherence tomography (OCT) testing were analyzed preoperatively, and at 1, 3, and 6 months postoperative intervals.

Results: Two-hundred and twenty-two eyes were screened for inclusion, and those without optical coherence tomography within 32 days of surgery were excluded. A total of 47 eyes were included, comprised of 31 females and 16 males. The mean preoperative macular hole size was 428.7 microns.

Outer foveolar defects were identified on postoperative OCT in 15 of 47 patients (31.9%). Preoperative hole diameter in the with defect group was 476.3 um, while that of the without-defect group was 428.7 um. The difference in average preoperative hole diameter between the two groups was not significant ($p = 0.39$).

Pre-operative, 1-month, 3-month and 6-month visual acuities for the with-defect group were 0.841, 0.493, 0.466 and 0.416, respectively. Those for the without-defect group were 0.793, 0.596, 0.474 and 0.313, respectively. Differences in visual acuity preoperatively ($p = 0.54$), at 1 month ($p = 0.28$), 3 months ($p = 0.94$) and 6 months ($p = 0.22$) were insignificant.

Conclusion: Outer layer foveal defects are a significant issue following macular hole surgery; however, there is no difference in visual acuity at any timepoint postoperatively between patients with foveal defects and those without foveal defects. Therefore, we do not find it beneficial to perform sequential postoperative OCTs after macular hole repair.

*IRB-approved for human research.

*None of the authors have any financial interests associated with this study.

Reid, Daniel Keith (Daniel)

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Dr Shawn Gilbert

Co-Authors

Title Development of novel HIF activating compounds for musculoskeletal application

Abstract

Hypoxia-inducible factor (HIF) is a master regulator of the cellular and tissue response to low oxygen and nutrient availability and is needed for normal skeletal development. HIF affects gene programs that influence angiogenesis and cellular metabolism. Using a High-throughput screening technique, new compounds have been discovered that activate HIF. We hypothesize that the lead compounds will activate HIF and increase vascularity to a greater degree than desferrioxamine (DFO) based on *in vitro* results.

In this study, the effect on Human Umbilical Vein Endothelial Cells by two lead compounds (ML228 and HA-1) was evaluated in three *in vitro* assays: cell proliferation, migration, and tubule formation assay.

Cell proliferation was decreased in the compounds when compared to the negative control phosphate buffered saline (PBS). The cell migration assay was indeterminate due to significant migration of the negative control PBS. Tubule formation was not strongly induced. The negative control used was PBS and the positive control used was Vascular Endothelial Growth Factor (VEGF). The tubule formation for both of these controls was approximately equal to each other, thus making the results of the lead compounds indeterminate.

The negative control for these assays showed a higher response than anticipated. This made the results indeterminate as they could not be properly compared to the negative and positive controls. These experiments need to be repeated to evaluate any flaws in the design or technical errors that might have occurred during the first trial.

Reish, Nicholas Joseph (Nicholas)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Alecia Gross
Co-Authors	Alecia Gross, Gwendalyn King
Title	Uncovering Klotho in the Retina

Abstract

Klotho is a recently described protein with glycosidase activity that exists in both transmembrane and secreted forms. Mice that are severely hypomorphic for klotho exhibit a phenotype that resembles accelerated aging. These mice have pathologies in multiple organ systems and do not live to be more than four months of age. The protein itself is only expressed in select tissues including kidney and brain. The retina of klotho mice had never been previously examined for disease phenotypes or expression of klotho. Here, we describe a novel retinal phenotype in the klotho mouse. Retina function was measured at 6 weeks of age by electroretinography (ERG) in klotho mice and wild-type littermate controls. Klotho mice were found to have a severely decreased b-wave amplitude in both dark- and light- adapted states. Morphological examination of the retina revealed no apparent pathology or degeneration. In light of these findings, we sought to determine if klotho was expressed in the retina. Total RNA was extracted from wild-type retina and reverse-transcription PCR performed for the klotho gene as previously published. Klotho was detected at the transcript level from retinal RNA. No product appeared with RNA extracted from mutant retina. In-situ hybridization of wild-type retina also showed expression in the retina. Expression of the protein was assayed by western blot and immunohistochemistry. Taken together, these results characterize a previously unknown role for klotho in normal retinal function.

Richardson, Brittany Shea (Brittany)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center
Advisor	Andrea Cherrington
Co-Authors	Amanda Willig, April Agne, Andrea Cherrington
Title	Diabetes Connect: African American Patients' Perceptions of the Community Health Worker Model for Diabetes Care

Abstract

Background: African Americans with diabetes tend to experience higher mortality rates, poor glycemic control, and other diabetes related complications compared to European Americans. Community health worker (CHW) interventions are increasingly employed to improve diabetes outcomes and reduce health disparities. However, few studies have explored the perspectives of African Americans concerning peer-delivered diabetes education. The purpose of this qualitative study is to investigate possible benefits as well as risks of community health worker-delivered peer support for diabetes from the perspectives of African-Americans living with type 2 diabetes in the Deep South.

Methods: Four ninety-minute focus groups were guided by a trained moderator with a written guide to facilitate discussion on the topic of community health workers (CHWs) and diabetes management. Participants were recruited from the diabetes education database at Cooper Green Mercy Hospital in Birmingham, AL. Two independent reviewers performed content analysis to identify major themes using an iterative, combined deductive and inductive approach.

Results: There were 25 female participants. Mean years with diabetes was 11.2 (range 0 to 42 years). Participants were knowledgeable about methods for self-management and cited transportation and stress as major barriers. As preferred CHW roles participants included liaison to the healthcare system and easily accessible information source. Participants preferred that the CHW be knowledgeable and have personal experience managing their own diabetes or assisting a diabetic family member. Negative perceptions of the CHW-model were possible breaches of confidentiality and privacy. Participants also had concerns about unsolicited medical advice and frequency of contact. The need for emotional support and partnership from a peer educator was also expressed.

Conclusion: The self-management strategies and barriers to management identified by participants were reflected in their preferred CHW roles and traits. These results suggest that African American women with diabetes in Alabama would support peer-led diabetes education that is community-based and socially and emotionally supportive.

Saag, Harry Switow (Harry)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	
Advisor	Dr. Benjamin B Taylor
Co-Authors	Lee Hammonds, MHA, MBA
Title	Impact of Healthcare Reform on UAB Hospital

Abstract

This project aims to project how UAB Hospital will be affected by the changes proposed in the recently passed comprehensive health care reform act, the Patient Protection and Affordable Care Act (PPACA). Among other things, this bill drastically changes Medicaid eligibility criteria, Disproportionate Share Hospital (DSH) funding, and the private insurance market with the creation of health care exchanges. Our project looked at various hospital service lines' current revenue and projected how these anticipated changes would affect these particular service lines' bottom line. Our method to accomplish this was to analyze a current service lines' payor mix and Diagnostic Related Groups (DRG's) and apply a sophisticated model to predict how the new changes proposed in the PPACA would shift these parameters. The conclusion is that the most important determinant to how a particular service line will be impacted by these proposed changes is dependent on how many patients move from private insurance into the newly created health care exchanges. Although there is still some ambiguity surrounding these exchanges, it is widely believed that their re-imburement rates will more closely resemble Medicare rates rather than private rates. Thus, the shift in patients from a private payor source to a health exchange payor source will have significant negative impact on that service lines' bottom line despite the uptick in Medicaid coverage for the currently uninsured. Although based on UAB Hospital's experience, these results are likely applicable to other tertiary care academic centers. The modeling and conclusions derived in this project will aid hospitals as they make optimal strategic management decisions regarding the future of health care.

