Dale Benos Medical Student Research Day 2012

Judges

Dr. Farrukh Afaq
Dept. of Dermatology

Dr. Mark Bevensee
Dept. of Cell, Developmental and Integrative Biology

Dr. Todd Brown
Dept. of Medicine

Dr. Yiu- Fai Chen
Dept. of Medicine

Dr. Laura Cotlin
Dept. of Cell, Developmental and Integrative Biology

Dr. Gareth Dutton
Dept. of Medicine

Dr. Reed Estes
Dept. of Surgery

Dr. Gregory Friedman
Dept. of Pediatrics

Dr. Lianwu Fu
Dept. of Cell, Developmental and Integrative Biology

Dr. Catherine Fuller
Dept. of Cell, Developmental and Integrative Biology

Dr. Shawn R Gilbert
Dept. of Surgery

Dr. Julia Gohlke
Dept. of Environmental Health Sciences

Dr. Frederick Goldman
Dept. of Pediatrics

Dr. Fadi Hage
Dept. of Medicine

Dr. John Hartman
Dept. of Genetics

Dr. Ho-Wook Jun
Dept. of Biomedical Engineering

Dr. Silvio Litovsky
Dept. of Pathology

Dr. Julie Locher
Dept. of Medicine

Dr. Carmel McNicholas
Dept. of Physiology & Biophysics

Dr. David Resuehr
Dept. of Cell, Developmental and Integrative Biology

Dr. Steven Rowe
Dept. of Medicine

Dr. Peter Smith
Dept. of Cell, Developmental and Integrative Biology

Dr. Elizabeth Sztul
Dept. of Cell, Developmental and Integrative Biology

Dr. Laura Timares
Dept. of Dermatology

Dr. Henry Wang
Dept. of Emergency Medicine

Dr. John Waterbor
Dept. of Epidemiology

Dr. Douglas Weigent
Dept. of Cell, Developmental and Integrative Biology

Dr. Roger White
Dept. of Medicine

Dr. James Willig
Dept. of Medicine

Dr. Bradford Woodworth
Dept. of Surgery

Dr. Martin Young
Dept. of Medicine

Dr. Nabiha Yusuf
Dept. of Dermatology

Dr. Allan Zajac
Dept. of Microbiology

Oral Presentations
Lecture Room E

MS1/MS2 Short Term Research

10:00 – 10:15 am **Richard H. Cockrum, MS2**
"Diabetes Knowledge Retention and Glycemic Control in the ENCOURAGE Trial"
Mentor: Dr. Monika Safford

10:15 – 10:30 am **David Paul Dorn, Jr., MS2**
"Chemoembolization for hepatocellular carcinoma in cirrhotic patients with compromised liver function"
Mentor: Dr. Derek Dubay

10:30 – 10:45 am **Anna Joy Graves, MSTP (MS2)**
"The Monetary Value of Breastmilk in the United States"
Mentor: Dr. E. Michael Foster

10:45 – 11:00 am **Christa Renee Nevin, MS2**
"New Graduate Medical Education teaching strategies in a post-ACGME work-hour mandated environment"
Mentor: Dr. James H. Willig

11:00 – 11:15 am **Ryne Ramaker, MSTP (MS1)**
"Analysis of UV-Light Induced Modifications of the Lens Protein αB *-crystallin and Potential Protective Agents"*
Mentor: Dr. Stephen Barnes

11:15 – 11:30 am **Ashley Ladana Spann, MS2**
"Role of Primary Cilia in Canonical Hedgehog Signaling in Cancer"
Mentor: Dr. Andra Frost

11:30 – 11:45 am **Timothy Adrian Wang, MS2**
"Increased Protein O-GlcNAcylation Inhibits TNF-α--induced Inflammatory Mediator Expression in Rat Aortic Endothelial Cells"
Mentor: Dr. Suzanne Oparil

Oral Presentations
Lecture Room A

MS3/MS4 Short- Intermediate Term Research

10:00 - 10:15 am **Jennifer Porter Bynum – MS4**
"Validation of a New HIT ELISA: Comparison of Two Commercial ELISA kits with a Gold Standard ELISA"
Mentor: Dr. Jill Adamski

10:15 – 10:30 am **Thomas Clark Powell - MS3**
"Differences in the SLE Clinical Phenotype by Age of Diagnosis"
Mentor: Dr. Elizabeth Brown

10:30 – 10:45 am **Benjamin Todd Raines – MS3**
"Determinants of readmission: An analysis of 28,041 elective arthroplasty procedures"
Mentor: Dr. Mary Hawn

Long Term Research

10:45 – 11:00 am **Jennifer Ann Hadley – MSTP (GS3)**
"Antipsychotic drug treatment restores impaired limbic system connectivity in schizophrenia"
Mentor: Dr. Adrienne C. Lahti

11:00 – 11:15 am **Nicholas Joseph Reish – MSTP (GS5)**
"Rab11a Directs Rhodopsin Trafficking in Rod Photoreceptors"
Mentor: Dr. Alecia Gross

11:15 - 11:30 am **Brian Andrew Warmus – MSTP (GS3)**
"Molecular Mechanisms of Frontotemporal Dementia"
Mentor: Dr. Erik D. Roberson

Group A

A-1 Basu, Sambita (Sambita) – MS2
"*Assessment of sEH Activity by Oxylipin Metabolites: Relevance to Diabetes"*
Mentor: Dr. James Matthew Luther

A-2 Berry, Ryan D. (Ryan) – MSTP (MS2)
"Thioredoxin-interacting protein regulates beta cell islet amyloid polypeptide expression"
Mentor: Dr. Anath Shalev

A-3 DelaRosa, Hillary Jean (Hillary) – MS3
"Toll-Like Receptor-4 augments ultraviolet radiation induced cutaneous tumor development by DNA damage mechanism"
Mentor: Dr. Nabiha Yusuf

A-4 Hagan, Kenton Lee (Kenton) – MS2
"The Effect of a Catalytic Oxidoreductant on Concussion"
Mentor: Dr. Candace Floyd

A-5 Hunt, Raymond Bryce (Bryce) - MS2
"Aflatoxin effects in liver cancer and liver disease in Ghana"
Mentor: Dr. Pauline Jolly

A-6 Lin, Erica (Erica) – MS2
"Role of mitochondrial oxidant production in insulin secretion"
Mentor: Dr. Scott Ballinger

A-7 Weaver, Alice (Alice) – MSTP (MS2)
"Differential Susceptibility of Oropharyngeal Carcinoma to Targeted Therapy Based on Human Papillomavirus Status"
Mentor: Dr. Eddy Yang

A-8 Witcher, Adam Clarke (Adam) – MS2
"Mitochondrial Membrane Potential and Viability Post-exposure to Cl2 Gas in H441 Cells"
Mentor: Dr. Sadis Matalon

Group B

B-1 Barrington, David Allen (David) – MS2
"Obesity and Physeal Fractures"
Mentor: Dr. Shawn Gilbert, MD

B-2 Gray, William Hampton (Hampton) – MS3
"A Twenty Year Experience with the Surgical Correction of Aortic Arch Obstruction in Patients with Right Aortic Arches"
Mentor: Dr. Robert Dabal

B-3 Grayson, Jessica Warren (Jessica) – MS4
"Unilateral Endonasal Endoscopic Resection of an Intracranial Dermoid Cyst"
Mentor: Dr. Bradford Woodworth

B-4 Keith, Charles Joseph, Jr. (Charles) – MS4
"Comparison of Long-term Outcomes following Endovascular Repair of Abdominal Aortic Aneurysms Based on Size Threshold"
Mentor: Dr. Marc A. Passman

B-5 Martin, Morgan Sparks (Morgan) – MS3
"Successful treatment combination for refractory keloid scars on the upper back"
Mentor: Dr. Sherry Collawn

B-6 Novack, Andrew Scott (Scott) – MS2
"Iliotibial Band Stretching and Vastus Medialis Strengthening for the Prevention of Patellofemoral Syndrome and Iliotibial Band Syndrome in Track and Field Athletes: A Randomized Controlled Trial"
Mentor: Dr. Reed Estes

B-7 Raines, Benjamin Todd (Todd) – MS3
"Comparative effectiveness of prophylactic antibiotic choice and surgical infection in arthroplasty"
Mentor: Dr. Mary T Hawn

B-8 Salisbury, Charles Drew (Charles) – MS3
"Comparison of long-term survival for surveillance, open repair, and endovascular repair of abdominal aortic aneurysms"
Mentor: Dr. Thomas Matthews

B-9 Salisbury, Charles Drew (Charles) – MS3
"Long-term outcomes for non-operative surveillance of abdominal aortic aneurysms"
Mentor: Dr. Thomas Matthews

B-10 Thomas, Evan Marshall (Evan) - MSTP (GS3)
"Utilization of Dual Energy CT to Improve Treatment Planning for Patients with Metal Streak Artifact"
Mentor: Dr. John Fiveash

Group C

C-1 Abroms, Sarah Rachel (Sarah) – MS4
"Tuberculosis screening practices among newly enrolled HIV-infected patients at three HIV clinics in Lusaka, Zambia"
Mentor: Dr. German Henostroza

C-2 Addis, Dylan Robert (Dylan) – MS3
"Accuracy of Discharge Diagnoses for Identifying Sepsis Hospitalizations"
Mentor: Dr. Henry E. Wang

C-3 Carley, Joseph Anthony, IV (Joe) – MS4
"Cross-validation of the Novel Linear Assessment of Suicide Risk (LASR) Scale with the Standard Beck Scale for Suicidal Ideation (BSS) in Order to Provide an Updated Measure of Suicidality with a Linear Distribution of Scores for Initial Assessment and Tracking Response to Treatment"
Mentor: Dr. Cheryl McCullumsmith

C-4 Chen, Zsu-Zsu (Zsu-Zsu) – MS4
"Prevalence of beliefs about generic medications in Encourage study participants reporting medication non-adherence"
Mentor: Dr. Monika Safford

C-5 Luker, Austin Malory (Austin) – MS2
"Perceptions of Rural vs. Urban Primary Care Physicians Regarding Telepsychiatry"
Mentor: Drs. Lee Ascherman and Tolu Aduroja

C-6 Nguyen, Su Quoc (Su) and Mwakalindile, Edwin - MS4 (Co-first authors)
"The Accuracy of Automated Sepsis Detection in the Emergency Department"
Mentor: Dr. Henry Wang

C-7 Patel, Shaan Suresh (Shaan) – MS2
"Cost-effectiveness of colorectal cancer screening tests"
Mentor: Dr. Meredith Kilgore

C-8 Roddy, Ryan Rebekah (Ryan) – MS2
"Living the Story: The Evaluation of Translating Plot to Policy"
Mentor: Dr. Connie Kohler

C-9 Sloan, Meagan Elizabeth (Meagan) – MS2
"A Pilot Project to Assess Individual temperature and light exposures in urban and rural populations"
Mentor: Dr. Julia Gohlke

C-10 Wooten, Melanie Susannah (Melanie) – MS2
"Community-Level Barriers and Facilitators to Healthy Eating and Physical Activity Among African Americans Living in Rural Areas in the Deep South"
Mentor: Dr. Monica Baskin

C-11 Yuan, Yih Ying (Yih Ying) – MS4 (Poster display only - will not be presenting)

"A Simulation Course Focusing on Forensic Evidence Collection Improves Pediatric Knowledge and Standardizes Curriculum for Child Abuse"

Mentor: Dr. Marjorie Lee White

Group D

D-1 Azerf, Saji Pierce (Saji) – MS2
"Utilization of 17-Hydroxyprogesterone Levels in Newborn Screenings to Determine Congenital Secondary and Tertiary Adrenal Insufficiency"
Mentor: Dr. Hussein Abdullatif

D-2 Cotter, Alexander Patrick (Alex) – MS2
"Designing MyDiabetesConnect.com: A mixed methods approach to the development of a community resource website for type 2 diabetes (Glasgow, Boles et al. 2003)"
Mentor: Dr. Andrea Cherrington

D-3 Foster, Christy Anne (Christy) – MS4
"The Effect of Exogenous Growth Hormone therapy on lipid panel of Growth Hormone Deficient patients"
Mentor: Dr. Kenneth McCormick

D-4 Khan, Farah Naz (Farah) – MS4
"Assessing barriers to uptake of available services and diabetes education amongst patients with diabetes: A qualitative study in Delhi, India"
Mentor: Dr. Andrea Cherrington

D-5 Kukkamalla, Rene (Meghana) – MS2
"The Impact of Group Size on Weight Loss Interventions"
Mentor: Dr. Gareth Dutton

D-6 Le, Phuong Thanh To (Thanh) – MS4
"Early Insulin Therapy Improves Glycemic Control and Diabetic Dyslipidemia in Adolescents with Type 2 Diabetes Mellitus"
Mentor: Dr. Ambika Ashraf

D-7 Patel, Shweta Naran (Shweta) – MS2
"Calorie Restriction and Cancer Progression: From Mice to Men"
Mentor: Dr. Julie Locher

D-8 Prater, Ginnie
"Recognition of At-risk Nutritional Status in Hospitalized Geriatric Patients"
Mentor: Dr. Cynthia Brown

D-9 Sriram, Neeraj (Neeraj) – MS2
"Changes in resting energy expenditure effect changes in blood pressure over time in premenopausal women"
Mentor: Dr. Gary Hunter

D-10 Strickland, Leah Ray (Leah) – MS2
"Type 2 Diabetes with Partial Lipodystrophy of the Limbs: a New Lipodystrophy Phenotype"
Mentor: Dr. W Timothy Garvey

D-11 Tagayun, Christine Anne (Christine) – MS4

"Retrospective Analysis of the Effect of Weight on the Levonorgestrel Intrauterine System"

Mentor: Dr. Todd Jenkins

Group E

E-1 Clemons, Jason Lee (Jason) – MS4 (Residency Interview – Poster Only)
"The Use of High Fidelity Simulation in Genetic Counseling and Genetic Medical Education"
Mentor: Dr. Nancy Tofil

E-2 Coker, Joshua Allen (Josh) – MS4
"Evaluation of an Advanced Physical Diagnosis Course using Consumer Preferences Methods: the Nominal Group Technique"
Mentor: Dr. Carlos Estrada

E-3 Eschborn, Samantha Rae (Samantha) – MS4
"Diagnostic Error in the Care of Simulated Pediatric Inpatients"
Mentor: Dr. Marjorie Lee White

E-4 Hughes, Jacob Tyler (Tyler) – MS4
"Teaching Fellows to Teach Through the Use of Simulation"
Mentor: Dr. Marjorie Lee White

E-5 Jarrell, Seth Adam (Seth) – MS4 (Residency Interview – Poster Only)
"Simulated Ventricular Fibrillation in an Anesthetized Pediatric Patient"
Mentor: Dr. Nancy Tofil

E-6 Kezar, Carolyn Elise (Carolyn) – MS4
"Survey of United States Medical Schools Basic Clinical Skills Curricula"
Mentor: Dr Gustavo Heudebert

E-7 Parris, Tyler Christian (Tyler) – MS4
"Selecting the Best Clinical Vignettes for Academic Meetings: Further Modification of a Scoring Tool"
Mentor: Dr. Carlos Estrada

E-8 Pierce, Caleb Andrew (Caleb) – MS4
"Interprofessional high-fidelity simulation training improves knowledge and teamwork in nursing and medical students during internal medicine third year clerkship"
Mentor: Dr. Marjorie Lee White

Group F

F-1 Baker, Brandi (Brandi) – MS2
"Low Baseline Expression of Toll-Like Receptor and Interferon Pathway Genes Correlates with Decreased Joint Destruction in Rheumatoid Arthritis"
Mentor: Dr. S. Louis Bridges

F-2 Blosser, Emily Greenwood (Emily) – MSTP (GS3)
"Maternal Antibiotics Increase Risk of Klebsiella Late-Onset Sepsis in Neonatal Mice"
Mentor: Dr. Casey Weaver

F-3 DiToro, Daniel Francis (Daniel) – MSTP (GS1)
"Potential Role for Insulin-like Growth Factors in CD4-T Cell Differentiation"
Mentor: Dr. Casey Weaver

F-5 Handley, Guy Hartwell, IV (Guy) – MS2
"Effects of Cigarette Smoke Condensate on LTA4H Aminopeptidase Activity"
Mentor: Dr. J. Edwin Blalock

F-6 Meehan, Margaret Janice (Maggie) – MS2
"The CD200/CD200R interaction is a potential target for relieving T cell exhaustion"
Mentor: Dr. Allan Zajac

F-7 Moseley, Carson Edward (Carson) – MSTP (MS3)
"Functional characterization of transcription factors in CD4+ T cell development and autoimmunity"
Mentor: Dr. Casey T. Weaver

F-8 Poholek, Catherine Helen (Katie) - MSTP (GS3)
"The Pathogenicity of Interleukin-21 in Inflammatory Bowel Disease"
Mentor: Dr. Laurie E. Harrington

F-9 Singer, Jeffrey Robert (Jeff) – MSTP (GS1)
"Using the HAT-BAC mouse model to define cis-regulatory elements in the Human Interferon gamma locus"
Mentor: Dr. Casey Weaver

F-10 Stone, Sara Lynn (Sara) – MSTP (MS2)
"T-bet supports differentiation of B-effectors into antibody secreting cells"
Mentor: Dr. Frances Lund

F-11 Zelickson, Adam Mendel (Adam) – MS3
"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

Group G

G-1 Barrett, Olivia Claire (Olivia Claire) – MS4
"Hormone receptor expression and risk of recurrence in patients with high-risk endometrial carcinoma treated with chemotherapy"
Mentor: Dr. O. Lee Burnett III