Sahinoglu, Efe (Efe)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center
Advisor	Suzanne Oparil
Co-Authors	Efe Sahinoglu, Dongqi Xing, Yiu-Fai Chen, Suzanne Oparil
Title	Anti-inflammatory effect of O-GlcNAcylated NF- κ B p65

Abstract

It has been shown that acutely augmenting O-linked-N-acetylglucosamine (O-GlcNAc) protein modification with glucosamine (GlcN) or O-(2-acetamido-2-deoxy-D-glucopyranosylidene) amino-N-phenylcarbamate (PUGNAc) attenuates inflammatory responses and neointima formation following endoluminal injury of the rat carotid artery. We hypothesized that GlcN or PUGNAc treatment protects rat aortic smooth muscle cells (RASMCs) against inflammatory stress induced by tumor necrosis factor (TNF)- α by inhibiting TNF- α -induced NF κ B signaling activation. To determine the effect of GlcN and PUGNAc on TNF- α -induced NF κ B signaling pathway, the RASMCs were pretreated with GlcN (5 mM), PUGNAc (10⁻⁴ M), or control, and then were stimulated with TNF- α (10 ng/ml). NF κ B DNA binding activity was measured by TransAM ELISA, NF κ B phosphorylated (p-) and total p65 were measured by Western Blot. O-GlcNAcylated p65 and binding of p65 to I κ B α were measured by co-immunoprecipitation. Inflammatory cytokine mRNA expression was assessed by real-time RT-PCR. Both treatments increased O-GlcNAcylated NF κ B p65 and inhibited TNF- α -induced expression of chemokines and adhesion molecules. GlcN and PUGNAc treatments inhibited TNF- α induced phosphorylation of NF κ B p65, NF κ B DNA binding activity and promoted the binding of I κ B α and NF κ B p65. In conclusion, increased protein O-GlcNAc modification inhibited TNF- α -induced expression of inflammatory mediators in RASMCs through inhibition of NF κ B signaling. Ongoing studies are directed toward identifying the specific protein targets for O-GlcNAcylation in the NF κ B pathway.

Salisbury, Charles Drew (Charles)**Project Length** Short**Prior Research Experience** No**Funding Source****Advisor****Co-Authors** Steve Charles, Jorge Calzada, John Randolph, Aneesh Nikhra, Nathan Littlejohn**Title** Arcuate Retinotomy for the Repair of Large Macular Holes**Abstract**

This retrospective case series describes a novel technique that involves the creation of an arcuate retinotomy in the repair of large macular holes after failed primary repair. Six eyes (six patients) with large macular holes, all of which had failed primary macular hole repair, underwent 25 gauge pars plana vitrectomy coupled with full thickness arcuate retinotomy temporal to the macular hole and fluid-gas exchange. The main outcome measure was anatomic macular hole closure based on optical coherence tomography (OCT), with visual acuity and visual field evaluation as secondary outcome measures. Five of the six patients (83%) had successful hole closure with three of the six patients (50%) exhibiting improvement in visual acuity. Arcuate retinotomy is a new approach that may aide in the repair of large macular holes not otherwise amenable to closure with traditional techniques.

Schmit, Erinn Ojard (Erinn)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	
Advisor	Drs. Marjorie Lee White and Nancy Tofil
Co-Authors	Drs. Philip Tatum, Marjorie Lee White, and Nancy Tofil
Title	Neonatal Intubations Among Pediatric Providers

Abstract

Introduction: Neonatal intubation is a mandatory competency requirement for pediatric training programs. With the current climate of decreased work hours, some question whether residents are able to become competent at this skill. Our goal was to assess the success rates and characteristics of neonatal intubations performed.

Methods: This is a prospective observational study of pediatric intubations at two level three neonatal intensive care units, located at Children's of Alabama and UAB Women and Infants Center, in Birmingham, Alabama. Data was collected at intubation events. Providers included pediatric residents, fellows, physician assistants, nurse practitioners, and attending physicians, all of whom have completed Neonatal Resuscitation Program training.

Results: Data is available for a total of 43 intubations. The most common indications for intubation were impending respiratory failure (36%) and elective intubation (20%). Common reasons for failure to intubate were desaturation (30%), bradycardia (20%), and inability to visualize (20%). The number of attempts required was 1 (35%), 2 (23%), 3 (21%), 4 (14%), and >4 (7%). First attempt success rates varied by level of training: ranging from 12.5% by residents to 80% by attending physicians. Residency year did not correlate with increased success. Mean duration of intubation for residents was 63 seconds, fellows was 27 seconds, and attendings was 38 seconds. The mean duration for successful vs. failed attempts varied for residents (50 vs. 68.5 seconds) but was similar among fellows (26 vs. 29 seconds) and attendings (38.5 vs. 37.5 seconds).

Conclusions: Our data supports reduced proficiency at neonatal intubations among pediatric residents. A need for additional training to improve neonatal intubation competency exists.

Schmitt, Jessica Ann (Jessica)

Project Length	Short
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Andrey Frolov
Co-Authors	Alevtina Mikhaylina, Michael Ludwig, Chris Klug, J. Pablo Arnoletti
Title	An Analysis of EGFR and ErbB3 Pathways in K-ras Knock-in, p53 Knock-out Murine Model of Pancreatic Ductal Adenocarcinoma

Abstract

EGFR and ErbB3 pathways are involved in pancreatic ductal adenocarcinoma (PDAC) progression. Novel chemotherapy agents targeting these pathways are studied in murine xenograft models using human tumor cells. Xenograft models, however, have limited utilization in studying PDAC initiation. Genetically engineered *K-ras* knock-in, p53 knock-out (KPC) mice have mutations common in a subset of PDAC. They spontaneously develop tumors, providing a convenient model for studying PDAC initiation. The goal was to determine whether the KPC model could be used to study EGFR and ErbB3 pathways using human chemotherapeutics. The secondary goal was to determine the homology between KPC mouse and human EGFR and ErbB3 signaling in PDAC. Finally, we studied effects of EGFR, ErbB3, and pan-EGFR family inhibitors (erlotinib, MM-121, and PF-299) on KPC cells. Following treatment with erlotinib, MM-121, or PF-299, and subsequent stimulation, KPC cells were tested for proteins in EGFR and ErbB3 pathways. Growth assay examined the effects of single versus daily drug dosing on KPC cell proliferation. All drugs tested inhibited KPC cell proliferation. The effect of a single dose of MM-121 was transient; after 72 hours, there was no difference between proliferation of controls and MM-121-treated cells ($p=0.20$). A single dose of erlotinib and PF-299 was effective in inhibiting proliferation for 72 hours ($p<0.001$). Daily drug dosing was more effective than a single dose. Similar to human PDAC, KPC cells constitutively express EGFR and ErbB3. Erlotinib, MM-121, and PF-299 inhibited these pathways in KPC cells, reducing phosphorylation of EGFR, ErbB3, and AKT. Erlotinib and PF-299 also reduced phosphorylation of ERK1/2. Agents developed for humans inhibited EGFR and ErbB3 pathways and proliferation of KPC cell line *in vitro*, suggesting enough homology between human and KPC mouse EGFR family to support use of this model in studying roles of EGFR and ErbB3 pathways in initiation of PDAC.

Sellers, Thomas Rutherford (Thomas)**Project Length** Short**Prior Research Experience** Yes**Funding Source****Advisor** Dr. Joseph G. Khoury**Co-Authors** Brad Culotta, M.D., Shawn Gilbert, M.D., Jeffrey Sawyer, M.D., Thomas Sellers, B.S.**Title** Weight Gain Following the Surgical Treatment of Blount Disease**Abstract**

Background: The association between obesity and Blount Disease is well documented. Surgical treatment for this disease is aimed at correcting the deformity to restore function, alleviate pain, and enable return to physical activity. An effective treatment is osteotomy followed by gradual correction with a circular external fixator. This requires a non-weight-bearing period that may exacerbate the patient's weight problem. Prior outcome analyses for Blount patients undergoing surgical correction have examined radiographic and clinical parameters. In this study we assessed weight change over the treatment period, as it impacts restoration of normal development, safety, bone health, and self-esteem.

Methods: Retrospective analysis was performed on 39 patients undergoing surgical osteotomy with external fixation for the treatment of Blount Disease. Patient medical records were analyzed and body weight was recorded at time of operation, at fixator removal with return to weight-bearing, and 1 year post operation (when available). Identical analysis was performed on a control group consisting of 12 patients suffering trauma fractures of the distal femur, proximal tibia, or tibial shaft who were treated with external fixation.

Results: Blount patients were significantly heavier than controls ($p < .0001$) at the time of surgery. The majority of patients in both the study and control groups gained weight during the non-weight-bearing treatment period, with Blount and control patients sustaining an average weight gain of 3.9 and 2.9 kilograms, respectively. Average length of the non-weight-bearing period was similar for both groups. For Blount patients with follow-up weights available at 1 year post-operation, average weight gain following surgery was 11.75 kg.

Conclusions: The majority of Blount patients gained weight during the post-surgical period, and it was greater than would be predicted for normal growth and development. This suggests that adolescents undergoing correction for Blount deformity are at significant risk for further weight gain, which bears numerous health consequences.

Sewell, Keri Deanna Lawrence (Keri)**Project Length** Short**Prior Research Experience** Yes**Funding Source****Advisor** Monika Safford**Co-Authors** Susan Andreae, Elizabeth Luke, Monika Safford**Title** Perceptions and barriers to usage of generic medications in a rural African-American Population**Abstract**

Generic medications usage in chronic diseases has many benefits, such as similar efficacy for lower price, leading to increased adherence. However, there is significant generic medicine underuse in African American communities, as well as communities with low socioeconomic status and low health literacy. These communities have lower trust of generics, particularly for chronic or serious diseases, as well as increased reluctance to switch from brand to generic. To gain further qualitative insight into causes of low usage of generic medications, focus groups were conducted in Alabama's underserved and low income Black Belt area. Inclusion criteria included age over 18, residence in Alabama's Black Belt, African American race, and currently taking a daily medication for chronic disease. 30 community members participated in 4 focus groups. Afterwards, two authors independently coded themes, then reached a consensus on themes before coding together. The participants were primarily middle aged women, with half having a highschool education or less. Most were not employed, and almost one third had no health insurance. Themes included perceived differences in efficacy and side effects of generic vs. brand medications; the perception that generics were not "real" medicines; willingness to take generics for minor but not serious illnesses; the role of trust in the doctor and health system; and the perception that while generics cost less, people of limited means had to "settle" for less. It appears that these barriers include both misinformation about the safety and efficacy of generic medications, as well as deeper feelings of mistrust and abuse by the medical system. While education about generics can help rectify some incorrect facts, other views, such as mistrust and the sense of "settling" for generics, may be more challenging to overcome. Policy makers and physicians should consider these perspectives when working to increase generic drug usage in these populations.

Shafferman, Ashley Corinne (Ashley)**Project Length** Short**Prior Research Experience** No**Funding Source****Advisor** Dr. Amit Gaggar**Co-Authors** Dr. Amit Gaggar, Dr. Xin Xu**Title** Prolyl endopeptidase expression in human airway epithelial cells and its regulation by LPS**Abstract**

Severe and persistent neutrophil-dominated endobronchial inflammation and chronic bacterial infection are characteristic hallmarks of cystic fibrosis (CF) lung disease. Understanding the mechanisms underlying ongoing inflammation is a key to better therapies for CF. Prolyl endopeptidase (PE), a serine protease that cleaves after proline residues in oligopeptides, is expressed in lung tissue. We have recently demonstrated that PE, in concert with matrix metalloproteases (MMPs) such as MMP-8 or 9, can generate PGP (proline-glycine-proline), a novel neutrophil chemoattractant from collagen. An increasing role for PGP as a mediator of neutrophil inflammation in CF has been strongly suggested. Whether CFTR dysfunction results directly in an increased predisposition towards dysregulated inflammation via this proteolytic pathway in CF airways remains to be established. In this project, we hypothesize that, as a result of the inflammatory stimulus lipopolysaccharide (LPS) which acts through Toll-like receptor (TLR)-4, there is increased endogenous production of PE from epithelial cells which enhance the generation of PGP, resulting in a feed-forward cycle of inflammation. This increased PE production and release may be modulated by the presence or absence of wild type (WT) CFTR. Improving our understanding of the pro-inflammatory role for PE raises the possibility of understanding a self-sustaining pathway of neutrophilic inflammation and may provide biomarkers and therapeutic targets for diseases such as CF.

Shafferman, Ashley Corinne (Ashley)**Project Length** Short**Prior Research Experience** No**Funding Source****Advisor** Dr. Amit Gaggar**Co-Authors** Dr. Amit Gaggar, Dr. Xin Xu**Title** Prolyl endopeptidase expression in human airway epithelial cells and its regulation by LPS**Abstract**

Prolyl endopeptidase (PE) in combination with matrix metalloproteases 9 or 8 (MMP-9/8) cleaves collagen to generate neutrophil chemoattractant peptide proline-glycine-proline or acetylated proline-glycine-proline (PGP/Ac-PGP), which is a novel biomarker for airway chronic inflammation diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). It has been demonstrated that PE is expressed in human lung and neutrophils, and PE levels are increased in the sputum of CF and COPD patients. Additionally, it has been shown that toll-like receptor (TLR)-4 is expressed on airway epithelial cells. In this project, we hypothesize that the inflammatory stimulus lipopolysaccharide (LPS), which acts through TLR-4, enhances PE expression in cystic fibrosis transmembrane conductance regulation (CFTR) mutated epithelial cells compared to wild type epithelial cells. An increased expression of PE, would thus, increase the production of PGP/Ac-PGP, contributing to the destructive cycle of inflammation. To investigate this hypothesis, we measured PE mRNA expression and PE protein expression following stimulations with LPS. In conclusion, it was found that LPS stimulation resulted in up-regulation of PE expression in airway epithelial cells. The results of this project warrant future research is to investigate PE expression on primary epithelial cells involving air-liquid interface growth conditions. Furthermore, the investigation of PGP and Ac-PGP generation from the incubation of collagen with airway epithelial cells and the effect of CF sputum from CF patients with *Pseudomonas aeruginosa* infection on PE expression would be vital information to improve our understanding of the pro-inflammatory role of PE in lung diseases such as CF.

Shafferman, Ashley Corinne (Ashley)**Project Length** Short**Prior Research Experience** No**Funding Source****Advisor** Dr. Amit Gaggar**Co-Authors** Dr. Amit Gaggar, Dr. Xin Xu**Title** PROLYL ENDOPEPTIDASE EXPRESSION IN HUMAN AIRWAY EPITHELIAL CELLS AND ITS REGULATION BY LPS**Abstract**

Prolyl endopeptidase (PE) in combination with matrix metalloproteases 9 or 8 (MMP-9/8) cleaves collagen to generate neutrophil chemoattractant peptide proline-glycine-proline (PGP), which is a novel biomarker for airway chronic inflammation diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). It has been demonstrated that PE is expressed in human lung and PE levels are increased in the sputum of CF and COPD patients. Additionally, it has been shown that toll-like receptor (TLR)-4 is expressed on airway epithelial cells. This study aims to determine the PE expression in airway epithelial cells and investigate the role of TLR-4 signal pathway on PE expression. Protein and mRNA were extracted from primary human bronchial epithelial cells and human bronchial epithelial cells (Calu-3, CFBE41o⁻, 16HBE14o⁻) in the absence or presence of LPS. PE mRNA, protein levels and activity were determined using real-time polymerase chain reaction (RT-PCR), Western blot and PE activity assays. In primary human bronchial epithelial cells, PE expression in mRNA and protein were confirmed by RT-PCR and immunoblot. PE activity was detected in both apical and basolateral medium. In human epithelial cells, PE mRNA and protein are expressed in different levels. Calu-3 showed higher expression than CFBE 41o⁻ and 16HBE14o⁻. When the CFBE 41o⁻ cells were treated with LPS, PE mRNA expression increased by 2-fold at 24 h in the LPS group compared with controls. However, PE activities in the culture medium were not markedly altered by LPS treatment compared with controls. In conclusion, PE expresses in human airway epithelial cells and increases by TLR-4 activation, suggesting that epithelial cell-derived PE might contribute to pulmonary inflammation and lung matrix degradation in airway neutrophilic disease and deserves further investigation as a potential therapeutic target.