G-2 Bhullar, Sukhkamal Kaur (Sukhkamal)
"Intra-Operative Respiratory Dynamics in Obese Patients Undergoing Robotic Gynecological Surgery"
Mentor: Dr. Jared Roberts

G-3 Bryant, Mary Katherine (Mary) – MS2
"Radiographic predictors of chemoembolization-induced hepatocellular carcinoma necrosis"
Mentor: Dr. Derek DuBay

G-4 Dobbin, Zachary Christopher (Zachary) – MSTP (GS3)
"The "Holograft" Model: An optimized primary ovarian cancer xenograft model that mimics patient tumor biology and heterogeneity"
Mentor: Dr. Charles Landen

G-5 Dover, Laura Lynne (Laura) – MS3
"Improved Post-operative Survival for Intraductal Growth Subtype of Intrahepatic Cholangiocarcinoma Compared to Other Histologic Subtypes"
Mentor: Dr. Derek DuBay

G-6 Ford, Samuel Edmond (Sam) – MS3
"*Salvage Surgery for Recurrent Cancers of the Oropharynx: How does TORS compare to standard open surgical approaches?"*
Mentor: Dr. Scott Magnuson

G-7 Foster, Katelyn Elizabeth (Katelyn) – MS2
"The Utility of Re-excision in Primary Vulvar Carcinoma"
Mentor: Dr. Warner K. Huh

G-8 Roszczynialski, Kelly Nicole (Kelly) – MS2
"Repair of osteoradionecrosis using microvascular free tissue transfer is associated with worsened quality indicators"
Mentor: Dr. Eben Rosenthal

G-9 Snead, Benjamin Ross (Ben) – MS3
"Dual-Energy CT Analysis of Ablation Therapy for Hepatocellular Carcinoma"
Mentor: Dr. Desiree Morgan

G-10 Toneva, Galina Dimitrova (Galina) – MS4
"Oral Antibiotic Bowel Prep Reduces Length of Stay and Readmissions Following Colorectal Surgery"
Mentor: Dr. Mary Hawn

Group H

H-1 Bray, Alexander Wendell (Alexander) – MSTP (MS2)
"The Role of Mitochondrial Genetic Background in Melanoma Growth"
Mentor: Dr. Scott Ballinger

H-2 Burch, Major Benjamin (Ben)
"Expression of Bone Morphogenetic Protein 6 in Oral Cavity Squamous Cell Carcinoma is Associated with Bone Invasion"
Mentor: Dr. Eben Rosenthal

H3 Dussaq, Alex Maurice (Alex) – MSTP (GS1)
"Creation of a collaborative, RDF based web ecosystem for kinomic peptide arrays"
Mentor: Drs. Jonas Almeida and Chris Willey

H-4 Frederick, John William (John) – MS4
"Anti-CD147 and the EGFR pathway in cutaneous squamous cell carcinoma"
Mentor: Dr. Eben Rosenthal

H-5 LeGrand, Jason Nathaniel (Jason) – MSTP (GS1)
"A Mouse Model of inv(16) and Kras Acute Myeloid Leukemia"
Mentor: Dr. Christopher Klug

H-6 Mays, Melissa Ann (Melissa) – MS2
"Progress Toward a Crystal Structure of the GBF1-ARF Interface for Therapeutic Drug Design"
Mentor: Dr. Elizabeth Sztul

H-7 Mitchell, Chase Matthew (Chase) – MS2
"Regulation of Catalytic Activity of the ARF GEF GBF1 by Non-catalytic Domains and its Role in Cancer Cell Survival"
Mentor: Dr. Elizabeth Sztul

H-8 Outlaw, Darryl Alan, Jr. (Darryl) – MS2
"Understanding How Yeast Gene Interaction Networks Modulate Cancer Chemotherapy Cytotoxicity: A Pilot Study of Drug-Media Interaction"
Mentor: Dr. John Hartman IV

H-9 Patel, Toral Rohit (Toral) – MS2
"The Effect of the Antioxidant N-Acetylcysteine (NAC) on Proliferative Defects in Dyskeratosis Congenita"
Mentor: Dr. Frederick Goldman

H-10 Simanyi, Eva (Eva) – MS2
"Toll-Like Receptor-4 augments ultraviolet radiation induced cutaneous tumor development by DNA damage mechanism"
Mentor: Dr. Nabiha Yusuf

H-11 Sollie, Rebecca Susan (Rebecca) - MS2
"Runx2 Transcription Factor Regulates Heparanase-Induced Bone Resorption in Multiple Myeloma"
Mentor: Dr. Yang Yang

H-12 Stanley, Jennifer Anne (Jennifer) –MSTP (GS1)
"Targeting Human Epidermal Growth Factor Receptor Pathways to Render Triple Negative Breast Cancer Cells Susceptible to PARP Inhibition"
Mentor: Dr. Eddy Yang

H-13 Zimmerman, Jacquelyn Winifred (Jackie) – MSTP (GS4)
"Specific modulation frequencies inhibit cancer cell proliferation in vitro and in vivo"
Mentor: Dr. Boris Pasche

H-14 Chen, Chongjia (ChaCha)
"Protective Effects of a Novel Pro-Electrophile in Human Retinal Pigmented Epithelium and a Rat Model of Light-induced Retinal Damage"
Mentor: Tayebeh Rezaie

Group I

I-1 Cho, Yun Ju (Janis) – MS2
"The Effect of Apathy on Life-Space Mobility among Older Adults with Parkinson's Disease"
Mentor: Dr. Cynthia J. Brown

I-2 Collins, Megan Elizabeth (Megan) – MS1
"Predictive Value of Dynamic Cancellation Testing to Inpatient Rehabilitation Outcomes"
Mentor: Dr. Victor Mark

I-3 Eick, John Francis (John) – MS2
"Exploring virtual walking as a potential treatment for spinal cord injury neuropathic pain: an fMRI study"
Mentor: Dr. Elizabeth Richardson

I-4 Elkhetali, Abdurahman Said (Abdurahman) – MSTP (GS2)
"Mechanisms of Attention in Auditory and Visual Cortex"
Mentor: Dr. Kristina M. Visscher

I-5 Huynh, Thy Nhat (Thy) – MS4
"Health Flow Care of Neurofibromatosis Type 1 Patients with Plexiform Neurofibromas (PN) or Malignant Peripheral Nerve Sheath Tumors (MPNST)"
Mentor: Dr. Bruce Korf

I-6 McCormick, Don Earl, III (Don) – MS3
"Antidepressant Therapy Following Spinal Cord Injury Inhibits Functional Recovery"
Mentor: Dr. Candace Floyd

I-7 Smith, Cody Brian (Cody) – MS4
"MEG Contributes to Surgical Management in Lesional Epilepsy"
Mentor: Drs. Jeffrey P. Blount and Robert Knowlton

I-8 Williams, Frank Bernard, III (Will) – MS4
"Subtle Hippocampal Asymmetry on Magnetic Resonance Imaging in Temporal Lobe Epilepsy"
Mentor: Dr. Lawrence Ver Hoef

Group J

J-1 Allen, Heather Elizabeth (Heather) – MSTP (GS2)
"Role of complement in an alpha-synuclein based mouse model of Parkinson Disease"
Mentor: Dr. David Standaert

J-2 Brosius, Stephanie Nicole (Stephanie) – MSTP (GS1)
"Tyrosine Kinase Inhibitors Sorafenib and Canertinib Inhibit Malignant Peripheral Nerve Sheath Tumor Proliferation and Survival"
Mentor: Dr. Steven Carroll

J-3 Childs, Daniel Self (Daniel) – MS2
"Cocaine experience dynamically alters DNA methylation at plasticity genes within the nucleus accumbens"
Mentor: Dr. David Sweatt

J-4 Cohen, Joshua L. (Joshua) – MSTP (MS2)
"Antidepressive Effects of DNA Methyltransferase Inhibition"
Mentor: Dr. Sarah Clinton

J-5 Figge, David Anthony (David) – MSTP (MS2)
"Striatal DNA methylation in a rat model of L-DOPA-induced dyskinesia"
Mentor: Dr. David Standaert

J-6 Gaston, David Curtis (David) – MSTP (GS5)
"Oncolytic HSV-1 Expressing Interleukin-15 for Brain Tumor Therapy"
Mentor: Dr. Richard J. Whitley

J-7 Guzman Karlsson, Mikael Carl Gustav (Mikael) – MSTP (GS1)
"The Involvement of DNA Methylation in Conditioned Taste Aversion"
Mentor: Dr. David Sweatt

J-8 Raborn, Joel (Joel) – MS2
"Pediatric Medulloblastoma Cells from a Patient-Derived Xenograft Contain a Stem Cell Fraction that is Sensitive to Engineered Herpes Simplex Virus Therapy"
Mentor: Dr. Gregory K Friedman

J-9 Rutherford, John Matthew (Matt) – MSTP (GS4)
"Hyperexcitability in hippocampus with loss of MeCP2: Pathophysiology of Rett syndrome"
Mentor: Dr. Lucas Pozzo-Miller

J-10 Shah, Nishi M.- MS2
"Myristoylated Alanine Rich C-kinase Substrate (MARCKS) is a Key Regulator of Cell Survival in Glioblastoma"
Mentor: Dr. Christopher Willey

J-11 Sultan, Faraz (Faraz) – MSTP (GS4)
"Genetic deletion of gadd45b, a regulator of active DNA demethylation, enhances long-term memory and synaptic plasticity"
Mentor: Dr. J. David Sweatt

J-12 Watkins, Stacey Michelle (Stacey) – MSTP (GS4)
"Invading glioma cells disrupt the neurovascular coupling mediated by astrocytes"
Mentor: Dr. Harald Sontheimer

Group K

K-1 Dunlap, Quinn Alexander (Quinn) – MS2
"Primary rabbit nasal septal epithelial cultures for studies of cystic fibrosis sinus disease"
Mentor: Dr. Bradford Woodworth

K-2 Haritha, Abhishek (Abhishek) – MS2
"Influenza M2 alters Cystic Fibrosis Transmembrane Conductance Regulator Activity in Human Bronchial Epithelial Cells"
Mentor: Dr. Sadis Matalon

K-3 Honasoge, Avinash Vinayak (Avinash)- MSTP (GS2)
"Expression and function of proton-permeable cation channels in human glioma cells"
Mentor: Dr. Harald Sontheimer

K-4 Kadish, Robert (Robert) – MS2
"Recovery of CFTR Function in vitro and in vivo after Smoking Cessation"
Mentor: Dr. Steven M. Rowe

K-5 Laufer, Vincent Albert (Vincent) – MS2
"Characterization of Astrocytes Co-Cultured with Human Glioblastoma Multiforme Cells"
Mentor: Dr. Harald Sontheimer

K-6 Meadows, Jarrod Phillip (Jarrod)- MSTP (GS1)
"Epigenetic Control of Homeostatic Plasticity"
Mentor: Dr. John J Hablitz

K-7 Nwaobi, Sinifunanya Elvee (Sini) - MSTP (GS3)
"Epigenetic Regulation of Kir4.1 During Normal Astrocytic Development"
Mentor: Dr. Michelle Olsen

K-8 Ranganath, Neel Kiran (Neel) – MS2
"CFTR activation by the solvent ethanol: Implications for CF drug testing and delivery"
Mentor: Dr. Bradford Woodworth

K-9 Robert, Stephanie Marie (Stephanie) – MSTP (GS1)
"Two classes of gliomas defined by the expression and function of distinct Cystine/Glutamate Transporters"
Mentor: Dr. Harald Sontheimer, PhD

Group L

L-1 Antipenko, Sergey (Sergey) – MSTP (MS2)
"Correction of Sickle-Cell Mutation and Differentiation of Human Embryonic Stem Cells to Hematopoietic Progenitors"
Mentor: Dr. Tim Townes

L-2 Cunningham, Rachel Elizabeth (Rachel)- MS4
"Development of novel stem cell based treatment of burn wounds"
Mentor: Dr. Robert J. Christy

L-3 Hull, Travis David (Travis) – MSTP (GS2)
"Heme Oxygenase-1 Expression Protects the Myocardium from Cre-Induced Systolic Dysfunction"
Mentor: Drs. James George and Anupam Agarwal

L-4 Ma, Elizabeth Yean (Elizabeth) – MSTP (MS2)
"Potential Role of Kinases in Fetal to Adult Globin Gene-switching"
Mentor: Dr. Tim Townes

L-5 McKay, Jack Edward (Jack) – MS3
"Increasing Vascularity to Improve Healing of Segmental Defects"
Mentor: Dr. Shawn Gilbert

L-6 Osula, Daniel Oluwatomidimu (Daniel) – MS2
"Age and Hormone Status Dependence of Anti-Inflammatory Effect of Estrogen in Macrophages Derived from Pre- and Post-menopausal Women"
Mentor: Dr. Fadi Hage

L-7 Peden, Bradley Wilson (Brad) – MS2
"The Cardiac Circadian Clock Regulates Myocardial Glycogen Metabolism"
Mentor: Dr. Martin Young

L-8 Powell, Stephen Lee (Stephen) – MS3
"Biomarkers of Inflammation, Endothelial Cell Activation, and Chronic Kidney Function and Risk of Acute Kidney Injury After Sepsis"
Mentor: Dr. Henry E. Wang

L-9 Waits, George Sidney, IV (George) – MS2
"Anti-inflammatory Gene Expression of a Nitric Oxide Releasing Nanomatrix for Cardiovascular Stents"
Mentor: Dr. Ho-wook Jun

L-10 Webb, William Mitchell (William) – MSTP (MS1)
"Varying Residue Number of Polyglutamate Domains Facilitates Differential Loading to and Release from Hydroxyapatite and Allograft Bone"
Mentor: Dr. Susan L. Bellis

Group M

M-1 Appell, Lauren Elizabeth (Lauren) – MS2
"Development of a Chart Abstraction Tool and Pilot Data Collection to Compare Microsize MIs to Usual MIs"
Mentor: Dr. Todd M. Brown

M-2 Bynum, Jennifer Porter (Jennifer)- MS4
"Prospective Evaluation of HIT Expert Probability (HEP) Scoring System: A Comparison of the HEP Score, Warkentin's 4Ts, and Laboratory Test Results"
Mentor: Dr. Jill Adamski

M-3 Bynum, Jennifer Porter (Jennifer) – MS4
"Institution of a Novel Testing Strategy to Reduce Misdiagnosis of Heparin-Induced Thrombocytopenia"
Mentor: Jill Adamski

M-4 Ehlinger, Megan Colleen (Megan) – MS2
"Survey of Heart Rhythm Specialists Hopes to Gain New Information on Genetic Services Offered to Long QT Syndrome Patients"
Mentor: Dr. Nathaniel Robin

M-5 Oliver, James Caleb (James) – MS4
"The success of blood management programs depends on an institution-wide change in transfusion practices"
Mentor: Dr. Marisa Marques

M-6 Oliver, James Caleb (James) – MS4
"Can we predict the need for PRBC transfusions based on current utilization?"
Mentor: Dr. Marisa Marques

M-7 Ozaki, Masayo (Masayo) – MS2
"Identification of sudden deaths due to Chagas disease in an indigenous community in Bolivia"
Mentor: Dr. Caryn Bern

M-8 Patel, Pratik Prafulchandra (Pratik) – MS3
"Quantification of Pulmonary/Systemic Shunt Ratio by Single-Acquisition Phase-Contrast Cardiovascular Magnetic Resonance"
Mentor: Dr. Steven G. Lloyd

M-9 Raper, Jaron Drew (Jaron) – MS2
"Urine Output Changes Associated with Post-Cardiac Arrest Therapeutic Hypothermia"
Mentor: Dr. Henry E. Wang

Abroms, Sarah Rachel (Sarah)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Other
Advisor	German Henostroza
Abstract Approved By Advisor	Yes
Co-Authors	Sarah Abroms, Sally Trollip, Andrew O Westfall, Jennifer Harris, Eleanor Turnbull, Nzali Kancheya, Peter Mwaba, Nathan Kapata, Stewart Reid
Title	Tuberculosis screening practices among newly enrolled HIV-infected patients at three HIV clinics in Lusaka, Zambia

Abstract

Background: At the time of this study, Zambian TB screening in HIV-infected patients followed the WHO 2009 guidelines, which recommends TB screening in HIV-infected patients with cough greater than 2 weeks. In 2011, the WHO released recommendations that all HIV-infected persons with any cough, fever, weight loss or night sweats should be screened for TB. To better understand current screening systems and the implications for adopting the WHO recommendations in Zambia, we reviewed charts at three Lusaka HIV clinics. *Methods:* A retrospective chart review was performed. All new enrollees to HIV care at three clinics in Lusaka between June and December 2009 were selected. Demographic data, history of TB, TB symptoms, diagnostic tests, and diagnostic outcomes were collected. A descriptive analysis was performed. *Results:* A total of 1784 patients were included in the analysis, of whom 372 were screened and 199 were diagnosed with TB. The median age was 33 years, 59% female, 10% history of TB, the median BMI 19.4, and the median CD4 count 169. 36% of patients were screened at Clinic 2, compared to 12% at Clinic 3 and Clinic 1. Patients most likely to be screened presented with shortness of breath (70%) and hemoptysis (86%). Overall, 56% of the most symptomatic patients (cough plus three or more symptoms) were screened. In bivariate analyses, lower CD4 cell count and BMI were associated with greater odds of being screened, but in multivariable analyses only BMI was associated at Clinic 3 and Clinic 2, whereas only CD4 was associated at Clinic 1. Only cough was independently associated in multivariate analysis at *all* sites. The factors associated with being diagnosed with TB in the multivariable models were having a history of TB, lower CD4 counts, and reporting shortness of breath. *Conclusions:* TB screening practices in HIV-infected patients vary by clinic, highlighting the need to standardize screening practices. Continuous education of typical TB symptoms and reinforcement of guidelines through mentoring could improve the diagnosis of TB in HIV-positive patients.