Singer, Jeffrey Robert (Jeff)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Casey T. Weaver
Co-Authors	Karen M. Janowski, Mathew T. Palmer
Title	The HAT-BAC Mouse Model: A New Tool in Functional Genomics

Abstract

While only 2% of the human genome codes for protein, genetic studies over the last century have focused almost exclusively on these regions. What was once termed “junk” DNA is now known to play an essential role in gene regulation. However, uncovering the complex network of *trans*-regulatory protein interactions with *cis*-regulatory DNA elements remains challenging — regulatory regions may be kilobases away from the coding region itself. The lack of tools available for characterizing these distal non-coding elements remains a major technical hurdle in the field of genomics.

Here, we describe a novel mouse model to study distal non-coding *cis*-regulatory elements in human genes. Using recombineering and homologous recombination, we engineered a universal docking site into the hypoxanthine phosphoribosyltransferase-1 locus of a C57BL/6 mouse embryonic stem (ES) cell. Using the phage Phi-C31 integrase, this docking site accepts a bacterial artificial chromosome (BAC) 100s of kilobases long. Following BAC integration, ES cells are selected using hypoxanthine-aminopterin-thymidine (HAT) medium and injected into blastocysts to generate chimeric mice. Thus, the HAT-BAC mouse allows an entire gene and distal regulatory region to be inserted in a single copy manner to a known location.

Interferon gamma (*IFNG*) is an ideal gene for study using the HAT-BAC model. Interferon gamma is an important cytokine in both innate and adaptive immunity. While the protein is small, the *IFNG* locus spans 63kb upstream and 119kb downstream in humans. At these boundaries exist CCCTC-binding factor transcription factor (CTCF) binding sites that act as transcriptional insulator elements. Recently, a third CTCF site has been proposed in the first intron of the gene. Murine studies suggest its importance, but no role in humans has been described. We have engineered a BAC transgene for targeting into the HAT-BAC system to determine the functional role of the middle CTCF binding site in human *IFNG*.

Smith, Alexander Thomas (Alex)

Project Length Short
Prior Research Experience Yes
Funding Source NIH T35 Short Term Training Grant
Advisor Steven Rowe, MD
Co-Authors

Title Relationship between the Viscoelastic Properties of Cystic Fibrosis and Chronic Obstructive Pulmonary Disease Airway Mucus

Abstract

Small airway mucus obstruction is characteristic of smoking related lung disease and is associated with accelerated loss of lung function and mortality. Although the cause of mucus occlusion is not fully understood, increased mucus production and elevated viscoelasticity lead to airway infection, inflammation and progressive airflow limitation, resembling the pathologic events associated with cystic fibrosis transmembrane receptor (CFTR) defects in cystic fibrosis (CF). New drugs developed to rescue CFTR function in CF may have implications in patients with COPD. We hypothesize that acquired CFTR dysfunction in COPD results in highly viscoelastic mucus that exhibits reduced clearance due to disruptions in mucus biogenesis stemming from defects in CFTR. In this study we examined the relationship between CFTR phenotype and the macro- and micro-rheologic features of mucus from patients with smoking related lung disease using a controlled stress rheometer and nanoparticle tracking microrheology (PTM), thereby establishing a mechanistic link between CFTR dysfunction and the physical properties of mucus in COPD patients. Induced sputum was collected from human subjects using inhaled 3% hypertonic saline. Spontaneously expectorated sputum was collected from CF patients. Macrorheology data confirmed a more than nine-fold increase in viscosity in CF sputum vs. healthy controls (n=12, P<0.005). CF patients administered the CFTR potentiator VX-770 exhibited reduced mucus viscosity compared to CF controls. Similar viscoelastic measurements were obtained when comparing macro- (Plate Rheometer) to micro- (PTM) rheologic techniques. Smokers, with and without COPD, displayed sputum with higher viscoelastic properties than normal controls. We observed increased viscosity and elasticity by both conventional rheometry and PTM, and that COPD mucus exhibits reduced pore size. Further research in this area could indicate an innate defect in mucin biogenesis. These preliminary data indicate there are similar properties in the mucus of CF and COPD and suggest that CFTR potentiating drugs may be appropriate therapies for patients with smoking related lung diseases.

Stephens, Lauren A (Lauren)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Cynthia J. Brown
Co-Authors	Cynthia J. Brown
Title	Validation of the Acute Care Mobility Assessment in Older Adults

Abstract

Validation of the Acute Care Mobility Assessment in Older Adults

Lauren Stephens, MS-3: UAB School of Medicine

Cynthia J. Brown, MD, MSPH: Birmingham/Atlanta VA GRECC, Division of Gerontology, Geriatrics, and Palliative Care

Background: While bed rest has been challenged as a therapeutic intervention in recent years, it remains a common practice during hospitalization. A significant barrier to identification and intervention for those patients at risk of bed rest and low mobility has been the lack of a simple bedside tool.

Objective: To validate a bedside assessment tool, the Acute Care Mobility Assessment (ACMA) questionnaire.

Methods: Potential patient participants were ≥ 65 years, admitted to UAB Highlands Acute Care for Elders (ACE) Unit for an acute medical condition. Participants completed a functional assessment including the UAB Life-Space Assessment, and the Geriatric Depression Scale. The wireless monitors were applied to the thigh and ankle on the same leg and were left in place for 24 hours. Following removal of the monitors, patients and their primary nurses were asked to separately complete the ACMA questionnaire to assess the patient's mobility level over the previous 24 hours. ACMA scores are currently being correlated with data from the previously validated wireless mobility monitors.

Results: 9 patients (mean age 78.6 years, 55.6%% male, 66.7% white and 33.3% black) consented to the study with 8 completing all assessments. Participants had a mean gait speed of 0.5 m/s, and 3 (33%) were depressed based on their GDS score. Comparing nurses and patients responses to the ACMA, patients were 44.4% more likely to rate themselves as having achieved more out of bed mobility than the nurses, and 77.7% rated themselves as having greater than or equal to the nurse-reported ACMA scores. Correlation with the wireless monitor data is ongoing.

Conclusions: Development of a validated tool that could be used to assess level of mobility among hospitalized older adults could be very beneficial in identifying patients at risk of low mobility and associated adverse outcomes.

Stone, Sara Lynn (Sara)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Paul Goepfert
Co-Authors	Steffanie Sabbaj, Jennifer Jones, Olaf Kutsch
Title	HIV modulation of HLA-E surface expression on CD4 T cells

Abstract

HIV is well known for its ability to evade immune control. One immunoevasive mechanism HIV employs is modulation of surface expression of MHC molecules on infected cells. Downregulation of MHC class I molecules by HIV has been shown to decrease antigen-dependent killing of HIV-infected CD4 T cells by CD8 T cells. However, reduced MHC-I expression stimulates natural killer cell (NK) mediated cytotoxicity. NKs measure MHC-I expression levels in part through interaction with HLA-E. HLA-E presents MHC-I leader sequences, which are cleaved during normal processing. It has been demonstrated that HIV increases surface expression of HLA-E and that this reduces NK-mediated cytotoxicity. However, no mechanism has been shown. We hypothesized that the HIV protein Nef, which is necessary for progression to AIDS and is responsible for modulation of MHC-I, CD4, MAPK, Src tyrosine kinases, and other molecules within the infected cell, also modulates HLA-E. To test our hypothesis we infected phytohemagglutinin-activated human peripheral blood mononuclear cells with Nef-deficient or Nef-competent HIV and subsequently analyzed the infected CD4 T cells by flow cytometry. HLA-E levels correlated with markers of activation in both uninfected and HIV-infected CD4 T cells, but were significantly higher in HIV-infected cells. Further analysis revealed that HLA-E increased dramatically following integration of viral DNA into the host genome, but was only marginally increased pre-integration. No difference in HLA-E levels was found between CD4 T cells infected with Nef-deficient and Nef-competent HIV, suggesting Nef is not responsible for HLA-E modulation. Unlike other HLAs, which demonstrate remarkable allelic variation, only two HLA-E alleles exist, which differ by just one amino acid. Our preliminary studies show HLA-E changes following HIV infection are dependent on HLA-E genotype, which corroborates previous work demonstrating differential rates of HIV acquisition based on HLA-E genotype.

Stooksberry, Timothy Noah (Tim)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Rizk El-Galley
Co-Authors	Shyam Patel, Rana Festok
Title	The Risk of Prostate Cancer in Patients with Zigzag PSA Patterns

Abstract**Purpose**

Elevated and rising serum prostate-specific antigen (PSA) levels are indicators of prostate cancer. Very little research indicates how we should look at zigzagging PSA levels. The purpose of this study was to compare PSA progression patterns to determine prostatic adenocarcinoma risk of each pattern.

Materials and Methods

Of 1876 trans-rectal ultrasound guided biopsies (TRUSB) performed between 1994-2011, 681 met the inclusion criteria by being preceded by at least 3 PSA screenings, at least 3 months apart, over 2 years prior to the patient's biopsy. Indications for TRUSB included elevated and/or rising PSA, abnormal digital rectal exam, and previously abnormal biopsy. This database was stratified into rising, stable, falling and zigzag PSA patterns using a percentage change model with a cutoff percentage of 20%.

Results

Of the 681 biopsies, 350 (51.4%) were positive for prostatic adenocarcinoma. The highest positive biopsy rate was rising PSA (55.6%), followed by stable (47.6%), zigzag (40.4%), and falling (29.6%). The only statistically relevant indicator within the zigzag pattern was pre-biopsy PSA, which showed a 16.4% higher positive biopsy rate if elevated. There was no difference between consistently elevated PSA patterns and patterns including normal readings or between an overall rising and falling pattern.

Conclusions

Zigzag PSA patterns show an elevated risk of prostate cancer regardless of normal PSA values or rising or falling trend. This risk is 40.4% at the 20% level. This information should be discussed with patients and should be considered when making decisions on whether to perform a prostate biopsy.

Thomas, Evan Marshall (Evan)

Project Length	Short
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	John Fiveash
Co-Authors	John Jarboe; Christopher Willey, MD/PHD; John Fiveash, MD
Title	Dose Rate Effect On Apoptotic Activity In Irradiated Glioma Cell Lines

Abstract

PURPOSE: The availability of flattening filter free (FFF) mode in recently installed modern linear accelerators has allowed increased utilization of significantly higher dose rates in clinical treatment regimens, especially those delivered stereotactically. This has led to a revitalized investigation into the relevance of the radiobiological consequences of varying the rate of delivery of a given therapeutic dose. A comprehensive 2010 review of the subject by Ling et al. revisited many of the mitigating factors implicated in possible dose-rate effects, and underscored the possible influence of dose rate in hypo-fractionated treatments. In this study, we chose to perform an in-vitro assay of the effect of varying the dose rate between the lowest and highest dose rates available to our clinical linear accelerator on two different glioma cell lines at separate doses of 15 and 30 Gy.

METHODS AND MATERIALS: We chose the more radiosensitive U251 and more radioresistant U87 glioma cell lines. For both cell lines, populations of 105 cells were plated and each given no treatment, 15 Gy at 400 MU/min, 15 Gy at 2400 MU/min, 30 Gy at 400 MU/min, or 30 Gy at 2400 MU/min. Irradiation was performed on a TrueBeam STx linear accelerator at a beam energy of 10MV in flattening filter free mode. Dose falloff was a maximum of 5% at the cell plate periphery. Apoptotic activity was assessed after an 18 hour incubation using a TACS Annexin V-FITC assay that detects both early and late state apoptosis.

RESULTS: For the U87 line, mean apoptotic activity in all irradiated groups was greater than in control ($p < 0.01$). At 15 Gy, apoptotic activity was greater at 400 MU/min than 2400 MU/min (9.4% vs 8.1%, $p = 0.019$). But for 30 Gy, apoptotic activity was greater at 2400 MU/min than 400 MU/min (15.6% vs 13.1%, $p = 0.002$). For the U251 line, mean apoptotic activity in all irradiated groups was greater than in control ($p < 0.04$). At 15 Gy, apoptotic activity was greater at 2400 MU/min than 400 MU/min (24.5% vs 16.8%, $p = 0.11$). At 30 Gy, apoptotic activity was greater at 2400 MU/min than 400 MU/min (23.2% vs 20.1%, $p = 0.01$).

Thompson, Maxwell Anthony (Maxwell)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Derek A. DuBay, MD
Co-Authors	David T Redden, PhD, Lindsey Glueckert, BS, Devin E Eckhoff, MD, and Derek A DuBay, MD
Title	Risk Factors Associated with Reoperation Due to Hemorrhage Following Liver Transplantation

Abstract

Introduction: Risk factors associated with hemorrhage following liver transplantation (LTx) are poorly defined. This study's objective was to identify risk factors associated with LTx hemorrhage requiring reoperation as well as the impact on mortality and short-term clinical outcomes.

Methods: A retrospective study of liver transplants was performed at the University of Alabama at Birmingham from 1999-2010. Operative and hospital billing reports were used to identify patients who underwent reoperation for hemorrhage within 90 days of LTx. Kaplan-Maier curves and Log-Rank tests were used to measure LTx survival. Univariate and multivariable Cox regression analyses were performed to assess for risk factors associated with LTx hemorrhage.

Results: Reoperation for hemorrhage following was observed in 10.6% (103/970) of LTx patients. The following characteristics were associated with reoperation on univariate analysis: higher Model for End-Stage Liver Disease (MELD) score ($p < 0.001$), Intensive Care Unit (ICU) treatment immediately prior to LTx ($p = 0.0049$) and fewer units of platelets transfused during the LTx ($p = 0.0385$). Recipient age, donor age, ischemia time, red blood cells transfused, fresh frozen plasma transfused, operative length and recipient epigastric surgical history were not associated with reoperation for hemorrhage. On multivariable analysis, only MELD (OR 1.05, 95% CI 1.03–1.08) and units of platelets transfused (OR 0.84, 95% CI 0.72–0.98) remained associated with reoperation for hemorrhage.

LTx patients who underwent reoperation for hemorrhage had a longer total ICU stay (9.3 days \pm 7.1 vs. 5.0 days \pm 4.1, $p < .001$) and hospitalization (23.6 days \pm 16.4 vs. 16.4 days \pm 18.2, $p < 0.001$). The risk of death increased in LTx patients who underwent reoperation for hemorrhage (HR 1.90, 95% CI 1.27–2.86).

Discussion: Reoperation for hemorrhage following LTx was associated with significant resource utilization and increased mortality. The only modifiable risk factor identified in our patient cohort was correction of intraoperative coagulopathy via additional platelet transfusion.