Addis, Dylan Robert (Dylan)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Henry E. Wang, MD, MS
Abstract Approved By Advisor	Yes
Co-Authors	Binh C Vu, Jessica R Bradford, Jordan Morgan, Joel Rodgers, John W Baddley, Henry E Wang
Title	Accuracy of Discharge Diagnoses for Identifying Sepsis Hospitalizations

Abstract

Introduction:
While widely used for characterizing sepsis epidemiology, there have been only limited efforts to validate the identification of sepsis through ICD-9 hospital discharge diagnoses.

Hypothesis:
Hospital discharge diagnoses accurately identify sepsis hospitalizations.

Methods:
We used multicenter hospital data from the national REasons for Geographic and Racial Differences in Stroke (REGARDS) study, a 30,239 subject population-based cohort. We randomly selected sepsis events over a maximum 8-year observation period. We defined “gold-standard” sepsis events as hospitalization for a serious infection with the presence of ≥2 SIRS criteria, determined through manual review of admission and Emergency Department records. We defined “gold-standard” severe sepsis as hospitalization for sepsis with ≥1 organ dysfunction. For each hospitalization, we identified discharge diagnoses for sepsis (ICD9 038, 020, 790.7) or severe sepsis (ICD9 infection + ICD9 organ dysfunction). Using the gold standard definitions, we determined the diagnostic accuracy of discharge diagnoses for sepsis and severe sepsis.

Results:
We selected medical records for 370 serious infection hospitalizations encompassing 156 gold-standard sepsis and 122 severe sepsis. Discharge diagnoses correctly identified 56 (35.9%) of 156 sepsis; sensitivity 27.6%, specificity 93.9%, PPV 76.8%, NPV 64.0%. Discharge diagnoses correctly identified 88 (72.1%) of 122 severe sepsis; sensitivity 41.8%, specificity 85.1%, PPV 58.0%, NPV 74.8%. When stratified by infection type (lung, kidney, skin, gastrointestinal), sensitivity for sepsis remained low (range 4.4-40.0%), while specificity remained high (90.0-98.8%). When stratified by infection type, sensitivity for severe sepsis remained low (range 36.8-43.5%), while specificity remained high (76.5-90.2%).

Conclusion:
Using data from the REGARDS study, discharge diagnoses underestimated the number of sepsis and severe sepsis cases presenting to the hospital. Studies of sepsis epidemiology must account for the limitations of hospital discharge diagnoses.

Allen, Heather Elizabeth (Heather)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	David Standaert
Abstract Approved By Advisor	Yes
Co-Authors	Heather Allen, Caitlin Thomas, Ashley Harms, David Standaert
Title	Role of complement in an alpha-synuclein based mouse model of Parkinson Disease

Abstract

Parkinson disease (PD) is a neurodegenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra (SN) and aggregates of alpha-synuclein (α -syn). In human PD and animal models, chronic neuroinflammation is important for dopaminergic neurotoxicity, however, the mechanism by which α -syn-induced neuroinflammatory changes lead to neurotoxic effects is unclear. This study investigates a role for the complement system in a-syn-based models of PD.

We used a mouse model of PD where α -syn is overexpressed in the substantia nigra using an adeno-associated viral vector (AAV-SYN). We assessed complement component production via qPCR, ELISA and immunohistochemistry at 2 and 4 weeks post-injection in wildtype mice. We assessed IgG deposition and microglial activation 4 weeks post-injection of AAV-SYN in wildtype and C5-deficient mice (C5-/-).

In wildtype mice, at 2 and 4 weeks post-injection, we observed induction of C3 mRNA. C3 protein was present in both AAV-GFP and AAV-SYN tissue 4 weeks and 6 months post-injection as observed by ELISA and immunohistochemistry. At 4 weeks, distribution of C3 staining in AAV-SYN animals was similar to AAV-GFP controls. At 6 months, there appears to be an increasing concentration of C3 in association with dopaminergic neurons. We observed little evidence for C5 presence in our mouse model: C5 mRNA was undetectable at 2 or 4 weeks post injection of AAV-SYN, C5 protein was not detected by western blot or immunohistochemistry, and C5a ELISA did not detect C5 cleavage in AAV-SYN injected animals. In C5-/- mice injected with AAV-SYN, the inflammatory response appeared unchanged.

Our observations suggest enhanced expression of C3 in this α -syn-based mouse model of PD. We found no evidence for C5 component participation in this PD model. It will be important to determine whether enhanced expression of C3 contributes to dopaminergic cell loss.

Antipenko, Sergey (Sergey)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Tim Townes
Abstract Approved By Advisor	Yes
Co-Authors	Li-Chen Wu, Dewang Zhou
Title	Correction of Sickle-Cell Mutation and Differentiation of Human Embryonic Stem Cells to Hematopoietic Progenitors

Abstract

Sickle-cell Disease is caused by a point mutation of the β-globin chain in hemoglobin. Under low oxygen conditions red blood cells form into a characteristic sickle shape, which also decreases their elasticity, leads to occlusion, and causes ischemia. Anemia also results from destruction of these red blood cells.

We have taken two different approaches to attempt to correct the Sickle-cell phenotype. The first approach is to correct one of the β^S genes by replacing it with the correct β^A gene via electroporation. This would be done in skin fibroblasts which would be reprogrammed to induced pluripotent stem (iPS) cells, which would then be differentiated to hematopoietic progenitors and transplanted into irradiated patients.

The second approach would be to activate fetal hemoglobin expression which prevents sickling under low oxygen conditions. This can be achieved by knocking down KLF1 which modifies local chromatin structure to permit β-globin transcription. This can also be achieved by knocking down kinases that activate KLF1 expression essentially having the same effect.

Correction of genetic mutations with the use of viruses in embryonic stem cells or fibroblasts reprogrammed to induced pluripotent stem cells has great clinical promise if certain hurdles can be jumped. These include efficient gene targeting as it was unsuccessful in this study, improving efficiency of reprogramming to iPS cells, and improving differentiation efficiency which was very low all while being compliant with GMP requirements for human use.

As well as exploring the mechanism of fetal to adult hemoglobin switching, looking at the kinases that regulate KLF can have clinical relevance for drug targeting. In clinical cases of sickle-cell patients with persistent fetal hemoglobin, there is no sickling of red blood cells under low oxygen conditions and all complications of sickle-cell disease seem to be avoided.

Appell, Lauren Elizabeth (Lauren)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	Dr. Todd M. Brown
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Development of a Chart Abstraction Tool and Pilot Data Collection to Compare Microsize MIs to Usual MIs

Abstract

Introduction. The clinical significance of myocardial infarction (MI) with small elevations in cardiac troponin, or "microsize MI," is currently unknown due to a lack of published literature on the topic. We developed a tool in Microsoft Excel to facilitate the abstraction of data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study to show that these microsize MIs deserve clinical attention. This chart abstraction tool is one part of a larger clinical cohort study of microsize MIs.

Objective. In order to further develop research on microsize MIs, our goal was to develop a chart abstraction tool. We have since used this tool in a pilot data collection.

Methods. The chart abstraction tool was developed after deciding upon the categories and subcategories necessary for abstraction, using Microsoft Excel to assist in chart abstraction from the REGARDS database. We then examined 10 participants in the REGARDS study using the chart abstraction tool.

Results. Using the chart abstraction tool, we gathered data from the REGARDS database including admission medication, discharge medication, diagnoses present upon admission, new diagnoses made upon discharge, and relevant lab data in order to compare the microsize MI group to the usual MI group. We are waiting on comparisons between the groups for our 10 participants. We anticipate that the chart abstraction tool will expedite the collection of data that will demonstrate the clinical relevance of microsize MIs.

Conclusions. The abstraction tool we have developed will allow us to demonstrate the clinical value of microsize MIs. The data we will gather using this tool will allow us to compare microsize MIs to usual MIs to show the relevance of microsize MIs, which is why developing an abstraction tool was a necessary allocation of time and resources in the development of this overall project.

Azerf, Saji Pierce (Saji)

Project Length	Short
Prior Research Experience	No
Funding Source	Cunningham Fellowship
Advisor	Dr. Hussein Abdullatif
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Utilization of 17-Hydroxyprogesterone Levels in Newborn Screenings to Determine Congenital Secondary and Tertiary Adrenal Insufficiency

Abstract

Newborn screening captures a broader public health perspective by universally testing the population of asymptomatic and presymptomatic infants for numerous congenital conditions. All newborns in the United States are checked for certain medical conditions, such as, congenital hypothyroidism and congenital adrenal hyperplasia. These screenings are intended to discover problems early, allowing prompt treatment, preventing disabilities, and reducing mortality. Screening for these congenital conditions has allowed for earlier medical management and lifestyle modifications.

17-Hydroxyprogesterone (17-OHP) is a natural progesterone that is produced during the production of glucocorticoids and sex steroids. 17-OHP levels are utilized in newborn screenings as an indicator of congenital adrenal hyperplasia (CAH) due to specific gene mutations and are associated with cortisol-related enzyme deficiencies. Because elevated 17-OHP levels detect the common form of CAH, a 21-hydroxylase deficiency, the rarer 17-hydroxylase deficiency is overlooked and diagnosed much later in life with the discovery of hypertension, hypokalemia, ambiguous genitalia, and a lack of pubertal progression. This rare form of CAH causes the adrenal glands to not produce enough of its hormones. While there are different outcomes in the newborn, low levels of 17-OHP are present in 17 hydroxylase deficiency, secondary, and tertiary adrenal insufficiency.

Potentially, newborns with abnormally low levels of 17-OHP could provide health practitioners an indicator of congenital secondary and tertiary adrenal insufficiency. Low 17-OHP numbers have not been reported currently as a marker of disease; however, these low 17-OHP levels may provide a useful and vital tool in newborn screenings. To determine the number of low level 17-OHP newborns that were in Alabama, pediatricians around the state were contacted through mail and a follow-up phone call. These research methods yielded one newborn that fit the criteria and future newborns with these inclusion criteria may arise.

Baker, Brandi (Brandi)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Department of Medicine Fellowship
Advisor	S. Louis Bridges, Jr. MD, PhD
Abstract Approved By Advisor	Yes
Co-Authors	Xiangqin Cui, Zenoria Causey, Lauren Parks, Martin R Johnson, Maria Danila, Richard J Reynolds, S. Louis Bridges, Jr
Title	Low Baseline Expression of Toll-Like Receptor and Interferon Pathway Genes Correlates with Decreased Joint Destruction in Rheumatoid Arthritis

Abstract

Rheumatoid Arthritis (RA) is a chronic autoimmune disease affecting ~0.5-1% of the population that primarily targets synovial joints, causing progressive destruction of articular cartilage and erosions of bone. One of the major problems facing physicians treating patients with RA is distinguishing patients who will have relatively mild disease from those who will have severe joint damage. Identification of predictive gene expression profiles to allow stratification of patients with early RA according to risk of radiographic severity would improve quality of life for RA patients and benefit society by substantially lowering morbidity and treatment costs. Furthermore, genetic influences on radiographic severity of RA may vary by race/ethnicity, and African Americans are significantly under-represented in RA research studies. An NIH-funded multicenter registry, the Consortium for the Longitudinal Evaluation of African Americans with Early RA (CLEAR), was created by Dr. Bridges and his colleagues that contains extensive demographic, socioeconomic, clinical and radiographic information on ~1,100 African American patients with RA. The CLEAR biorepository contains samples of genomic DNA, RNA from peripheral blood mononuclear cells (PBMCs), plasma and serum, allowing for a comprehensive analysis of factors influencing disease susceptibility and severity. Using quantitative real-time PCR analysis, we tested the hypotheses that gene expression in Peripheral Blood Mononuclear Cells (PBMCs) differ in: a) severe vs mild radiographic damage; b) early or longstanding disease; c) RA vs control in African American patients. Our data suggests that low baseline expression of genes in the Toll-like receptor and interferon pathways correlate with reduced radiographic severity in the long-term. Therefore, assessment of these genes may help appropriately stratify patients into low- and high-risk populations and allow for a more personalized approach to treatment in African American patients with RA.

Barrett, Olivia Claire (Olivia Claire)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Dr. O. Lee Burnett III
Abstract Approved By Advisor	Yes
Co-Authors	Michael G. Conner, Yufeng Li, Jacob Michael Estes, Jennifer F. De Los Santos
Title	Hormone receptor expression and risk of recurrence in patients with high-risk endometrial carcinoma treated with chemotherapy.

Abstract

Background: Poor long-term survival in high-risk endometrial cancer patients attests to a need for new therapeutic strategies. Estrogen (ER) and progesterone receptors (PR) prevalence among high-risk endometrial carcinomas has not been systematically studied and is a target to which individualized therapies may be tailored.

Methods: 41 women with high grade, stage III/IV and/or aggressive histology endometrial cancer who received post-hysterectomy chemotherapy were identified. Patient, tumor and treatment characteristics were recorded. Immunohistochemical staining of ER and PR was scored on a 0-4 scale incorporating intensity and extent of expression. Receptor-positivity was defined as a score of >= 2**.** Univariate and multivariate logistic regression analysesand the Cox proportional hazards model were performed to examine hormone receptor expression and recurrence risk.

Results: Median age at surgery was 59 years (range 34-79). Median follow up time was 39 months (range 1-82). Recurrence occurred in 21 women (51%) with median time to first recurrence of 19 months (range 1-71). 22 cancers (54%) were ER+ and 21 (51%) PR+. Median ER and PR expression was 2 and 2, respectively (range 0-4). While ER and PR were not independent factors for recurrence, on multivariate logistic regression analysis ER and PR as continuous values showed recurrence associated with greater ER expression (p = 0.0836) and lesser PR expression (p = 0.0986). Cox proportional hazards model supported the association between increasing ER and decreasing PR with shorter recurrence free survival (p=0.0034, p = 0.0021). An increase in ER score of 1 corresponded to a hazard ratio (HR) of 2.647 (95% CI 1.38-5.08); an increase in PR score of 1 corresponded to a HR of 0.362 (0.19-0.693).

Conclusions: More than 50% of high-risk endometrial cancers in this retrospective cohort receiving cytotoxic chemotherapy expressed positive hormone receptors. Multivariate analyses of hormone receptors suggest increased recurrence with discordant ER and PR expression.

Barrington, David Allen (David)

Project Length	Short
Prior Research Experience	No
Funding Source	T35
Advisor	Dr. Shawn Gilbert, MD
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Obesity and Physeal Fractures

Abstract

Introduction

As the American obesity epidemic continues to plague the country, we are learning more about the negative impact obesity has on all aspects of health. As we look more carefully at pediatric obesity we have growing cause for concern reagarding the negative impact of obesity on childhood health. Obesity has been linked to musculoskeletal complications, such as Slipped Capital Femoral Epiphysis (SCFE) and tibia vara. Furthermore, obese children may be at increased risk of fracture.

In the current study, we investigate the differences in fracture patterns and management of distal radius fractures between obese and non-obese pediatric patients. We hypothesized that obese patients are more likely to sustain physeal fractures when suffering injuries to the distal radius than non-obese patients. We also suspected obese patients would have greater difficulty with cast management, suffering more frequent loss of reduction following treatment. We performed a retrospective review of the distal radius fracture registries from a level I pediatric trauma center in Birmingham, Alabama.

Methods

For the 219 patients included in the study, weight, age, and ethnicity of patient, were recorded as well as fracture location (physis or metaphysis) and mechanism of injury. Upon radiographic review, displacement and angulation of the fractures were recorded at the time of injury, post reduction, and at follow up intervals of one, two, and six weeks. Physeal fractures were classified according to the Salter-Harris fracture classification system Radiographs were read by a medical student after training by a pediatric orthopedist. A selection of films were also classified by the principal investigator to evaluate inter-observer agreement.

Results:

Our data is currently being analyzed and reviewed by a statistician, and we expect to have the results by the end of the week.