Turner, Julie Anne (Julie)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	Nancy M. Tofil, MD and Marjorie Lee White, MD, MPPM, MEd
Co-Authors	Julia M. Niebauer, MD; Dawn Taylor Peterson, PhD, EdS, MEd; Amber Q. Youngblood, BSN, RN; J. Lynn Zinkan, MPH, BSN, RN; Diego Lara, MD, MPH; Brett Jakaitis, MD; Mary Orr, MS, BA
Title	Breadth versus Depth? Repeated versus Mixed Case Selection in Pediatric Resident Simulation

Abstract

Introduction: High fidelity simulation in medical education is a valuable way to improve residents' knowledge and skill acquisition. Repeated practice is important in acquiring technical skills, but more research is needed to demonstrate its effectiveness in medical decision-making. However, by repeating cases, the repertoire of exposure will decrease. Our hypothesis is that residents exposed to repeated scenarios with opportunities for deliberate practice will out-perform residents exposed to a variety of scenarios. **Methods:** Senior residents in pediatrics and medicine/pediatrics participated in a one-hour simulation session with three scenarios and a scripted debriefing after each case. Residents were randomized to either a repeating scenarios group (RP) or a mixed scenarios group (MIX). RP completed the same scenario with different stems (Pulseless Electrical Activity [PEA]) three times (Case 1,2,3). MIX completed three different scenarios consisting of PEA (Case 1), seizure (Case 2), and ventricular tachycardia (Case 3). Four months after the initial session, participants returned for a second hour to complete three more cases. The follow-up session included PEA with a different stem (Case 4), seizure with a different stem (Case 5), and critical coarctation (Case 6). Times to perform key actions were recorded. All participants were PALS certified. All cases were performed using a high fidelity infant simulator. Statistical analysis was conducted using SPSS. **Results:** 23 of 24 (96%) senior residents participated, including 14 pediatrics residents, 8 medicine/pediatrics residents, and 1 pediatrics/genetics resident. There were no significant differences between groups in regards to age, gender, or program. Residents were randomized into either RP (n=12) or MIX groups (n=11). RP showed a statistically significant improvement in the time to start chest compressions (45 ± 32 seconds in Case 1 vs. 22.5 ± 30 seconds in Case 4, $p=.03$); whereas MIX showed no significant improvement (32 ± 12 seconds in Case 1 vs. 34 ± 26 seconds in Case 4, $p=.84$). None of the participants chose to use a backboard for chest compressions in the first session (0/12 RP and 0/11 MIX), but backboard use improved significantly in Case 4 for RP but not for MIX (7/12 RP and 1/11 MIX). Correct identification of PEA was poor in Case 1 for both groups (7/12 RP and 6/11 MIX) and improved for both groups in Case 4 (12/12 RP and 10/11 MIX). In all instances of incorrect rhythm identification, sinus bradycardia was designated instead of PEA. Performance in the seizure scenario was similar except for time to check glucose, which was significantly faster in MIX, who had previous exposure to a seizure scenario (51 ± 51 seconds in Case 2 vs. 38 ± 99 seconds in Case 5, $p=.05$). No difference was noted in the performance between groups in Case 6, which was new to both during the follow-up session. **Discussion:** Repeating simulation scenarios enhances certain measures of resident performance over single exposure. Despite PALS training, only 53% of senior residents correctly identified PEA and none used a backboard with chest compressions in the initial scenarios. However, substantial improvement was seen in both groups during the follow-up scenarios. Multiple exposures to a scenario appears to be beneficial in certain measures but can lower performance in new scenarios with no previous exposure (i.e., RP was slower to check glucose in the seizure scenario). It is unclear as to what combination of breadth vs. depth is the most effective in pediatric residency training.

Van Gerwen, Olivia Telle (Libby)

Project Length	Short
Prior Research Experience	Yes
Funding Source	HSF Community and Rural Health Fellowship
Advisor	Nathaniel Robin
Co-Authors	Audie Woolley, Mandy Mahalak
Title	Comparison of Language Skills and Educational Development in Post-Cochlear Implant Children with Non-Syndromic Deafness Due to GJB2 Gene Mutations to That of Their Hearing Peers

Abstract

Congenital deafness resulting in non-syndromic hearing loss is prevalent, with an estimated prevalence of 1/1000 newborns. The most common genetic cause is mutations in the *GJB2* gene, which encodes for the gap junction protein Connexin 26. With the advent of hearing aids and, more recently, cochlear implant surgery, deaf children are able to gain hearing function. Long term speech performance, however, is not uniform all deaf children. The level of speech intelligibility most likely depends on the genetic cause of deafness in the child. Anecdotal evidence suggests that children with the *GJB2* mutations are high performers in academics and speech even when compared to hearing peers and, therefore, have significantly better outcomes than children with other forms of deafness following cochlear implant surgery. In an attempt to confirm this observation we examined a cohort of 10 patients with the *GJB2* gene defect who received cochlear implants, and compared their scores on various language assessments recorded during audiology sessions post operatively with age equivalents of hearing peers. After determining the level of performance of each child on these language tests, we discovered that the results were variable from child to child, as each child participated in a unique series of tests. 4 of the children performed below the average for their age on the majority of their testing and 6 of the children performed at or above average for their age. While these results support our hypothesis, a more standardized measure for language performance as well as a larger sample size are necessary to draw a significant conclusion.

Vu, My-Hanh Thi (Hanh)

Project Length

Prior Research Experience No

Funding Source

Advisor Dr. Stephenie Wallace and Dr. Heather Austin

Co-Authors

Title Determining common parental styles for obese adolescents at a weight management clinic

Abstract

Background: Approximately 17% of US children age 2-19 are obese according to the CDC. Understanding factors, such as family functioning is critical to dealing with this epidemic. Studies identify positive correlations between the effects of family oriented interventions (such as general parenting skills) in preventing and treating childhood obesity. Diane Baumrind proposed three types of parental style: authoritative (high warmth, high control), authoritarian (low warmth, high control), and permissive (low/no warmth, no control). Characteristics of warmth are being responsive and reasonable to the child. Characteristics of control are setting rules and making sure rules are followed. Based on these types of parental styles, a 30-item Parental Authority Questionnaire (PAQ) was established.

Objective: The purpose of this pilot study was to determine the most prevalent parental style for families who attend a Pediatric weight management clinic.

Method: The PAQ was administered to patients, aged 13-19, during regularly scheduled appointments at the clinic.

Results: Of the 30 participants, 10% reported primarily permissive parenting, 50% reported primarily authoritarian parenting, and 53.3% reported primarily authoritative parenting. Four participants reported equal scores for two parenting styles. Compared to norm values calculated from a population of high school students, PAQ scale scores of weight management adolescents were higher for authoritarianism and authoritativeness.

Conclusion: The most prevalent parental style for obese adolescents presenting in a weight management clinic is authoritative and authoritarian. Although studies show that most obese adolescents have parents who are either permissive to authoritarian, our study was based on a specific population, parents who are actively involved enough to seek care for their obese child. Therefore, it makes sense for this sample of parents to either be authoritarian or authoritative. Understanding more specific characteristics of the family dynamic will be helpful in guiding family based interventions in families seeking weight management treatments.

Warmus, Brian Andrew (Brian)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Erik D. Roberson
Co-Authors	Brian A. Warmus, Dheepa R. Sekar, Gerard D. Schellenberg, Erik D. Roberson
Title	Repetitive Behavior and Salience Network Dysfunction in a Mouse Model of Frontotemporal Dementia

Abstract

Frontotemporal dementia (FTD) is one of the most common dementias and is characterized by behavioral problems such as personality changes, social disturbances, and repetitive behavior. Repetitive behavior in FTD can be highly disabling and includes complex compulsive behaviors, motor and vocal stereotypies, and self-injurious pathological grooming. There is no treatment for these symptoms because the underlying neurobiology is unclear. However, it is known that mutations in the microtubule associated protein tau gene can cause FTD. We examined a transgenic mouse model with the FTD-associated V337M human tau mutation (hTauV337M mice) and found that they exhibited age-dependent repetitive behavior relevant to FTD patients. Repetitive behavior was not seen in a related line expressing similar levels of wild-type human tau, suggesting that the abnormality is mutation-specific. Because FTD patients have a distinct pattern of connectivity dysfunction and atrophy in a network of brain regions termed the salience network, we hypothesized that hTauV337M mice would have abnormalities in these regions. To test this hypothesis, we measured dendritic branching patterns by Golgi stain, neuronal population by stereological counts, synaptic protein levels by western blot, and excitatory transmission by electrophysiological recordings. We found that salience network regions had age-dependent dendritic simplification and cell loss. In addition, there were fewer postsynaptic densities, decreased excitatory receptors, and depressed excitatory transmission in salience network regions. These results suggest that FTD-associated tau mutations cause age-dependent repetitive behavior by disrupting postsynaptic function in the salience network.