Basu, Sambita (Sambita)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center Fellowship
Advisor	James Matthew Luther, M.D., M.S.C.I.
Abstract Approved By Advisor	Yes
Co-Authors	Ginger L. Milne, Ph.D.
Title	Assessment of sEH Activity by Oxylipin Metabolites: Relevance to Diabetes

Abstract

Arachidonic acid derivatives include prostaglandins, leukotrienes, and epoxyeicosantrienoic acids (EETs). EETs are formed by cytochrome P450 (CYP450) enzymes, specifically the CYP2C or CYP2J epoxygenases, and are degraded to biologically inactive dihydroxyeicosatetraenoic acids (DHETs) by epoxide hydrolases. EETs have beneficial effects on glucose metabolism *in vitro* and *in vivo*. Increased concentrations of 5,6-EET induces insulin release by isolated pancreatic islet cells. EETs also prevent hyperglycemia *in vivo* by preserving islet mass through prevention of apoptosis. Blocking EET degradation with a soluble epoxide hydrolase (sEH) inhibitor or sEH knockout increases glucose-stimulated insulin secretion. Therefore, EETs may attenuate the development of diabetes in high-risk individuals (those with an impaired glucose tolerance or with impaired fasting glucose). sEH activity can be assessed by measuring the ratio of EETs to DHETs in plasma. EETs, however, are relatively unstable and found in low amounts in plasma. CYP2C and CYP2J epoxygenases oxidize linoleic acid, yielding 9,10- and 12,13-epoxy-octadecenoic acids (EpOMEs), which sEH also degrades to dihydroxy-octadecenoic acids (DHOMEs). As EpOMEs and DHOMEs circulate in higher levels than EETs and DHETs, plasma EpOME/DHOME ratio has provided a more reliable measure of sEH activity *in vivo*. This study tested the hypothesis that sEH activity is associated with impaired insulin secretory response in humans, using the ratio of EpOME/DHOME in plasma to assess endogenous sEH activity. Development and validation of the assay to quantify EpOME/DHOME in human plasma was the primary focus of this research experience. Optimization of collection and processing conditions for plasma was performed in order to assess sEH activity across studies. Blood was collected into citrate, EDTA, and as serum and underwent solid phase extractions using Waters Oasis HLB 60 mg SPE cartridges. Analysis was conducted by UPLC/MS/MS by the Vanderbilt Eicosanoid Core. Samples were quantified and calibrated with deuterated standards (Cayman) for 9,10 EpOME, 12,13 EpOME, 9,10 DiHOME, 12,13 DiHOME. EpOME degradation into their corresponding DHOME species was noted using previously published methods; modification of the protocol by removal of acidic components in both the solid phase extraction and UPLC/MS/MS methods improved epoxide yield. Ongoing studies include synthesis of EpOME standards, optimization of the extraction protocol, optimization of various collection methods (plasma, serum), and determining the stability of stored plasma (freeze/thaw cycles). sEH inhibitors are presently in development for treatment of hypertension, and may provide additional beneficial metabolic side-effect profiles, including glycemic control. This LC/MS method to quantify the ratio of EpOME/DHOME as a measure of sEH activity will be used to assess sEH activity, and to correlate with glucose tolerance, insulin resistance, and insulin secretion measurements in humans.

Berry, Ryan D. (Ryan)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Anath Shalev
Abstract Approved By Advisor	Yes
Co-Authors	Gu Jing
Title	Thioredoxin-interacting protein regulates beta cell islet amyloid polypeptide expression.

Abstract

Beta cell apoptosis is a key factor the pathogenesis of both Type 1 and Type 2 diabetes mellitus (T1/2DM) (Butler *et al*., 2003). In T2DM, apoptosis can be triggered by one of two signaling pathways, mitochondrial death or endoplasmic reticulum stress (Cnop *et al*. 2005). A key mediator of the mitochondrial death pathway is Thioredoxin interacting protein (TXNIP) which binds to thioredoxin and allows the accumulation of reactive oxygen species (Saxena *et al*, 2010). This protein is of such importance that when it is knocked out in mice it prevents β-cell death and protects against T2DM in the presence of obesity (Chen *et al*. 2008; Chen *et al*. 2010). TXNIP has many regulatory functions and has recently been tied to inflammasome activation and interleukin-1β production, two major factors in β-cell apoptosis in T1DM (Zhou, 2010). We have now shown that stable TXNIP over expression in INS-1 cells positively regulates the expression of islet amyloid polypeptide (IAPP). IAPP aggregates into insoluble amyloid fibrils and deposits are found in islets of most T2DM patients and thought to contribute to beta cell damage. We also establish that this regulatory relationship occurs via the transcription factor FOXA2 by showing that IAPP promoter activity is diminished significantly in INS-TXNIP cells with FOXA2 knock down compared to INS-TXNIP cells transfected with scrambled control. Thus, these findings reveal yet another mechanism by which TXNIP might contribute to beta cell loss of T2DM.

Bhullar, Sukhkamal Kaur (Sukhkamal)

Project Length	Short
Prior Research Experience	Yes
FundingSource	Other
Advisor	Dr. Warner K. Huh
Abstract Approved By Advisor	Yes
Co-Authors	Dr. Jared Roberts
Title	Intra-Operative Respiratory Dynamics in Obese Patients Undergoing Robotic Gynecological Surgery

Abstract

OBJECTIVE: To evaluate intra-operative respiratory dynamics in obese patients undergoing robotic gynecological surgery.

METHODS: This was a retrospective study of obese women with a BMI greater than or equal to 30 undergoing robotically assisted surgeries at University of Alabama at Birmingham Department of Obstetrics and Gynecology. The surgeries included, but were not limited to, total hysterectomies with bilateral salpingoophorectomies, omentectomies, pelvic and para-aortic lymph node dissections, myomectomies, and microsurgical tubal reanastomoses. Initially, 770 patients undergoing robotically assisted surgeries in the departments of Ob/Gyn and Gyn/Onc between 2006 and 2011 were chosen. Patients were further segregated based upon BMI calculations and 417 patients were found to have a BMI greater than or equal to 30. Extensive chart review was completed to compile data on various parameters including past medical history, social history, gynecological history, past surgical history, pre-op diagnosis, post-op complications, estimated blood loss, mode of removal, conversion to laparotomy, weight and dimensions of uterus, post-op diagnosis, pathology, pre-op/post-op hematocrit, length of stay, and last follow up visit. Furthermore, surgical anesthesia records were studied and the following parameters and mean values were noted: length of time in trendelenberg, tidal volume, peak inspiratory pressure, respiratory rate, SPO2, and FIO2. Then, this data was analyzed using the student's t-test and values were compared for patients successfully undergoing robotically assisted surgery vs. patients requiring conversion to exploratory laparotomy.

RESULTS/CONCLUSIONS: Robotic surgery can be tolerated safely in most patients with BMI > or equal to 30 with minimal intra-operative or post-operative complications. Less than 10 patients required conversion to exploratory laparotomy secondary to respiratory complications of surgery or inability to tolerate trendelenburg. Data currently being analyzed.

Blosser, Emily Greenwood (Emily)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Other
Advisor	Casey Weaver, MD
Abstract Approved By Advisor	Yes
Co-Authors	David Randolph, MD, PhD
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 worldwide. 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 mature 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 development directly. The purpose of this study was to determine if maternal antibiotics increase risk of LOS in pups by altering or delaying natural gut colonization, and to determine if restoring conventional flora in pups is sufficient to reverse the effects of maternal antibiotics. We have developed a model of neonatal LOS in which 5 day-old 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. We show that maternal antibiotics increased risk of LOS in pups. PCR for *K. pneumoniae* in stool samples indicates delayed pathogen clearance in surviving pups of antibiotic-treated dams compared to conventional pups. Further, germ free pups monocolonized with probiotic *L. acidophilus* or polymicrobial Altered Schaedler's Flora were not protected from LOS. 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 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
Advisor	Scott Ballinger
Abstract Approved By Advisor	Yes
Co-Authors	Kyle P. Feeley, David G. Westbrook, Douglas R. Hurst
Title	The Role of Mitochondrial Genetic Background in Melanoma Growth

Abstract

Melanoma incidence rates have been increasing for at least 30 years and it is estimated that an additional 76,250 individuals will be diagnosed with the disease in 2012. While presence of metastasis remains the single most important factor in determining prognosis, tumor thickness and mitotic rate also possess a well-documented mathematical relationship with patient outcome. Although several nuclear genes and polymorphisms have been implicated in melanoma susceptibility and progression, a resurgence of interest in the metabolic properties of cancer cells has also generated curiosity surrounding the contribution of mitochondrial genetics to carcinogenesis. Our lab has developed a novel technique to examine this phenomenon in the form of Mitochondrial – Nuclear eXchange (MNX) mice. These mice possess nuclear DNA from one inbred mouse strain coupled with mitochondrial DNA from another. Preliminary studies in our lab have demonstrated that certain pre-existent mitochondrial DNA polymorphisms may influence tumor latency and growth rate. Similarly, we hypothesized that melanoma growth and progression are regulated by the mitochondrial haplotype of the parent organism. To address this hypothesis, we injected B16F1 mouse melanoma cells into the flanks of syngeneic C57BL6 (B6) wild-type mice and those carrying CH3 mouse mitochondria ($B6_nCH3_{mt}$ MNX). Our results indicate that the latency period preceding development of grossly measurable tumors significantly differed between $B6_nB6_{mt}$ and $B6_nCH3_{mt}$ MNX mice. Based on these findings, mitochondrial haplotype may prove to be an important prognostic indicator for individuals diagnosed with malignant melanoma.

Brosius, Stephanie Nicole (Stephanie)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Dr. Steven Carroll
Abstract Approved By Advisor	Yes
Co-Authors	Steven Carroll
Title	Tyrosine Kinase Inhibitors Sorafenib and Canertinib Inhibit Malignant Peripheral Nerve Sheath Tumor Proliferation and Survival

Abstract

Malignant peripheral nerve sheath tumors (MPNSTs) are the most common cause of death in patients with the genetic tumor susceptibility disorder neurofibromatosis type-1 (NF1). These highly aggressive sarcomas are mainly treated via resection, as radiotherapy is ineffective and no chemotherapeutics have been identified. Therefore, the development of targeted chemotherapeutics is critical to improving the survival of patients diagnosed with MPNSTs. Our lab has shown that dysregulated growth factor signaling by the Schwann cell mitogen neuregulin-1 (NRG1), via the erbB3 and erbB4 receptor tyrosine kinases, promotes the pathogenesis of MPNSTs. Treatment of tumor cells with the pan-erbB inhibitor canertinib leads to a decrease in tumor proliferation. However, we hypothesize that multiple receptor tyrosine kinases are co-activated in these tumors, thereby requiring combinatorial therapy to prevent the development of resistance. Here we test the efficacy of five receptor tyrosine kinase inhibitors in different MPNST cell lines via calcein-AM survival assay. These drugs include canertinib; sorafenib, which inhibits platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR) and Raf kinases; crizotinib, which inhibits c-Met/hepatocyte growth factor receptor (HGFR) tyrosine kinase; sunitinib, which inhibits Kit, PDGFR and VEGFR; and nilotinib, which inhibits PDGFR, c-kit and Bcr-Abl. Our data show that multiple different growth factor receptors promote tumorigenesis, with erbB membrane tyrosine kinases being of primary importance. This suggests that inhibitors of the secondary cascades such as sorafenib and crizotinib may form an effective combinatorial therapy for treatment of MPNSTs when used with the erbB inhibitor canertinib.

Bryant, Mary Katherine (Mary)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Derek DuBay
Abstract Approved By Advisor	Yes
Co-Authors	David Dorn, Jessica Zarzour, Kevin Smith, MD, David Redden, Souheil Saddekni, Ahmed Kamel, Devin Eckhoff, Derek Dubay
Title	Radiographic predictors of chemoembolization-induced hepatocellular carcinoma necrosis

Abstract

Background: Transarterial chemoembolization (TACE) is the recommended oncologic treatment for non-transplantable, non-resectable, non-ablatable hepatocellular carcinoma (HCC). TACE is indicated in roughly 50% of all new HCC diagnoses. Radiographic features associated with a favorable response to TACE are poorly defined for patients with HCC.
Hypothesis: We hypothesize that the following HCC characteristics will be associated with a >90% or complete tumor necrosis: smaller tumor size, peripheral tumor location, arterial-phase tumor enhancement and portal venous-phase tumor washout.
Methods: All first TACE interventions for HCC performed at UAB from 2008 – 2012 were retrospectively reviewed. Only patients with a pre-TACE CT scan and a post-TACE CT scan within 75 days of the intervention were included in the analyses (n=115). HCC tumor response to TACE was quantified via the modified RECIST criteria (a National Cancer Institute-recommended scale for measuring solid tumor response to therapies). Univariate and multivariable analyses were constructed to examine the association between response variables.
Results: On univariate analysis, arterial enhancement ($p=0.046$), smaller tumor size ($p<0.001$) and peripheral tumor location ($p=0.015$) were associated with a >90% or complete tumor necrosis whereas only smaller tumor size (OR 0.72/cm, 95% CI 0.58 - 0.89, $p<0.002$) and peripheral location (OR 4.50, 95% CI 1.30 - 150.60, $p=0.018$) were significant on multivariable analysis. Surprisingly, HCC tumor arterial enhancement and portal venous washout were not associated with a >90% or complete tumor necrosis in the entire cohort on multivariable analyses. Arterial enhancement and portal venous washout also were not associated with a >90% or complete tumor necrosis in subgroup analyses of centrally located HCC tumors <5cm (p=ns) and peripherally located HCC tumors <5cm (p=ns).
Conclusions: Peripherally located smaller HCC tumors are most likely to experience a >90% or complete tumor necrosis following TACE. Arterial-phase tumor enhancement and portal venous-phase tumor washout were not predictive of TACE-induced tumor necrosis.

Bynum, Jennifer Porter (Jennifer)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Jill Adamski MD, PhD
Abstract Approved By Advisor	Yes
Co-Authors	David Arndt, Marisa Marques MD
Title	Validation of a New HIT ELISA: Comparison of Two Commercial ELISA kits with a Gold Standard ELISA

Abstract

Background: Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening complication of treatment with heparin products. It is a clinical diagnosis which is supported by ELISA laboratory testing with notably poor specificity. The consequences of HIT diagnosis or misdiagnosis are significant, and because of over-testing with the ELISA, many patients are given a false diagnosis of HIT. 4 index cases of false positive results with the “A”-ELISA kit were discovered at UAB in December of 2010, two of whom underwent multiple plasma exchanges and delayed surgeries. On review, “A”-ELISA was found to have a cross-reactive bovine contaminant, which led to a search for a better test to use at UAB.

Purpose: The goals of this prospective study were to 1) Compare the sensitivity and specificity of “A” vs “B” commercial ELISA kits against an ELISA performed at a national reference lab(RL) and 2) Validate the “B”-ELISA kit for use at UAB.

Methods: For each patient for whom HIT testing was requested between April 22, 2011-July 7, 2011, “A-,” “B-,” and RL-ELISAs were run. The RL-ELISA was used as the gold standard.

Results: 209 total ELISA tests were run in parallel and 16 had confirmed positive results with the RL-ELISA. There were 11 false positives with the “A”-assay, but only 1 false positive with the “B”-assay. 193 patients were negative for HIT antibodies. 2 and 3 false negatives were identified using assay “A” and assay “B,” respectively; however, none of the false negative cases represented clinically significant antibodies. The sensitivity and specificity of the “A”-assay were 87.5% and 94.3%, and for the “B”-assay were 81.3% and 99.5%, respectively.

Conclusion: The “B” HIT assay had less false positive results than the “A”-assay, and while both kits had a similar number of false negative results, these were clinically insignificant.

Bynum, Jennifer Porter (Jennifer)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Other
Advisor	Jill Adamski MD, PhD
Abstract Approved By Advisor	Yes
Co-Authors	David Arndt, Marisa Marques MD
Title	Prospective Evaluation of HIT Expert Probability (HEP) Scoring System: A Comparison of the HEP Score, Warkentin's 4Ts, and Laboratory Test Results

Abstract

Background: Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening complication of heparin treatment. It is a clinical diagnosis; however, the diagnosis is often "supported" by ELISA tests with poor specificity. Because of over-testing with the ELISA, many patients are given a false diagnosis of HIT, and the consequences of HIT diagnosis are significant. The Warkentin's 4Ts probability score has traditionally been used to evaluate the risk of HIT, but a new probability method, the HEP Score, has recently been proposed. Both scoring systems have been validated at UAB and currently all HIT ELISA orders require pre-approval based on 4Ts and HEP scores.

Purpose: The goal of this study was to correlate the 4Ts and HEP scores with HIT laboratory results to determine if one score is superior.

Methods: Each request for HIT ELISA testing between July 2011 and July 2012 was evaluated by applying the 4Ts and HEP methods. Patients with a 4T score ≥ 4 or a HEP score ≥ 2 were tested at UAB using a commercial HIT ELISA test. If the ELISA was positive, a patient sample was sent to a reference lab for functional SRA testing.

Results: By requiring at least one pre-test criterion, the total number of HIT tests was reduced by 57%. By using only the 4T score, HIT testing could be reduced by 60%, missing no clinically significant positive results but not eliminating any false positive results. By using only the HEP score, HIT testing could be reduced by 73%, missing 1 true positive and eliminating 9 false positives. By requiring both pre-test criteria, HIT testing could have been reduced by 76%, missing 1 true positive and eliminating 9 false positives.

Conclusion: The HEP score is superior to the 4Ts in eliminating unneeded testing and false positive results, but it missed one true positive.

Bynum, Jennifer Porter (Jennifer)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Other
Advisor	Jill Adamski MD, PhD
Abstract Approved By Advisor	Yes
Co-Authors	David Arndt, Marisa Marques MD
Title	Institution of a Novel Testing Strategy to Reduce Misdiagnosis of Heparin-Induced Thrombocytopenia

Abstract

Background: Heparin-Induced Thrombocytopenia (HIT) is a potentially life-threatening complication of heparin therapy caused by an antibody-mediated response against heparin and platelet factor-4 complexes. Making a diagnosis of HIT is complex, and two pre-test probability scoring systems, the 4T's and the HIT Expert Probability (HEP), estimate its likelihood and laboratory tests can identify HIT antibodies. ELISA-based assays are widely used but have poor specificity. The ^{14}C-Serotonin Release Assay (SRA) is the "gold standard" HIT test but is only performed at specialized reference labs. Given the low specificity of the ELISA and the ordering practices at UAB, patients are at risk of being misdiagnosed with HIT.

Purpose: The goal of this study was to determine if strict testing criteria may be used to increase the diagnostic accuracy of HIT.