Watkins, Stacey Michelle (Stacey)

Project Length Long

Prior Research Experience Yes

Funding Source

Advisor Harald Sontheimer

Co-Authors

Title Hydrodynamic cytoplasmic and nuclear changes aid cell invasion

Abstract

Malignant gliomas are highly invasive brain tumors which currently lack effective treatment. Cells frequently invade the brain along blood vessels or nerve tracts adjusting their shape to facilitate migration through tortuous extracellular spaces. Whether shape changes are associated with a dynamic regulation of cell volume, however, is not known. To examine this question, we developed several model systems to visualize and quantitatively assess cell volume changes of invading cells *in vivo*, *in situ*, and *in vitro* using 3-dimensional multi-photon and confocal time-lapse microscopy. Regardless of model systems, invading cells decrease their volume by 30-35%, a value that was independent of barrier and cell size. Invading cells decreased nuclear volume by an average 48%. Through osmotic challenges, we demonstrate that the observed cellular and nuclear volume changes represent the smallest achievable volumes and require cells to release all free unbound cytoplasmic water. Water osmotically follows the release of Cl⁻ through ion channels and blockade of Cl⁻ channels inhibits both volume changes and cell invasion. Hence, invading cells use hydrodynamic volume changes to meet the spatial constraints imposed within the brain, utilizing essentially all free, unbound cytoplasmic water to maximally reduce their volume as they invade.

Weber, Adam Craig (Adam)

Project Length	Short
Prior Research Experience	Yes
Funding Source	
Advisor	Richard Feist
Co-Authors	Weber A, Pomerleau D, Feist R
Title	Corneal opacity as a prognostic factor in endophthalmitis

Abstract

Purpose: Determine prognostic value of corneal opacity for visual acuity and complications in patients with endophthalmitis.

Methods: IRB-approved, HIPAA-compliant retrospective study of patients presenting to private practice, five-physician vitreoretinal group for treatment of endophthalmitis. Subject's charts were reviewed for history of procedures to affected eye. Patient age, acuity, intraocular pressure, hypotony, presence of hypopyon, retinal detachment, and corneal opacity at presentation were recorded. Follow-up visits at 1, 4 and 12-week intervals were reviewed and variables recorded included: visual acuity, intraocular pressure, hypotony, presence of corneal opacity, evidence of retinal detachment, and ocular procedures. Acuity was measured as logarithm of minimal angle of resolution (logMAR). Patients were divided into two subject groups based on presence of absence of corneal opacity during the 12-week observed period. T-tests and Fischer tests were used to determine statistical significance of differences between the groups. Corneal opacity was defined as edema compromising view of anterior chamber structures.

Results: A study population of 51 separate eye encounters (21 male) with average age of 68 years (range 21-92) was examined. Values for opacity (N=14) and non-opacity (N=37) groups, respectively, at presentation were: logMAR= 2.12 and 1.64 (p=0.003); IOP= 28 and 17 (p=0.01); history of ocular procedure in 93% (13/14) and 89% (33/37). At the completion of 12 weeks follow-up, the opacity group had logMAR=1.73, 1 patient with opacity, 5 retinal detachments, and 9 procedures. The non-opacity group had logMAR=1.07, 4 retinal detachments, and 16 procedures. The differences between the two groups for acuity (p=0.09) and detachments (p=0.05) were near significant cutoffs. One patient in each group required evisceration. A single patient in each group was LP and NLP.

Conclusion: Corneal opacity can be used a marker of advanced or aggressive endophthalmitis that portends a poor outcome for the patient. Prompt and aggressive treatment is indicated for endophthalmitis patients who develop corneal opacity.

Weber, Adam Craig (Adam)

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Desiree Morgan MD

Co-Authors Naomi Fineberg PhD

Title Dual-Energy Single-Source CT for Diagnosis of Adrenal Lesions

Abstract

Purpose: Differentiate adenomatous and nonadenomatous adrenal lesions using single source dual-energy multidetector CT (SSDE CT).

Methods: IRB-approved, HIPAA-compliant retrospective inpatient study of 40 consecutive adults with adrenal pathology who underwent standardized multiphase protocol on SSDE CT scanner for hepatic or pancreatic indications. Arterial phase images were acquired with dual-energy and precontrast images with standard MDCT. Lesions were diagnosed based on accepted criteria for unenhanced MDCT. Arterial images were evaluated on an independent workstation with dual-energy software for variables: Hounsfield units (HU) on monochromatic 140keV images, density on material decomposition water (-iodine), fat (-iodine) images, correlated with MDCT HU (Pearson coefficients). Values for adenomatous and nonadenomatous lesions were compared with ANOVA and Tukey's HSD test. ROC analysis was performed to identify dual energy thresholds equivalent to 10 HU on unenhanced MDCT, and linear regression was used to calculate an equation to convert SSDEMDCT values to standard HU.

Results: 47 lesions were evaluated in 40 subjects (19 females) mean age 66.5 years (range 34-81): 29 adenomatous and 18 nonadenomatous lesions were examined. (N), Mean±SD on unenhanced MDCT were: adenomas (12), -8.5±13.9; lipid poor adenomas (4) 27.4±8.8; malignant nodule (8) 40.9±12.3; myelolipoma (7) -71.9±24.0; hyperplasia (6) 17.4±6.0; adenomatous hyperplasia (10) -7.36±11.44. SSDE measures correlated well with HU $r=0.90-0.95$, $p<0.001$. ANOVA showed differences between myelolipomas, adenomatous and nonadenomatous lesions, $p<0.001$ for all dual energy variables. Areas under ROC curve for HU140 keV, fat(-iodine) and water(- iodine) were: 0.946 ± 0.03 , 0.933 ± 0.04 , 0.929 ± 0.04 , respectively ($p<0.001$), with 83.8 % of adenomatous lesions having a HU140keV <12.1 HU, 86% having fat(-iodine) <990 mg/cc and 86% having water(-iodine) <997 mg/cc.

Conclusion: There is very good correlation between SSDE measures and standard MDCT accepted values for adenomatous and nonadenomatous adrenal lesions, with clinically relevant cutoffs on dual energy to differentiate between the two classes of lesions.

Whisenhunt, James Dylan (Dylan)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Jere P. Segrest
Co-Authors	Martin K. Jones, Andrea Catta
Title	Length-Dependent Behavior of Beta Amyloid Polypeptide Within the Lipid Bilayer Immediately Following Generation by Gamma Secretase

Abstract

Amyloid beta peptide ($A\beta$) is the primary pathological molecule in Alzheimer's disease (AD). The relative serum concentrations of different lengths of $A\beta$, specifically 40 and 42 amino acid lengths ($A\beta_{40}$ and $A\beta_{42}$), are good prognostic indicators for the progression and severity AD, with $A\beta_{42}$ being significantly worse. Current research explains the pathology of AD by formation of disruptive calcium-channel-like $A\beta$ oligomeric pores in neuronal membranes. The reason $A\beta_{42}$ forms pores more quickly than $A\beta_{40}$ is unknown. This research aims to explain the phenomenon through molecular dynamics. Computer models of monomers and homodimers of truncated amyloid beta precursor protein were constructed within Visual Molecular Dynamics. These were seated in a lipid bilayer and physiologically solvated according to current structural knowledge. The assemblies were then minimized, heated, and simulated in Not (just) Another Molecular Dynamics program. Once at equilibrium, they were cleaved at residues 40 and 42, forming monomeric and dimeric $A\beta_{40}$ and $A\beta_{42}$ ($mA\beta_{40/42}$ and $dA\beta_{40/42}$). The $A\beta$ monomers and homodimers were then minimized, heated, and simulated for thirty nanoseconds. Significant differences were observed between species. $mA\beta_{40}$ adopted a globular formation at the boundary of the outer leaflet within its hydrophobic intramembrane domain while maintaining a semi-helical structure in its extracellular hydrophilic domain, implying that it may even eventually leave the bilayer completely. $mA\beta_{42}$'s intramembrane domain adopted an extended helical structure and spanned the entire lipid bilayer, directly interacting with intracellular water molecules. Both dimeric species extended from the outer to inner leaflet, but $dA\beta_{42}$ retained more water molecules within the membrane throughout the simulation than did $dA\beta_{40}$. $dA\beta_{40}$ may eventually disassociate from water all-together and behave similarly to $mA\beta_{40}$. Membrane-embedded $A\beta$ could serve as nuclei for pore formation or form previously unknown, novel channels, thus explaining the difference in clinical prognosis and providing new approaches for pharmacotherapy.