Methods: From May 1-July 7, 2011, all orders for HIT antibody testing were prospectively evaluated via medical record review and application of pre-test models. Since July 2011, orders require pre-approval based on 4T and HEP scores. Data on HIT testing and diagnosis 9 months before and after institution of the new testing strategy were compared.

Results: 158 HIT orders were prospectively evaluated. 53% did not meet testing criteria based on 4T and HEP scores; 18% of these were for heparin naïve patients. 18 positive ELISAs resulted in 18 patients receiving a diagnosis of HIT; however, only one patient had a positive SRA. In the 9 months following implementation of pre-approval based on pre-test scores, the number of tests performed has decreased by 75%, and the number of HIT diagnoses have decreased by 88% (73 based on ELISA vs. 9 based on probability score, ELISA and SRA).

Conclusion: The use of strict testing criteria has increased the diagnostic accuracy of HIT which has improved the quality of patient care at UAB.

Carley, Joseph Anthony, IV (Joe)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Dr. Cheryl McCullumsmith
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Cross-validation of the Novel Linear Assessment of Suicide Risk (LASR) Scale with the Standard Beck Scale for Suicidal Ideation (BSS) in Order to Provide an Updated Measure of Suicidality with a Linear Distribution of Scores for Initial Assessment and Tracking Response to Treatment

Abstract

Suicide is a leading cause of death worldwide and its prevention presents a unique challenge. Of the suicide risk assessment scales, there are few well-validated clinical scales. Of these the BSS is one of the most well-validated however the BSS has several limitations: patients often have difficulty understanding and correctly completing the BSS, the BSS often results in a bimodal distribution of scores (low or high), and the BSS is proprietary and is quite costly for routine use. Therefore, a novel suicide assessment tool was developed with updated language and simplified formatting. The hypotheses being that this would increase completion rates and result in a more linear distribution of scores. The end goal was cross-validate a screening tool with improved differentiation among individuals which also provides a measure to track response to treatment. The methods used to test these hypotheses involved the implementation of routine screening of all psychiatric consults in the UAB's Emergency Department (ED) with both the BSS and the novel LASR scale. The results from 199 dual screens showed increased completion rate and a linear distribution of scores in the LASR with highly correlated scores on chi square descriptive analysis compared to the BSS. The results support the hypotheses in that the LASR has an increased completion rate and shows a linear distribution of scores. These findings also provide cross-validation of the LASR with the well-validated BSS. In conclusion, the LASR scale provides an updated and simplified suicide assessment tool to delineate a range of suicidality in patients; future work will use the LASR in patients over time to demonstrate a graduated response in LASR scores with treatment.

Chen, Chongjia (ChaCha)

Project Length	Short
Prior Research Experience	Yes
Funding Source	American Federation for Aging Research MSTAR Fellowship
Advisor	Tayebeh Rezaie
Abstract Approved By Advisor	Yes
Co-Authors	Tayebeh Rezaie, Scott McKercher, Stuart Lipton
Title	Protective Effects of a Novel Pro-Electrophile in Human Retinal Pigmented Epithelium and a Rat Model of Light-induced Retinal Damage

Abstract

Approximately 11 million Americans currently have age-related macular degeneration (AMD). The disease affects 2% of the population at age 40 and affects 25% of people by age 80. As a result of the aging population in this country, it is estimated that 22 million Americans will have AMD by 2050. Furthermore, treatment of AMD is largely an unmet need: the existing FDA approved therapies treat only a small percentage of individuals, most of whom have end-stage disease.

Oxidation plays a role in causing damage that results in age-related macular degeneration. AMD has been found to progress to late stages due to inadequate neutralization of oxidants and free radicals. Studies have shown that mice deficient in Nrf2, a transcription factor that induces the expression of genes that encode several antioxidant enzymes, develop AMD-like retinal pathology as they age.

Previous studies of a novel compound derived from rosemary, carnosic acid, have shown protective benefits for oxidatively stressed human retinal pigmented epithelium (RPE) cells. Carnosic acid also protects against damage in a rat model of light-induced retinal damage. When carnosic acid is activated by reactive oxygen species, it changes from a pro-electrophile to a quinone that allows Nrf2 to translocate to the nucleus. It is hypothesized that this turns on downstream antioxidant enzymes, protecting both the *in vitro* and *in vivo* models against oxidative damage.

DA-1 is a novel compound, also derived from a natural substance, with a chemical structure similar to that of carnosic acid. DA-1 was found to have protective benefits for oxidatively stressed RPE cells, at levels below significant toxicity. DA-1 also up-regulated expression of antioxidant response element proteins, notably HO1. DA-1 was also shown to be non-toxic for rats with intraperitoneal injections of 10mg/kg. At 10 mg/kg, the compound could be detected in plasma, though it could not be detected in retinal tissue.

Further studies of higher doses of DA-1 should be conducted to determine whether it could be transported to the retina.

Chen, Zsu-Zsu (Zsu-Zsu)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Monika Safford
Abstract Approved By Advisor	Yes
Co-Authors	Susan Andreae, Marquita Lewis, Keri Sewell
Title	Prevalence of beliefs about generic medications in Encourage study participants reporting medication non-adherence.

Abstract

Background:
Medication adherence is suboptimal for individuals with chronic diseases like diabetes. Cost is a major barrier to adherence, but a few reports suggest that lay opinions about generic medications, which cost less than brand name medications, may include several erroneous beliefs. These beliefs were more common in lower income and minority New Yorkers. The extent to which such beliefs are present in the rural South, the area of highest diabetes prevalence in the US, however, has not been reported.

Central Question:
What beliefs about generic medications are prevalent in southern rural Alabama?

Methods:
We included 103 participants in a community-based trial testing the effectiveness of a peer-delivered coaching intervention in improving diabetes outcomes conducted in the Alabama Black Belt, a rural, resource poor area with high poverty. These individuals had reported sub-optimal medication adherence at baseline. Based on themes generated during focus groups with area residents, we constructed a 9-item survey that was administered by telephone.

Results:
The mean age of respondents was 56.5 years, 67% were women and 49% were taking insulin. Fifty-one percent believed that generics do not work as well as brand medications; 54% believed that generics have more side effects; 79% were willing to take generics for a mild condition, but only 53% for a chronic disease like diabetes. Although 94% believed that their doctor changed medicines for the good of their health, only 83% expressed willingness to make changes if it meant taking a larger dosed pill.

Conclusions:
Among these diabetic individuals reporting suboptimal medication adherence, erroneous beliefs about generic medications were highly prevalent, creating barriers to optimal medication adherence.

Childs, Daniel Self (Daniel)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	David Sweatt
Abstract Approved By Advisor	Yes
Co-Authors	Jeremy J. Day, Mercy Kibe, & J. David Sweatt
Title	Cocaine experience dynamically alters DNA methylation at plasticity genes within the nucleus accumbens

Abstract

Epigenetics refers to a set of covalent modifications of chromatin that can impact gene expression without disturbing the primary DNA sequence. One of the most important epigenetic modifications involves methylation of cytosine bases in DNA. DNA methylation can provide enduring transcriptional control over gene expression, thereby making it an intriguing candidate for the regulation of long-term cellular and behavioral memories. Given that drugs of abuse such as cocaine create especially potent memories that support the intractable nature of addiction, we hypothesize that cocaine induces alterations in DNA methylation mechanisms in brain reward regions that critically regulate the transcriptional and behavioral effects of cocaine.

We first examined alterations in gene expression following acute cocaine administration (1 dose, 20mg/kg) using RT-PCR and noted a significant induction of several plasticity related genes known to regulate cocaine sensitization and place preference. At one hour following acute cocaine, there is also downregulation of DNA methyltransferase 3a2 and upregulation of Gadd45b, a gene required for activity induced DNA demethylation. Similarly, repeated cocaine administration (7 daily doses, 20mg/kg) produced transient increases in important plasticity genes. Additionally, repeated cocaine exposure produced a decrease in DNMT3b (an enzyme responsible for de novo methylation of DNA) at 24 hours after cocaine treatment. These results provide novel evidence for modulation of DNA methylation/demethylation machinery in response to acute and repeated cocaine. Next, we evaluated gene specific changes in DNA methylation to see if they correspond to the changes in gene expression observed. Interestingly, there is a locus-specific decrease in DNA methylation within the promoters of several plasticity genes in response to repeated but not acute cocaine administration. These methylation changes persist for at least 24 hours, indicating that changes in methylation outlast the changes in gene expression observed here. These novel findings provide valuable information that advances our understanding of the molecular mechanisms underlying long-term neuroadaptions to cocaine.

Cho, Yun Ju (Janis)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Cynthia J. Brown
Abstract Approved By Advisor	Yes
Co-Authors	Victor W. Sung
Title	The Effect of Apathy on Life-Space Mobility among Older Adults with Parkinson's Disease

Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disease that has both motor and non-motor symptoms. Goal of management in PD is to allow patients to function as normally as possible. Apathy in PD has important prognostic implications and causes significant reductions in activities of daily living. Understanding the correlation between apathy and mobility among PD patients may be helpful for improvement of PD management and diagnosis.

Purpose: To examine the correlation between apathy level and community mobility among patients with PD.

Methods: All English-speaking, non-demented patients with primary PD visiting an outpatient neurology clinic were eligible. Self-reported age, gender, race and duration of PD were collected. Apathy levels were evaluated using the Starkstein Apathy Scale (SAS), which is 14 items questionnaire that has data on acceptable validity and reliability when used with the PD patients. The community mobility levels were assessed using the UAB Life-Space Assessment (LSA). LSA is used to determine a person's usual pattern of mobility during the month preceding the assessment by asking how far and how often the person leaves the residence and the amount of assistance required.

Results: Seventeen patients were recruited. Per self-report, the mean age of the population was 71 years with a range from 51 to 84 years. with 64% being male, 82% white, 12% black, and 6% being asian. Had mean SAS and LSA scores of 10.6 and 60.9, respectively. The average duration of PD is 6.2 years. 64.7% were male and 35.3% were female. The correlation between LSA and SAS had trendline slope of -1.6.

Conclusions: The pilot study showed a slight inverse relationship between apathy and community mobility indicating those with higher levels of apathy had lower life-space mobility. More study can be done to further understand the relationship without confounding variable and with larger patient pool.

Clemons, Jason Lee (Jason)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Other
Advisor	Dr. Nancy Tofil
Abstract Approved By Advisor	Yes
Co-Authors	Nancy Tofil, MD, Med; R. Lynn Holt, MS; Dawn Taylor Peterson, PhD; Jason Clemons, MS IV, MSHES; Amber Youngblood, BSN, RN; Jerri Zinkan, MPH, RN; Marjorie Lee White, MD, MPPM, MEd; Nathaniel Robin, MD
Title	The Use of High Fidelity Simulation in Genetic Counseling and Genetic Medical Education

Abstract

Genetic counselors and geneticists are routinely required to provide patients with abnormal test results or “bad news” as a part of their professional practice. However, there are often limited opportunities for genetic trainees to disclose this type of sensitive information during their training. We hypothesized that simulation would be an effective and valuable resource to use in teaching healthcare providers how to deliver the various components of testing results during genetic patient sessions. The aim of this project was to conduct a pilot study utilizing patient simulation for a high-stakes genetic counseling scenario as an education tool for genetics trainees. A prenatal scenario was developed in which each trainee (3 genetic residents and 5 second year genetic counseling students) had to disclose an abnormal amniocentesis result to a couple at 17 weeks of pregnancy and discuss all available pregnancy management options. Simulation patients were provided scripted guidelines to play the role of the parents. Session observers evaluated the trainees’ communication skills and factual knowledge during the session via a behavioral checklist. Each trainee was observed remotely during the session and was given immediate feedback after the counseling session utilizing a scripted debriefing. Each trainee also completed an open-ended evaluation about the educational experience. Few participants covered all fifteen topics of the checklist. The topics most discussed by the participants were related to genetic, neonatal issues, and early childhood, rather than school age/adult ($p = 0.069$). All of the participants found the simulation activity helpful. The behavioral checklist utilized by reviewers was an effective way to document each trainee’s performance and to provide documentation of the experience. Based on this small study, it appears that patient simulation is an effective educational tool for genetics trainees to demonstrate counseling and communication skills in high-stakes genetic scenarios that are common in clinical practice.

Cockrum, Richard H. (Richard)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center Fellowship
Advisor	Monika Safford
Abstract Approved By Advisor	Yes
Co-Authors	Chris Gamboa, Susan Andreae
Title	Diabetes Knowledge Retention and Glycemic Control in the ENCOURAGE Trial

Abstract

Knowledge about diabetes and self-care practices has long been considered a pre-requisite for proper disease management. However knowledge retention, defined as a sustained maintenance or improvement in knowledge, has not been as thoroughly investigated, especially in high risk populations like those living in the Alabama Black Belt. We hypothesized that individuals who retained or improved diabetes knowledge one year after baseline would have better glycemic control as measured by hemoglobin A1C than individuals whose knowledge declined.

Data were collected from 356 individuals as part of the ENCOURAGE cluster-randomized controlled trial in several counties of the Alabama Black Belt region. All participants received the same 1-hour educational session and a personalized diabetes report card with their A1C, BP, LDL, and BMI, with relevant advice. The Spoken Knowledge in Low Literacy in Diabetes (SKILLD) Scale was used to assess knowledge.

The characteristics of individuals who retained knowledge were not statistically significantly different than those who did not. 62% of all participants had low diabetes knowledge at baseline (score of $\leq$ 50%). Retainers had mean SKILLD scores at baseline and follow-up of 42.5 ± 1.7 and 58.4 ± 1.5, respectively. Non-retainers had mean SKILLD scores at baseline and follow-up of 62.0 ± 1.6 and 44.2 ± 1.7, respectively. The baseline hemoglobin A1C of retainers was 7.85% ± 1.9 and for non-retainers was 8.05% ± 1.9 (p=0.339). The diabetes knowledge retainers improved to 7.70% ± 1.9, and the non-retainers worsened to 8.15% ± 2.3 (p=0.051). However, a multivariable regression model showed that only a higher baseline A1C was a statistically significant predictor of A1C improvement.

Short, focused diabetes education coupled with report cards may be an excellent strategy to improve diabetes knowledge and possibly glycemic control in this region, especially for individuals with low baseline knowledge.

Cohen, Joshua L. (Joshua)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Sarah Clinton
Abstract Approved By Advisor	Yes
Co-Authors	Matthew E. Glover
Title	Antidepressive Effects of DNA Methyltransferase Inhibition

Abstract

Major depressive disorder (MDD) is a common and serious syndrome characterized by depressed mood, anhedonia, disturbed sleep, appetite, and energy, reduced concentration, excessive guilt, and suicidal. Despite its widespread prevalence little is known about the pathology of MDD. An emerging area of interest is the role that epigenetics may play in MDD as well as other mental illnesses.

Epigenetics refers to the state of DNA packing and chromatin structure, which controls transcription or silencing of genes by facilitating or blocking access to the gene by transcription machinery. Of particular interest, is a class of proteins called DNA methyltransferases (DNMTs) that methylate individual cytosine residues on DNA. Recent work by Sales *et al.* (2011) has shown that DNMT inhibition, by both systemic and intra-hippocampal administration, has anti-depressive effects in rats.

If DNMT inhibition is truly anti-depressive, then it is likely that epigenetic mechanisms play a role in the pathology of MDD. The goal of the present study was to replicate the findings of Sales *et al* in our selectively bred low responder (bLRs) model of depression. bLRs were bred based on low exploration behavior in novel environments, and have since been found to have enhanced anxiety and depressive-like behaviors/vulnerabilities. We show that intra-ventricular injections of the DMNT inhibitor RG-108 reduces time spent immobile by bLRs in a forced swim test, a measure of “depressive-like behavior,” and reduced overall cytosine methylation levels in the hippocampus.

Coker, Joshua Allen (Josh)

Project Length	Short
Prior Research Experience	No
Funding Source	
Advisor	Carlos Estrada
Abstract Approved By Advisor	Yes
Co-Authors	Analia Castiglioni, MD, Ryan R. Kraemer, MD, F. Stanford Massie, MD, Jason L. Morris, MD, Martin Rodriguez, MD, Stephen W. Russell, MD, Terrance Shaneyfelt, MD, MPH, Lisa L. Willett. MD
Title	Evaluation of an Advanced Physical Diagnosis Course using Consumer Preferences Methods: the Nominal Group Technique

Abstract

Purpose: To explore whether a technique to study consumer preferences - the nominal group technique - would elicit specific and prioritized information for curriculum evaluation from senior medical students participating in an advanced physical diagnosis course (4-week long, 100 hours of instruction).

Methods: In February 2012, 12 senior medical students participated in four nominal group technique sessions to generate and prioritize expectations for the course (before) and topics learned (after); students weighted their top three responses (top=3, middle=2, bottom=1).

Results: Before the course, students identified 23 topics expected to learn. The top two expectations were *"objectively learn the sensitivity/specificity of selected parts of the physical exam, learn the most useful techniques"* (percent of total weight, 18.5%) and *"improving skills for diagnostic purposes"* (13.8%). After the course, students generated 22 topics learned. The top two items learned were *"advanced maneuvers practice/proper techniques (basic) techniques to get better physical exam"* (percent of total weight, 25.4%) and *"gaining confidence in performing physical exam findings (heart sounds, abdominal exam, ascites, percussion pleural effusion, JVD)"* (22.5%).

Conclusions: In an advanced physical diagnosis course, senior medical students elicited specific and prioritized information using the nominal group technique. The course met student expectations regarding education of the evidence based physical exam, building skills and confidence on the proper techniques and maneuvers, and experiential learning. The novel use for curriculum evaluation may be used to evaluate other courses – especially comprehensive and multicomponent courses

Collins, Megan Elizabeth (Megan)

Project Length	Short
Prior Research Experience	No
Funding Source	Physical Medicine and Rehabilitation Fellowship
Advisor	Dr. Victor Mark
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Predictive Value of Dynamic Cancellation Testing to Inpatient Rehabilitation Outcomes

Abstract

Objective: Pen-and-paper cancellation tests have been shown to predict rehabilitation outcomes, but without evaluating their dynamic performance aspects. In this preliminary exploratory study we evaluated the sensitivity of two different cancellation test methods, including computerized dynamic measures, to rehabilitation outcomes. We hypothesized that dynamic measures would be superior to standard accuracy scores.

Participants and Methods: 13 adults with acute brain injury (stroke, TBI) and 2 hospitalized patients without brain injury completed the Star Cancellation Test 4 times each on both a touchscreen computer and sheets placed on a graphics tablet. Test method was randomized across subjects. Software automatically calculated the number of contacted targets, non-targets, and blank areas between stimuli and search organization measures, except that marking accuracy on paper tests was judged by 2 raters blinded to patients' identities. The Functional Independence Measure (FIM)—a standard assessment of basic self-care skills—was measured at admission and discharge, and the FIM efficiency (average FIM change per hospitalization day) was calculated. We then correlated cancellation measures to FIM efficiency. Results: Neither touchscreen nor paper tests were significantly correlated with FIM efficiencies. However, certain dynamic subtests on the touchscreen method were moderately correlated with FIM efficiency: target marking speed ($r = 0.45$) and search organization ($r = 0.4$). Conclusions: We preliminarily suggest that dynamic aspects of touchscreen computer testing may be most sensitive to rehabilitation outcomes. Touchscreen may be superior to paper testing because it is more affected by disturbances of motor control as well as self-organization, both of which are important to functional recovery. Our findings will be reevaluated in larger patient samples. Because prior work has shown that cancellation tests can be completed by the most language-impaired adults, the results may eventually lead to a novel way to evaluate mechanisms important to functional recovery in the most severely language-compromised patients.

Cotter, Alexander Patrick (Alex)

Project Length	Short
Prior Research Experience	No
Funding Source	Diabetes Research and Training Center Fellowship
Advisor	Dr. Andrea Cherrington
Abstract Approved By Advisor	Yes
Co-Authors	April A. Agne, MPH; Alfredo L. Guzman, CSE, MEng; Andrea L. Cherrington, MPH, MD, University of Alabama at Birmingham
Title	Designing MyDiabetesConnect.com: A mixed methods approach to the development of a community resource website for type 2 diabetes (Glasgow, Boles *et al*. 2003)

Abstract

INTORDUCTION: The prevalence of type 2 diabetes continues to grow in our country. The internet has been seen as a means to facilitate education and self-management behaviors for patients with type 2 diabetes. OBJECTIVE: The objective of the project was to design a community resource website to help patients locate resources in their local community that would aid in lifestyle modification and diabetes education. A mixed method approach was used, including a systematic literature review and a series of 8 semi-structured interviews with key members of local community based organizations and the local safety net hospital. METHODS: The systematic literature review was designed to understand how technology had already been applied to lifestyle modification while the semi-structured interviews focused on understanding the local resources and barriers to their utilization. RESULTS: Of the 2803 papers identified the 9 included in the review used static education and interactive components to effect lifestyle modifications and provided program evaluations. The studies that included interactive components were more successful; however no study improved all targeted areas of lifestyle modification. The interviews highlighted the need for a resource database for the local community, a desire for up-to-date information, and interactive components. Key barriers for the local community included: transportations, resource affordability, internet access, and a need for basic diabetes education. CONCLUSSION: With the information gathered we designed MyDiabetesConnect.com. The site is specific for the Birmingham area, allowing users to locate resources and events based on their location. MyDiabetesConnect.com also allows users to communicate with others in their community about their healthcare needs.

Cunningham, Rachel Elizabeth (Rachel)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Robert J. Christy Ph.D.
Abstract Approved By Advisor	Yes
Co-Authors	Shan Natesan Ph.D., Nicole Wrice, Robert J. Christy Ph.D.
Title	Development of novel stem cell based treatment of burn wounds

Abstract

Introduction: Burn injuries have been seen in increasing frequency and severity in our military personnel, and comprise 5-10% of all military casualties. Recent advances using adipose derived stem cells to produce “skin equivalent” autografts have allowed patients with large burn injuries to receive autografts engineered from normally discarded adipose tissue following debridement, yet techniques to enhance revascularization of the graft are still limited.
Purpose: Evaluate the growth and stability of vascular elements within a bilayer gel composed of adipose derived stem cells when exposed to the locally released extracellular growth factor VEGF.
Methods: Bilayer gels composed of adipose derived stem cells embedded within a PEGylated fibrin gel and layered with either de-cellularized human amniotic membrane or collagen gel and seeded with keratinocytes. Revascularization success was evaluated at the end of a two-week incubation period by histological analysis and immunocytochemical staining.
Results: Cells were verified as stem cells prior to incubation based on immunocytochemical staining for stem cell positive markers. Light photomicrographs of cell cultures on different days show growth of three dimensional microvascular networks in bilayer gels comparable to that of controls. Vascular growth is confirmed by immunocytochemical staining of endothelial specific von Willebrand factor, CD31 and vascular specific alpha smooth muscle actin.
Conclusion: Mature vascular networks were shown to grow in the presence of epidermal equivalents and growth factors released locally by keratinocytes with results comparable to that of controls. Further research into the stability and longevity of these vascular networks is necessary to determine the best epidermal equivalent to employ for autografts in patients.

DelaRosa, Hillary Jean (Hillary)

Project Length	Short
Prior Research Experience	No
Funding Source	Departmental or Mentor Funds
Advisor	Nabiha Yusuf, Ph.D.
Abstract Approved By Advisor	Yes
Co-Authors	Iman A Tamimi, Eva Simanyi, Israr Ahmad
Title	Toll-Like Receptor-4 augments ultraviolet radiation induced cutaneous tumor development by DNA damage mechanism

Abstract

Ultraviolet (UV) B radiation (290-320 nm) induced DNA damage is an important trigger for suppression of immune responses and for the initiation of non-melanoma skin cancers. UVB causes DNA damage, predominantly in the form of cyclobutane pyrimidine dimers (CPD). Reactive oxygen species (ROS), which are generated endogenously by cellular oxygen metabolism or exogenously by UV, also produce various types of DNA damage. 8-Oxo-2'-deoxyguanosine (8-Oxo-dG) is one type of oxidative DNA damage that can result in stable mutations. Toll-like receptor 4 (TLR4), a component of innate immunity, has been shown to play an important role in cancer. Previous studies from our laboratory indicate that TLR4 deficient mice developed significantly fewer CPD ($p<0.05$) in their skin upon UVB exposure. Our recent experiments indicate that when mice are exposed to single dose of UVB (200 mJ/cm^2), UVB-induced DNA damage mediated by ROS is greatly reduced in TLR4 deficient mice, indicated by significantly fewer 8-Oxo-dG lesions ($p<0.05$) in the skin of these mice. We also found that when mice were exposed to multiple doses of UVB radiation (200 mJ/cm^2), cutaneous carcinogenesis was inhibited in terms of tumor incidence and tumor latency in mice deficient in TLR4 compared to TLR4 competent mice, with significantly greater ($p<0.05$) number of tumors occurring in TLR4 competent mice. Together, our data indicate that TLR4-mediated UVB-induced DNA damage in the form of CPD and 8-oxo-dG lesions may be a molecular trigger for development of UVB-induced skin cancers. Thus, strategies to inhibit TLR4 may allow us to develop immunopreventive and immunotherapeutic approaches for management of UVB-induced cutaneous DNA damage and skin cancer.

DiToro, Daniel Francis (Daniel)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Casey Weaver
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Potential Role for Insulin-like Growth Factors in CD4-T Cell Differentiation

Abstract

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. Appropriate CD4-T cell differentiation is essential for both acute and memory responses, and inappropriate CD4-T cell differentiation has been linked to a variety of autoimmune diseases. Differential signaling by soluble factors and co-stimulatory molecules guides the maturation of naïve CD4-T cells into these effector populations. It has long been understood that cytokines influence CD4-T cell differentiation by activating specific Jak/STAT pathways and inducing expression of lineage-specific transcription factors, and that co-stimulation through mTOR is essential for proliferation of T cells following activation. But recent data suggests an expanded role for mTOR-dependent co-stimulation in CD4-T cell differentiation. Disruption of the mTOR pathway ablates effector CD4-T cell differentiation, and disruption of specific arms of the mTOR pathway prevents differentiation of specific effector populations. Indeed, mTOR has been suggested to function as a general co-stimulatory integrator, Many non-cytokine soluble factors also signal through mTOR, opening the possibility that as-yet undefined factors may influence T cell fate. Decades ago, insulin-like growth factors 1 and 2 (somatomedins A and B) were shown to be essential for development and proliferation of both B and T cells. Produced in large amounts by myeloid cells, lymphoid and bone marrow stromal cells and thymic epithelial cells, these molecules signal largely through mTOR. Microarray analyses, confirmed by quantitative PCR, of the various CD4 effector subsets by our labs and others consistently demonstrates differential expression of Igf-related genes among subsets, with Th17 cells appearing uniquely suited to respond to insulin-like growth factors. However, no attempt has been made to investigate a role for these peptides in CD4 differentiation.

Dobbin, Zachary Christopher (Zachary)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Dr. Charles Landen
Abstract Approved By Advisor	Yes
Co-Authors	Ashwini A. Katre, Angela Ziebarth, Monjri Shah, Ronald D. Alvarez, Michael G. Conner, Charles N. Landen
Title	The “Holograft” Model: An optimized primary ovarian cancer xenograft model that mimics patient tumor biology and heterogeneity.

Abstract

Background: Current xenograft models of ovarian cancer are mainly homogeneous and poorly predict response to therapy. While use of patient tumors represents a better model for tumor biology, poor take rates and questions of recapitulation of the patient tumors have limited this approach. We developed a protocol for such a model and examined its similarity to the patient tumor. We call this the “Holograft” model due to the mimicking of the patient’s clinical response.
Methods: Under IRB and IACUC approval, 23 metastatic ovarian cancer samples were collected at the time of tumor reductive surgery and implanted either subcutaneously (SQ), intraperitoneally (IP), in the mammary fat pad (MFP), or in the subrenal capsule (SRC) and monitored for tumor growth. Cohorts from 8 holografts were treated with combined carboplatin and paclitaxel and response to therapy was compared between holografts and patients. Tumor-initiating cell (TIC) markers expression of ALDH1, CD133, and CD44 was assessed by immunohistochemistry in tumors from patients and holografts.
Results: At least one SQ tumor developed in 91.3% of holografts, significantly higher than in the MFP (63.6%), IP (23.5%), or SRC (8%). The patients and holografts have similar responses to chemotherapy and similar expression of TICs. Holografts from patients with a partial response responded more slowly than those from patients achieving complete response (45 vs 21 days to 50%-tumor-reduction, p=.004). Treated holografts were more densely composed of TICs. ALDH1 increased to 36.1% from 16.2% (p=0.002) and CD133 increased to 33.8% from 16.2% (p=0.026).
Conclusions: Holograft development can be achieved effectively when tumors are implanted SQ and are similar to patient tumors with regard to chemosensitivity and TIC expression. This model may be more accurate for *in vivo* pre-clinical studies as compared to current models and is well positioned to evaluate targeted therapies aimed at aggressive populations in a heterogeneous tumor.

Dorn, David Paul, Jr. (David)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Derek Dubay, MD
Abstract Approved By Advisor	Yes
Co-Authors	Mary Kate Bryant, Jessica Zarzour, Kevin Smith, David Redden, Souheil Saddekni, Ahmed Kamel, Devin Eckoff, Derek Dubay
Title	Chemoembolization for hepatocellular carcinoma in cirrhotic patients with compromised liver function

Abstract

Background: Transarterial chemoembolization (TACE) is the recommended oncologic treatment for non-transplantable, non-resectable, non-ablatable hepatocellular carcinoma (HCC). TACE is indicated in roughly 50% of all new HCC diagnoses. TACE is currently recommended only to cirrhotic patients with normal underlying liver function. The efficacy of TACE for cirrhotic patients with compromised liver function is not known.

Hypothesis: We hypothesize that post-TACE survival and TACE-induced HCC tumor necrosis will be greater in patients with normal liver function compared to patients with compromised liver function.

Methods: All “first” TACE interventions for HCC performed at UAB from 2008 – 2011 were retrospectively reviewed (n=190). Liver function was quantified via the Child’s score. Log-Rank tests were used to measure survival estimates following TACE. HCC tumor response to TACE was quantified via the modified RECIST criteria (a National Cancer Institute-recommended scale for measuring solid tumor response to therapies) and compared with the Chi-Squared test.

Results: There were 100 Child’s A and 90 Child’s B/C cirrhotic patients undergoing a first TACE procedure available for analysis. The 6, 12, 24 and 36 month survival estimates were significantly higher in Child’s A (90%, 78%, 47% and 28%) compared to Child’s B/C (79%, 52%, 37% and 30%) following the first TACE episode (p=0.03, log rank test).
In contrast, there were no significant differences in the mRECIST measures of TACE induced tumor necrosis (complete, partial, stable/progressive) between Child’s A (43%, 36%, and 21%) and Child’s B/C (61%, 23%, and 16%) following the first TACE episode (p=0.2, omnibus test).

Conclusions: Contrary to our hypothesis, TACE appears to be equally efficacious in cirrhotic patients regardless of their Child’s classification based upon equivalent mRECIST measures of tumor necrosis. However, inferior survival following TACE was observed in the Child’s B/C cohort compared to the Child’s A cohort.

Dover, Laura Lynne (Laura)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Derek DuBay
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Improved Post-operative Survival for Intraductal Growth Subtype of Intrahepatic Cholangiocarcinoma Compared to Other Histologic Subtypes

Abstract

Background: Intrahepatic cholangiocarcinoma, formerly known as metastatic adenocarcinoma of unknown primary, is an uncommon hepatic neoplasm with an increasing incidence and stubbornly poor prognosis. The only curative alternative for these patients is surgical resection, with reported 5-year survivals between 25%-40%. Recent histological classifications include mass forming, periductal infiltrating and intraductal growth subtypes.
Hypothesis: The aim of this study is to measure patient survival following surgical resection for intrahepatic cholangiocarcinoma. Our hypothesis is that patients with intraductal growth histologic subtype will have improved survival compared to other histologic subtypes.
Methods: A retrospective review was performed identifying all surgical patients treated at UAB for cholangiocarcinoma. Patients with perihilar and distal cholangiocarcinomas were excluded, as were all patients undergoing aborted or palliative procedures. Survival estimates were quantified using Kaplan Meier curves. Differences between groups were compared with Fisher's exact test and t-test where appropriate.
Results: Between 2004-2011, 37 patients treated at UAB with a partial hepatectomy with curative intent were identified. The 1, 3 and 5-year overall survivals were 80%, 63% and 51%. There were no significant patient demographic characteristics associated with patient survival: younger age (p=0.08), female gender (p=0.19) and Caucasian race (p=0.65). Similarly, there were no significant tumor pathologic characteristics associated with patient survival: well differentiation (p=0.47), >1mm surgical margin (p=0.47), tumor satellitosis (p=0.44), lymphovascular invasion (p=0.65) and perineural invasion (p=0.68). Neither adjuvant radiotherapy (p=0.39) nor chemotherapy (p=0.9) was associated with survival. Significant differences in patient deaths were observed between histologic subtypes: 11/27 mass forming, 3/3 periductal infiltrating, and 0/8 intraductal growth (p=0.03).
Conclusions: Although limited by the small sample size of this rare cancer, this study demonstrates a better than expected overall survival following partial hepatectomy for intrahepatic cholangiocarcioma. Recently proposed histologic subtypes were strongly predictive of post-surgical survival, with no deaths observed in the 8 patients with intraductal growth subtype.

Dunlap, Quinn Alexander (Quinn)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Dr. Bradford Woodworth
Abstract Approved By Advisor	Yes
Co-Authors	Neel Ranganath, Shaoyan Zhang, Dan Skinner
Title	Primary rabbit nasal septal epithelial cultures for studies of cystic fibrosis sinus disease

Abstract

Transgenic cystic fibrosis (CF) murine models have greatly facilitated studies of CF pathogenesis and treatment. We recently described and characterized a primary cell culture model of murine nasal septal epithelium (MNSE) grown at an air-liquid interface. However, small rodents do not reproduce key aspects of human airway physiology. For example, molecules developed with the intent of restoring CFTR function may exhibit species specificity – a fact underscored by lack of CFTR activation in MNSE by the potentiator VX-770. As experimental epithelia, rabbit tissue provides an excellent model for human sinus disease. Rabbit sinonasal epithelium consists of 80 to 90% ciliated cells similar to the human sinus and nasal cavities as judged by scanning electron microscopy, and an *in vivo* rabbit sinusitis disease model is established and well suited for studies of therapeutic intervention. The objectives of the current experiments were to develop primary rabbit nasal septal epithelial (RNSE) cultures and evaluate their usefulness as a model of transepithelial transport and CFTR function in particular.