Wilkins, Sara Anne (Sara Anne)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Cunningham Fellowship (Pediatrics)
Advisor	Dr. Drew Davis, Dr. James Johnston, Dr. Chevis Shannon
Co-Authors	CN Shannon, MI Falola, GT Reed, H Jones, A King, D Davis, JM Johnston
Title	Defining Variation in Management of Children with Sports-Related Concussion: First Step to Standardization

Abstract

Introduction: Patients diagnosed with concussion have been traditionally evaluated in relative isolation across various medical specialties. Recent concussion legislation and emerging medical evidence mandate a guideline-based approach to diagnosis and to manage sports-related concussion. In preparation for the implementation of a multi-disciplinary concussion clinic, we performed a retrospective study to quantify variation in care for sports-related concussions at a single high volume pediatric hospital. We hypothesized that there was significant variation in the management and follow-up of these patients among the divisions at which they were first evaluated.

Methods: All patients up to 18 years of age evaluated for sports-related concussion between the years 2007 and 2010 were included in this retrospective study. Emergency Department (ED), Sports Medicine, and Neurosurgery consultation records were reviewed. Data included patient demographics, injury mechanism, presenting symptoms, discharge instructions and subsequent referrals for specialty care. Descriptive statistical analysis identified incidence trends and management variation across specialties and time.

Results: There were 270 sports-related concussions diagnosed during the study period in 224 boys (83%) and 56 girls (17%), with an average age of 13.5 years. Organized youth football was the most frequent associated sport (49.3%). Headaches, dizziness, nausea, and balance problems were the most common presenting symptoms. There was significant variation in diagnosis, imaging, coding, management, discharge instructions, and neuropsychological referral guidelines both within and across specialties.

Conclusions: As information regarding the long-term sequelae of concussion continues to emerge, patients will be best served by a coordinated multidisciplinary approach to management. Quantification of existing variations in care may be used to inform the successful design, implementation and maintenance of a uniform protocol for management of concussions based on best-practice guidelines.

Wiltrakis, Susan May (Susan)

Project Length Short
Prior Research Experience Yes
Funding Source NIH T35 Short Term Training Grant
Advisor David Kimberlin

Co-Authors

Title Comparing the Glasgow Coma Scale and Infant Face Scale in Pediatric Patients with Influenza Infection

Abstract

Objective: To compare the Glasgow Coma Scale (GCS) and the Infant Face Scale (IFS) in infants infected with virologically confirmed influenza to analyze the accuracy of the neurologic assessments and identify which is the better predictor of influenza morbidity and clinical outcome.

Methods: Data from an NIH study of oseltamivir in infants 0 through 23 months of age were analyzed. The study was conducted by the NIAID Collaborative Antiviral Study Group, and enrolled subjects from November 2006 through March 2010 at 16 academic medical centers across the U.S. GCS and IFS data were collected for all subjects, and number of influenza symptoms was captured at each study visit. GCS and IFS were correlated with assessment day (5 assessments over 30 day period) and cohort age (12-23, 9-11, 6-8, 3-5, 0-2 months).

Results: 87 subjects enrolled on the study. For all age groups, GCS verbal component scores less than 5 had significantly higher median number of influenza symptoms than scores of 5 ($p=0.008$), which was not significant for IFS verbal scores ($p=0.22$). In age group subset analyses, this difference is primarily seen in the youngest infants (0 through 2 months, $p=0.007$). Among all ages, verbal component scores of less than 5 correlated with higher mean and median times to influenza symptom resolution with the GCS ($p=0.04$) but not with the IFS ($p=0.57$).

Conclusion: Among young infants infected with influenza, GCS is a better predictor than IFS of influenza morbidity and clinical outcome. Differences between the two assessment tools are seen primarily in the verbal component and are more pronounced in younger infants.

Zelickson, Adam Mendel (Adam)

Project Length Short
Prior Research Experience Yes
Funding Source NIH T35 Short Term Training Grant
Advisor Dr. Shawn R. Gilbert
Co-Authors

Title Detection and Quantification of Bacterial Load in Open Fracture Models: Investigation of Desferrioxamine as a Novel Treatment for Open Fractures with Osteomyelitis

Abstract

Our group is evaluating the role of pro-angiogenic strategies to improve outcomes in a contaminated open fracture model developed to simulate severe extremity injury. An important outcome in this model is bacterial load and the progression of osteomyelitis. A quantitative PCR protocol is in development to supplement standard microbiological culture procedures in examining this endpoint. Primers and probes specific for *Acinetobacter baumannii* and *Staphylococcus aureus* genes were developed as well as primers/probes for the rat *Beta-actin* gene for normalization. An extensive literature review was done to search for adequate gene targets, followed by sequence analysis to rule out potential sequence homology and nonspecific amplification. DNA was extracted from forty-five common rat flora and pathogens to use for primer/probe specificity assays, and pure DNA was extracted from *A. baumannii*, *S. aureus*, and rat RBL cells for sensitivity assays. Though the *S. aureus* targets seem to have some sequence overlap with *Pseudomonas aeruginosa*, the primers/probes for *A. baumannii* and rat *actB* have shown remarkable specificity. Following further protocol optimization, simple assays for primer/probe sensitivity will ensue, and qPCR will serve as a simple method for directly quantifying bacterial involvement as well as the utility of the various treatments involved in this project. Additionally, testing was performed to rule out direct effects of the pro-angiogenic compound (DFO) on bacterial growth. A series of Minimum Inhibitory Concentration assays were performed to simulate the treatments that subjects received in our open fracture model. Inocula were prepared in concordance with NCCLS protocol, and Tobramycin MIC's were determined for our pathogens of interest as well as appropriate reference strains. Subsequently, DFO was analyzed alongside and in combination with Tobramycin to assess its effect on bacterial proliferation. It was determined that DFO neither suppresses nor aids bacterial growth, and that it has no effect on Tobramycin's antimicrobial properties.

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Title The Prognosis of Bone Invasion in Small Squamous Cell Carcinomas of the Oral Cavity

Abstract

There remains considerable controversy regarding the impact of bone invasion on the survival of patients with oral cavity squamous cell carcinomas (OCSCC). Current literature suggests that the current AJCC staging system over-stages OCSCC by upgrading small tumors to T4 on the basis of bone invasion. We sought to determine if the current AJCC grading system accurately predicts survival of patients with small tumors with bony invasion. Through a retrospective chart review we reviewed all patients with OCSCC without prior radiation treated surgically between March 2000 and March 2009. There were 197 patients who were pathologically staged by AJCC criteria as: T4 (73%, n = 144), T3 (9%, n=18), T2 (15%, n = 30), T1 (3%, n = 5). The majority were primary SCC (n = 166) with the remainder having had previous surgery. Bone invasion was present in 54% (n = 107) of resected tumors. The overall 2-year survival for this cohort was 64%. To determine if bony invasion influenced the prognosis of smaller tumors (<4cm), patients with T1/2 sized tumors with bone invasion (n = 53) were compared with T4 tumors. Overall survival and recurrence rates of these extracted patients (38% and 68%, respectively) were similar to T4 tumors based on conventional AJCC grading (34% and 66%, respectively). Despite significant controversy, upstaging of T1/2 sized tumors to T4 status when there is evidence of bone invasion demonstrated equivalent survival with tumors staged T4 by size.