RNSE was cultured at an air-liquid interface on filter supports to confluence and full differentiation. Optimization of culture conditions was conducted to achieve approximately 80-90% ciliated cells. Differentiation occurred within 14 days and all inserts attained resistance > 500 Ω/cm^2. Monolayers were mounted in Ussing chambers to investigate pharmacologic manipulation of ion transport. RNSE exhibited a change in forskolin-stimulated current (ΔIsc in $\mu A/cm^2$) compared to MNSE (6.3 +/- 0.2 vs. 16.8 +/- 2.1, respectively; $p<0.0001$). However, VX-770 stimulated CFTR-mediated Cl^- secretion in RNSE (1.4+/-0.1) whereas no measurable response was detected in MNSE. All cultures demonstrated inhibition of forskolin and VX-770 stimulated current by the specific CFTR inhibitor INH-172 (5 μM).

In summary, standardized, well characterized RNSE cultures represent a useful model for studying CFTR activity, and provide advantages over murine nasal epithelial tissues. Culture yield from the rabbit septum is 20-fold greater than the murine septum and, although forskolin-stimulated Cl^- secretion was modest in comparison to MNSE, activation with VX-770 indicates important molecular similarities between rabbit and human CFTR, including usefulness of rabbit epithelial cultures for testing CFTR potentiation in the future.

Dussaq, Alex Maurice (Alex)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Jonas Almeida, Chris Willey
Abstract Approved By Advisor	Yes
Co-Authors	Josh Anderson, Bade Iriabho
Title	Creation of a collaborative, RDF based web ecosystem for kinomic peptide arrays.

Abstract

Kinomics describes the activity of cellular kinases and shows great promise as a tool for personalized cancer treatment; however it lacks a standardized data model which is hindering the generation and use of reference data as well as the application of novel bioinformatics algorithms to improve patient care. While genetic sequencing has identified most kinases in the human genome, it does not describe the 'kinome' at the level of activity of the kinases against kinase targets. Several techniques for kinome examination exist, however, phosphorylatable-peptide chips show significant promise due to several key features: 1) They can be used for high-throughput screening, 2) they allow the investigator to directly measure the effects of a drug without cell cultures, 3) the peptide arrays are inexpensive to create and can be tailored for specific targets, 4) they maintain similar enzyme kinetics to in vivo kinases. The PamGene PamChip array records and compares the phosphorylation of 144 tyrosine or serine/threonine peptides. The data produced requires use of the manufacturers proprietary software to analyze data which does not allow the data to be easily shared or viewed with any other program, or by any other machine, essentially making collaborative data analysis very difficult. This environment, given the high stratification of molecular processes in human populations, serves as a major barrier to the understanding of the molecular basis for disease needed for drug development.

We created a tool that has two publically available backends: a HIPAA compliant, server based one, and an encrypted social media based file system. Social computing is emerging as the natural middle layer for the third generation of Web Technologies (Web 3.0). Accordingly by taking this route towards the bioinformatics of kinomics we also take pioneer steps towards collaborative science in a personalized medicine context.

Ehlinger, Megan Colleen (Megan)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Nathaniel Robin
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Survey of Heart Rhythm Specialists Hopes to Gain New Information on Genetic Services Offered to Long QT Syndrome Patients

Abstract

Long QT syndrome (LQTS) is an inherited cardiac channelopathy that predisposes individuals to syncope, seizures, torsades de pointes, and sudden cardiac death. This condition may be treated either medically or with an implanted cardioverter-defibrillator, but diagnosis is essential for proper management[1]. There are more than a dozen loci containing genes associated with LQTS, and there is evidence that there is a correlation between genotype and phenotype[2]. Although genetic testing has been available for years, its cost-effectiveness among different populations, including definitive and inconclusive index cases and potentially affected family members, has been debated and genetic testing is not routinely performed in all clinical settings[1]. Although gene specific stratification of LQTS has been shown to be of use in clinical management of LQTS[2], guidelines for testing individuals have not been established and little is known about the genetic services currently offered by heart rhythm specialists treating LQTS patients. The goal of this study is to determine how heart rhythm specialists utilize genetic services for definitive and inconclusive LQTS patients and potentially at-risk family members.

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[1] Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. Heart Rhythm. 2005;2(12):1294-300.

[2] Priori SG, Napolitano C, Vicentini A. Inherited arrhythmia syndromes: applying the molecular biology and genetic to the clinical management. J Interv Card Electrophysiol. 2003;9(2):93-101.

Eick, John Francis (John)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Elizabeth Richardson
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Exploring virtual walking as a potential treatment for spinal cord injury neuropathic pain: an fMRI study.

Abstract

Background: Spinal cord injury (SCI) neuropathic pain belongs to a group of pain syndromes that includes phantom limb pain in amputees. It is theorized that this pain is derived from a mismatch in motor output and sensory feedback. In amputees, mirror box therapy has been successful in diminishing pain by artificially reinstating sensory input via visual input. Virtual reality and 'virtual walking' is a potential way to do the same in SCI patients. It is not currently known what pattern of brain activation occurs when patients undergo visual input paradigms such as virtual walking. Given previous reports of functional changes in persons undergoing mirror box therapy, we predicted that virtual walking would activate the sensorimotor cortex in healthy controls.

Methods: Using a 3T Philips Achieva MRI, four healthy controls watched sequences of a fixation screen, first person virtual walking, and first person virtual wheeling while undergoing BOLD fMRI. They were instructed to imagine that they were the actor in the film, without actually performing the movements. Images were averaged and analyzed using SPM8 for activation patterns.

Results: We found that when contrasting walking and wheeling (walk minus wheel), there was activation in the leg region of the sensorimotor cortex of the right hemisphere corresponding to the sensorimotor homunculus. There was also significantly more supplementary motor area activation in the frontal cortex. When contrasting wheeling and walking (wheel minus walk), there was more activation laterally in the sensorimotor regions corresponding with arm region of the homunculus.

Discussion: We have provided evidence that virtual walking is capable of activating the sensorimotor cortex, which may underlie the effectiveness of this treatment paradigm. We also showed that our virtual reality design was able to target the legs, suggesting that this may be a viable therapy for SCI patients with neuropathic pain.

Elkhetali, Abdurahman Said (Abdurahman)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Kristina M. Visscher
Abstract Approved By Advisor	Yes
Co-Authors	Ryan J. Vaden
Title	Mechanisms of Attention in Auditory and Visual Cortex

Abstract

Attention and task performance influence information processing in both visual and auditory cortex. During our daily lives we are bombarded with sensory stimuli, especially through the auditory and visual systems, yet we are able to function because our brain is able to enhance processing of relevant stimuli and attenuate irrelevant distracters. This ability is impaired in many cognitive disorders such as ADHD and schizophrenia. In order to understand the mechanism behind maintaining attention, we used fMRI to measure neural activity during performance of auditory and visual tasks. We hypothesized that non-stimulus driven, or *intrinsic,* brain activity, in sensory cortex is important for attention and maintaining task performance. Intrinsic activity associated with preparing for and maintaining task performance were measured for twenty participants who performed a change detection task for auditory or visual stimuli. The visual stimuli were gray-scale horizontal gratings (Gabor patches), which cause sine wave patterns in the retina. The auditory stimuli, called "ripple sounds" cause sine wave patterns in the cochlea. In some conditions ("Unimodal"), the task stimuli were presented alone, and in other conditions ("Bimodal"), both types of stimuli were presented simultaneously, but the participants attended to only one. Regions of interest in visual and auditory cortex were created for each subject based on stimulus-driven fMRI activity.

In visual cortex, intrinsic activity was increased during preparation and maintenance of a visual task, relative to an auditory task. However intrinsic activity in auditory cortex showed no significant modulations as a result of task. This indicates that the visual and auditory systems have different mechanisms for preparing and maintaining task state. Our findings suggest that intrinsic activity within visual cortex, but not auditory cortex, is involved in preparing and maintaining a task state.

Eschborn, Samantha Rae (Samantha)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Departmental or Mentor Funds
Advisor	Dr. Marjorie Lee White
Abstract Approved By Advisor	Yes
Co-Authors	Lauren Nassetta, MD, Nancy Tofil, MD, MEd, Amber Youngblood, BSN, RN, Jerri Zinkan, MPH, RN, Dawn Taylor Peterson, PHD, Marjorie Lee White, MD, MEd
Title	Diagnostic Error in the Care of Simulated Pediatric Inpatients

Abstract

Introduction: Diagnostic errors in medicine result in substantial harm to patients. Premature closure, the tendency to accept a diagnosis before it has been completely verified, is the most common type of this cognitive error in inpatients. We hypothesized that premature closure could be demonstrated during simulation with residents on inpatient pediatrics rotations.

Methods: Residents on their General Inpatient Pediatrics rotations participated in teams given two cases in which they were asked to evaluate and treat simulated patients. Interns received a text page at the start of each case with a closed stem with an incorrect diagnosis for one case, and an open stem with a symptom for the other. In session 1, groups were randomized to cases of asthma(A)/not feeling well(B) or wheezing(B)/DKA(A) when the actual diagnoses were CHF cardiogenic wheeze/sepsis. Session 2, groups were randomized to cases of croup(A)/abdominal pain(B) or stridor(B)/pneumonia(A) when the actual diagnoses were VP shunt failure/appendicitis. Data regarding history, physical, work up, treatment, and correct diagnosis was collected by observers. Comparisons between stems (A vs. B) were analyzed with Fisher's exact test.

Results: 65 residents participated. Residents given the open stem considered or made the correct diagnosis 86% of the time, versus 72% of those who received the closed, incorrect stem ($p<0.05$). Similarly, those who received the open stem initiated appropriate therapy more frequently than the closed stem, at 60% and 53% of the time, respectively ($p<0.05$). Often those teams receiving the closed stem initiated treatments prior to examining or reviewing key features of the disease.

Conclusion: Premature closure can be demonstrated during simulated patient encounters in the inpatient setting. Residents who were given the open stem were more likely than those paged with the incorrect diagnosis to consider the correct diagnosis and begin appropriate therapy.

Figge, David Anthony (David)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	David Standaert
Abstract Approved By Advisor	Yes
Co-Authors	Jaunarajs KL
Title	Striatal DNA methylation in a rat model of L-DOPA-induced dyskinesia

Abstract

Parkinson's disease (PD), a common neurodegenerative disorder, is caused by the selective loss of dopaminergic neurons throughout the substantia nigra pars compacta. Following neuronal loss, PD patients develop progressive difficulties in various motor-related activities. One of the most effective pharmacological treatments for PD is levodopa (L-DOPA), a precursor to dopamine. However, a significant side effect from L-DOPA is the development of abnormal involuntary movements (AIM) called L-DOPA induced dyskinesia (LDID). LDID is long lasting and irreversible leading to a "priming effect" that causes subsequent administration to sensitize the dyskinesia following further L-DOPA treatments. Unfortunately, currently proposed mechanisms are unable to explain LDID's persistent nature. Epigenetic alterations, including DNA methylation, are known to be of pivotal importance in long term cellular memory, and have been shown to be specifically involved in the development of neuroplasticity and long term memory functions. Thus, we propose that following chronic L-DOPA administration significant epigenetic changes in the striatum will correlate to LDID behavioral phenotypes. To address this hypothesis, Sprague-dawley rats received hemilesions in the medial forebrain bundle using 6-hydroxydopamine. Three weeks later, rats received daily injections for 7 days of either L-DOPA+benserazide (6 mg/kg+ 15 mg/kg; s.q.) or vehicle (saline), and assessed for locomotor changes using the AIM scale to determine levels of LDID. Tissue from the striatum was then collected to investigate changes in DNA methylation following L-DOPA treatment. Global changes in DNA methylation were initially assessed to determine if overall levels of DNA methylation are correlated with LDID. Transcriptional activity of the DNA methyltransferase enzymes and other known genes suspected to be involved in LDID, including delta FosB and prodynorphin, were assessed using a combination of methylated DNA immunoprecipitation and QPCR. L-DOPA treatment is expected to alter the DNA methylation status of various genes involved in normal cellular processes leading to LDID.

Ford, Samuel Edmond (Sam)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Scott Magnuson MD
Abstract Approved By Advisor	Yes
Co-Authors	Hilliary White MD, Benjamin Bush BS, F Christopher Holsinger MD, Eric Moore MD, Tamer Ghamen MD, William Carroll MD, J Scott Magnuson MD
Title	Salvage Surgery for Recurrent Cancers of the Oropharynx: How does TORS compare to standard open surgical approaches?

Abstract

Objectives: To compare the oncologic and functional outcomes of patients with recurrent oropharyngeal squamous cell carcinoma (SCC) treated with transoral robotic assisted surgery (TORS) to traditional open surgical approaches.

Study Design: Retrospective multi-institutional case-control study
Methods: Between March 2003 and October 2011, 64 patients underwent salvage transoral robotic surgery (TORS) for recurrent squamous cell carcinoma (SCC) of the oropharynx at four tertiary care institutions (University of Alabama at Birmingham, MD Anderson Cancer Center, Mayo Clinic - Rochester, Henry Ford Hospital). Patient demographics, operative data, functional, and oncologic outcomes were recorded and compared to a matched patient group that underwent surgical resection by traditional open surgical approaches. Functional outcomes were defined as length of feeding tube use, tracheostomy duration, hospital stay and operative complications.
Results: In the TORS group (mean age = 61), 97% previously failed radiation treatments and in the open surgery group (mean age = 61) 71% failed radiation in the past. The 2 groups were similarly matched by tumor subsite and stage. The TORS patients had a significantly lower incidence of tracheostomy use (p=0.0005), feeding tube use at 6 months (p=0.0005), shorter overall hospital stay (4 days versus 8 days), decreased operative time (3.1 hours versus 6.8 hours) and significantly decreased incidence of positive margins (p=0.006). The recurrence free 1 and 2-year survivals were not significantly different between groups, 44% in TORS patients and 33% in open surgery patients (p=0.2).

Discussion: This study demonstrates that TORS offers an alternative surgical approach to recurrent tumors of the oropharynx with similar oncologic and better functional outcomes than traditional open surgical approaches. This adds to the growing amount of clinical evidence to support the use of TORS in select patients with recurrent oropharyngeal SCC as a feasible and oncologically sound method of treatment.

Foster, Christy Anne (Christy)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Other
Advisor	Kenneth McCormick, M.D.
Abstract Approved By Advisor	Yes
Co-Authors	Jenni Scholl, Mary Lauren Scott, M.D., Kenneth McCormick, M.D.
Title	The Effect of Exogenous Growth Hormone therapy on lipid panel of Growth Hormone Deficient patients

Abstract

Previous studies have confirmed that growth hormone (GH) deficient patients have an increased risk of cardiovascular events, often associated with a more atherogenic lipid profile. In growth hormone deficient adults, LDL particles have been shown to be smaller and thus they are more prone to plaque formation. An improvement in HDL and total LDL concentrations were reported in adult patients receiving exogenous GH therapy. There have been few such studies conducted longitudinally in GH deficient children.

Our study sought to determine what changes occurred to lipid profiles in confirmed GH deficient children following 6 months of exogenous GH treatment. Patients ages 6-13 were recruited from the Children's Hospital of Alabama pediatric endocrinology clinic who met criteria for growth hormone deficiency confirmed by a standard growth hormone stimulation test using 2 agents (either arginine, L-dopa, clonidine, or glucagon). In addition, the inclusion criteria consisted of 2 of the 3 following conditions: children less than the 3rd-centile for height, age-adjusted growth velocity less than 2 standard deviations below the mean, low serum IGF-1 (at least 2 standard deviations below the mean). In sum, 12 GH deficient children (10.43 $\pm$ 1.96 yrs) were enrolled who met these criteria and 11 control children (age 10.29 $\pm$ 1.95 yrs) who met all other inclusion criteria except, upon standard provocative GH testing, were found not to be growth hormone deficient.

Lipid profiles were obtained from all patients at an initial and 6-month follow-up visit. Lipid cholesterol subclasses were determined by an ultracentrifugation technique following a two-layer density gradient step. Five cholesterol subclasses were measured: HDL, LDL, VLDL, IDL, and Lp(a). Statistical modeling then calculated the Apo B/Apo A1 ratios. Comparisons between the two groups at each individual visit were made using a student's t-test. Significant differences between the control group and the treated growth hormone deficient group were analyzed using ANOVA to control for different ages, gender, Tanner staging, serum IGF-1 levels and bone ages. At baseline, BMI, age, height z-scores, and lipid profiles were matched between the two groups.

Results demonstrated an expected significant change in over time in the growth velocity ($p<0.05$) and IGF-1 levels ($p<0.05$) between the two groups, attesting that the growth hormone deficient children responded to hormone therapy. There were significant changes in LDL and non-HDL over the 6 months. Growth hormone deficient children had a significant difference in LDL(<0.05) and non-HDL($p<0.05$) concentrations versus the controls. A significant difference in the LDL-3 values over time was also noted between the two groups.

In conclusion, the study demonstrated significant salutary changes in the lipid profiles of GH deficient children treated with exogenous growth hormone therapy over 6 months, which may, in part, account for the cardiovascular protective action of GH therapy. Further studies are warranted to involve a more extensive population and to extend the observation period of the study.

Foster, Katelyn Elizabeth (Katelyn)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Warner K. Huh
Abstract Approved By Advisor	Yes
Co-Authors	Britt K Erickson, Yevgeniya Ioffe, Stewart L Massad, Warner K. Huh
Title	The Utility of Re-excision in Primary Vulvar Carcinoma

Abstract

Background: Punch biopsies have a high false-negative rate in diagnosing vulvar squamous cell carcinoma (SCC). Additionally, it is difficult to determine the true extent of disease based on clinical assessment. Thus, final pathology after primary vulvar excision is often worse than expected. Patiens with close surgical margins, surgical margins positive for SCC or vulvar intraepithelial neoplasia (VIN), and depth of invasion greater than 1 mm have a heightened risk of recurrence, leading some to advocate for re-excision in these circumstances. There is currently a paucity of literature describing the incidene of SCC in surgical specimens obtained by re-excision.

Objective: To determine the frequency of residual SCC in re-excisional specimens in patients with vulvar SCC who have undergone re-excision. Additionally, we sought to identify the risk factors predisposing patients to residual disease and to determine the risk of recurrent carcinoma in this cohort.

Methods: This is a multi-institutional retrospective cohort study. After IRB approval at UAB and Washington University in St. Louis, patients who underwent surgical resection of their vulvar carcinoma between 1999 and 2011 were identified. Patients who then underwent an immediate re-excision were included for analysis. Demographic information as well as cancer characteristics including stage, margin status, lesion size, and final pathology on re-excision was obtained.

Results: At UAB, of 737 patients evaluated, 42 patients were identified who met the inclusion criteria. Sixteen of 42 patients (38%) had initial margins positive for SCC. Pathology demonstrated residual carcinoma in 8/42 (19%) patients. Of those who had residual carcinoma, all eight (100%) had positive margins on primary excision. Zero patients with negative margins on primary excision had residual carcinoma on re-excision. Depth did not significantly correlate with residual carcinoma, although pooled data analysis is currently underway with results from Washington University. Final data analysis will be available 09/17/2012.

Conclusions: Forthcoming

Frederick, John William (John)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Eben Rosenthal
Abstract Approved By Advisor	Yes
Co-Authors	Sweeny L, Hartman Y, Rosenthal EL
Title	Anti-CD147 and the EGFR pathway in cutaneous squamous cell carcinoma

Abstract

Background: Cutaneous squamous cell carcinoma (cSCC) is the second most common skin malignancy. Up to 80% of cSCC occurs in the head and neck and a portion of these cancers are refractory to simple excision, with long term survival as low as 25%.

Objectives: Investigate the molecular pathway behind anti-CD147 treatment in cSCC.

Methods: CSCC 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. A murine flank tumor model was then used to assess in vivo response to anti-CD-147 treatment.

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 wound closure. In vitro phenotype, in response to anti-CD147 therapy, resulted in a 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. In vivo phenotype was then assessed by using a murine flank tumor model. Both the anti-CD147 treatment group and the silenced CD147 cell line showed decreased tumor growth and EGFR expression on histologic evaluation when compared to control.

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

Frojo, Gianfranco Alberto, Jr. (Gianfranco)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Gloria Ines Sanchez, Dr. Isabel Scarinci, Dr. Isabel Garces
Abstract Approved By Advisor	Yes
Co-Authors	Esteban Lopera, Victor Florez, Esteban Palacios, Jehidys Montiel, Armando Baena, Astrid M. Bedoya, Mary Luz Uribe, Katherine Quintero, Santiago Martinez, Giovanny Zabaleta, Gloria I. Sánchez
Title	Cervical cancer risk associated with Interleukin-10 gene single nucleotide polymorphisms in Colombian women

Abstract

Objective: Estimate the risk of cervical cancer associated with IL-10 promoter single nucleotide polymorphisms

Background: Cervical cancer is the second most common cancer among women living in countries of less developed regions. Three biallelic single nucleotide polymorphisms located in the promoter region of the Interleukin-10 gene, -1082 (G→A), -819(C→T) and -592(C→A), may influence the cytokine-mediated immune response to Human Papillomavirus, possibly modifying risk of cervical cancer. SNPs may serve as a marker of genetic susceptibility to cervical cancer among Colombian women and allow identification of women at higher risk for developing high-grade disease.

Methods: In this case-control study, peripheral blood mononuclear cell DNA was extracted from 125 cases (women with confirmed histological diagnosis of CIN3/SCC) and 153 frequency-matched by age and place of birth controls (women with normal or low-grade cytology) and genotyped using TaqMan genotyping assays (Applied Biosystems, Foster City, CA) using probes labeled with either FAM or VIC dyes. Odds ratios and 95% confidence intervals (95% CI) for each polymorphism using the co-dominant model were estimated using unadjusted models.

Results: There was a trend for increased risk of cervical cancer associated with TT IL-10 -819 (OR: 1.68, 95%CI = 0.74-3.83) promoter polymorphism that remained marginally significant (p=0.07). No increased risk was observed with any of the other SNPs evaluated.

Conclusion: The results suggest an increased risk associated with the -819 IL-10 promoter polymorphism in this population. Further analysis includes adjusting for known risk factors and stratification by ancestry groups.

Gaston, David Curtis (David)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Richard J. Whitley, M.D.
Abstract Approved By Advisor	Yes
Co-Authors	C.I. Odom, A.B. Cantor, Ph.D., JN Parker, Ph.D.
Title	Oncolytic HSV-1 Expressing Interleukin-15 for Brain Tumor Therapy

Abstract

Oncolytic herpes simplex type-1 virus (oHSV) vectors are promising therapeutics for malignant gliomas. Our laboratory group recently completed a microarray analysis of glioma samples from a phase Ib clinical trial in which patients with glioblastoma were administered oHSV. In samples obtained from patients with a positive response, transcript levels of the immunostimulatory cytokine interleukin-15 (IL-15), all receptors necessary for optimal IL-15 signaling, and transcripts indicating the presence of cytotoxic lymphocytes responsive to IL-15 ($CD8^+$ T and natural killer [NK] cells) were significantly increased. As immune responses can work in concert with oHSV lytic replication to combat tumors, we sought to determine whether IL-15 enhances oHSV efficacy. We hypothesize that IL-15 propagates $CD8^+$ T and NK cell anti-glioma immune responses, thus jointly contributing to tumor reduction with oHSV lytic replication. To investigate this hypothesis we constructed oHSV vectors expressing murine (m)IL-15 alone or with the IL-15 receptor α (IL-15Rα), which is necessary for IL-15 presentation and signaling. These vectors replicate identically, indicating that the insertions do not alter the direct lytic activity of the vectors. The vector encoding mIL-15 alone produces a low level of mIL-15, whereas the vector dually encoding mIL-15/IL-15Rα substantially improves mIL-15 production. The dual expressing vector also produces and secretes the bioactive complex of mIL-15 bound to mIL-15Rα (3ng/mL). Both vectors remain aneurovirulent (LD_{50} > $1x10^7$ plaque forming units, comparable to other oHSV vectors). Dual mIL-15/IL-15Rα expression from oHSV improved survival over saline in preliminary survival studies using an aggressive murine brain tumor model (median survivals: saline – 14 days; mIL-15/IL-15Rα oHSV – 25 days. p = 0.001), whereas mIL-15 expression alone did not (median survivals: saline – 14 days; mIL-15 oHSV – 17 days. p = 0.1128). In vivo studies investigating the stimulation of bystander immune-mediated tumor clearance by oHSV-produced mIL-15/IL-15Rα in murine models of malignant glioma are underway.

Graves, Anna Joy (Anna Joy)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	E. Michael Foster
Abstract Approved By Advisor	Yes
Co-Authors	
Title	The Monetary Value of Breastmilk in the United States

Abstract

Breastmilk is an important but undervalued economic resource. National accounting practices that fail to consider human milk as a food resource and investment in human capital produce incomplete estimates of national food production. To assess the monetary value of breastmilk in the United States, we analyzed data from the longitudinal Infant Feeding Practices Study II. Four economic methods for valuing unmarketed products—market alternative cost, opportunity cost, replacement cost, and commodity cost— were used. Actual breastmilk production was compared to “optimal” production, defined as 90% of US families breastfeeding exclusively for the first 6 months and partially until 1 year of age.

In the United States, infants under 1 year of age consume over 40 million liters of human milk per year. The market alternative cost, which values breastmilk by using the price of human milk prevailing in “the market” through milk banks, is in excess of 5.4 billion dollars. Maternal time spent breastfeeding was used to estimate the opportunity cost, which values maternal time cost of extracting breastmilk, and the replacement cost, which estimates the cost of employing a wet nurse, at $2.08 billion and $1.51 billion dollars respectively. Finally, the annual commodity cost of breastmilk substitutes such as infant formula would be $1,130 per infant or 186 million dollars nationally. Optimal breastfeeding would produce an average of 220 liters of breastmilk per infant and save the economy 170 million dollars annually– 55% of which is borne by taxpayers through the Woman, Infants, and Children (WIC) formula provision program for low-income families.
These results demonstrate the economic impact of breastmilk, an otherwise “politically invisible” food. Efforts to estimate the monetary value of human milk may assist in the promotion of breastfeeding, influence health policies that protect maternal time for breastfeeding, and recognize female economic activity and contribution to society.

Gray, William Hampton (Hampton)

Project Length	Short
Prior Research Experience	No
Funding Source	
Advisor	Robert Dabal
Abstract Approved By Advisor	Yes
Co-Authors	
Title	A Twenty Year Experience with the Surgical Correction of Aortic Arch Obstruction in Patients with Right Aortic Arches

Abstract

Coarctation of the aorta is a fairly common congenital anomaly representing 5-10% of congenital heart disease and has an incidence of 1 in 3-4000 in autopsy series. The overwhelming majority of these patients have a left-sided aortic arch. In radiographic studies along with multiple autopsy series, approximately 0.1% of cases among the general population have been reported to have a right aortic arch. Reports have also shown that the association between coarctation and a right aortic arch is approximately 4.1% of all right arches. Although this anomaly is extremely rare, there are multiple isolated case reports and two small series of patients with right-sided aortic arch obstruction in the surgical literature. However, most of these reports are over a decade old. This study is a descriptive case series and contributes to the existing surgical knowledge of the problem of right-sided aortic arch obstruction. It also describes a larger patient population than the majority of reports currently in the literature. The study population includes all patients who have undergone cardiothoracic surgery at UAB since 1991. The UAB pediatric cardiology database was queried and a total of four patients who underwent surgical repair for a coarctation with a right aortic arch were identified and included in the study. Medical records and operative notes for each patient were then obtained to describe the anatomy of the aortic arch and the surgical technique used in each operation. Of the four patients, three of them underwent surgical repair through an end-to-end anastomosis. All patients are alive and well and there were no early deaths. Our study shows that the preferred surgical technique in repairing coarctation with a right aortic arch is end-to-end anastomosis.

Grayson, Jessica Warren (Jessica)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Bradford Woodworth
Abstract Approved By Advisor	Yes
Co-Authors	Mohamad R. Chaaban, MD Kristen O. Riley, MD Bradford A. Woodworth, MD
Title	Unilateral Endonasal Endoscopic Resection of an Intracranial Dermoid Cyst

Abstract

Intracranial dermoid cysts are congenital ectodermal inclusion cysts that have a propensity to occur in the midline sellar, parasellar, or frontonasal regions. These cysts enlarge by means of glandular secretion and epithelial desquamation. Surgical resection has traditionally included a craniotomy, but endoscopic approaches are now employed with increasing regularity. A binostril approach is normally utilized to access dermoid cysts due to the midline nature of the lesions. Complete anosmia can be expected following both craniotomy and bilateral endoscopic techniques due to resection of a large portion of the cribriform plate. The current case report details a unilateral endoscopic approach to an intracranial dermoid cyst that permitted preservation of olfaction in the contralateral olfactory cleft.

Guzman Karlsson, Mikael Carl Gustav (Mikael)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	David Sweatt, PhD
Abstract Approved By Advisor	Yes
Co-Authors	
Title	The Involvement of DNA Methylation in Conditioned Taste Aversion

Abstract

Epigenetic mechanisms have long been associated with cell differentiation and development. However, recent studies have also implicated epigenetic mechanisms in several brain regions 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 and others suggest that DNA methyltransferase (DNMT) activity in hippocampal-cortical circuits is important for the consolidation and the maintenance of fear memory. Although much progress has been made in understanding the epigenetic mechanisms underlying fear learning, little is known regarding how these mechanisms might be involved in taste learning. A form of taste learning known as conditioned taste aversion (CTA) has been show to rely on similar intracellular signaling cascades employed during fear learning (eg. PKA, ERK/MAPK, CaMKIIα) that are known to converge on the nucleus to elicit epigenetic modifications. Our central hypothesis is that the encoding and storage of CTA memories in the insular cortex is dependent on DNA methylation. In order to determine if DNA methylation is necessary for consolidation of CTA memories, we infused the DNMT inhibitor RG-108 into the insular cortex of rats during CTA training for saccharine. Furthermore, to determine if DNA methylation is necessary for the maintenance of CTA memories, we infused RG-108 into the insular cortex 14 days after training. Neither of these RG-108 manipulations had an effect on the aversion index to saccharine, indicating the DNA methylation in the insular cortex is not necessary for the consolidation nor the maintenance of CTA memory. In future studies, we plan to investigate whether or not DNA methylation is necessary in other regions of the taste circuit, such as the amygdala and parabrachial nucleus, during the encoding and maintenance of CTA memories.

Hadley, Jennifer Ann (Jennifer)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Adrienne C. Lahti, MD
Abstract Approved By Advisor	Yes
Co-Authors	David M. White, Rodolphe Nenert, Mark S. Bolding, Kristina Visscher, Adrienne C. Lahti
Title	Antipsychotic drug treatment restores impaired limbic system connectivity in schizophrenia

Abstract

Antipsychotic drugs (APDs) alleviate some of the symptoms of schizophrenia, but up to 30% of patients do not respond; it is not currently possible to distinguish these patients from those who will respond to treatment. Imaging research in schizophrenia has revealed altered functional connectivity (FC) between brain regions, thought to reflect changes to the underlying neural circuitry associated with the disease. Previous studies of schizophrenia have found changes in regional cerebral blood flow in the medial prefrontal cortex (MPFC) and the hippocampus (HIP) in response to APDs (Lahti *et. al*, 2009). We sought to identify changes in FC from these regions observed between unmedicated schizophrenia (UMSZ) and healthy control participants (HC) and in response to one week of treatment with the APD risperidone, in order to test the hypothesis that changes in FC between limbic regions in the early stages of APD treatment would parallel abnormal patterns of FC between UMSZ and HC.

23 UMSZ and 23 HC were recruited and scanned using resting-state fMRI. UMSZ were scanned while unmedicated and after 1 week of treatment with risperidone. We identified 6 regions of interest (ROIs) for functional connectivity analysis: 4 that constituted the default mode network, (DMN, a well-characterized network to serve as a positive control), the MPFC, and the HIP. After data preprocessing (Power, *et al*., 2012), FC maps were created for each ROI using the Pearson's correlation coefficient between the specific ROI time series and all other brain voxels. The 4 DMN FC maps were z-transformed and averaged to create a DMN FC map. FC maps were compared using a factorial random effects model to assess changes in FC of the DMN, MPFC, and HIP, and reported for a false discovery rate-corrected p-value less than 0.05.

FC of the DMN was found to increase in UMSZ compared to HC in the precuneus, anterior cingulate cortex, and auditory cortex, replicating and expanding upon the findings of Whitfield-Gabrieli, *et al*. (2009). Several regions were identified where UMSZ showed both decreased in FC compared to HC and increased in FC after one week of APD treatment. From the MPFC, these regions included the left ventrolateral prefrontal cortex, the precuneus, and the middle cingulate cortex. From the HIP, these regions included the right dorsolateral prefrontal cortex and the precuneus.

This pattern indicates that some of the FC abnormalities observed in UMSZ are reversed following one week of APD treatment. Interestingly, the precuneus showed changing FC from both the MPFC and the HIP, suggesting that these regions may be important for the mechanism of APDs and prediction of treatment response.

Hagan, Kenton Lee (Kenton)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Candace Floyd
Abstract Approved By Advisor	Yes
Co-Authors	Katheryn Pate, Hubert Tse, Candace Floyd
Title	The Effect of a Catalytic Oxidoreductant on Concussion

Abstract

The Centers for Disease Control and Prevention estimate that 1.7 million persons per year sustain a traumatic brain injury (TBI) in the United States and that approximately 75% of these TBIs are concussion or other form of mild TBI (mTBI). Currently, there are no therapeutic agents approved to treat mTBI; thus, there is an unmet need to discover novel treatments. Our research group has developed and characterized novel catalytic oxidoreductant compounds, Mn (III) N-alkylpyridylporphyrins, which dissipate ROS and inhibit activation of NF-κB. We hypothesize that post-TBI administration of BuOE will dissipate ROS and inhibit NF-κB, reducing injury and ameliorating post-injury cognitive deficits in a murine model of single or multiple mTBI. To evaluate this hypothesis adult male mice received either one or three concussions (inter-injury interval of 24 hours) followed by the administration of BuOE. For biochemical analysis, the brains were then extracted at 24 hours after the final injury and were evaluated for tissue markers of oxidative stress, NF-κB activation, and neuroinflammation. A second cohort of mice was used to evaluate cognition. Mice were trained to complete complex tasks based on a novel training protocol using Bussey-Sakisda chambers. Our preliminary results indicate the BuOE reduced oxidative stress and neuroinflammation. Also, we found that mTBI induced alteration in cognitive performance as after injury mice declined in the ability to complete the required protocols in the assigned time period compared to their pre-mTBI performance. These findings suggest that mTBI induces a transient deficit in memory (accuracy) and a lasting deficit in attention (trial complete rate). The ultimate relevance of development of this potential new treatment would be that a person could take the therapeutic agent after a concussion to protect the brain and thereby lessen or eliminate the cognitive and emotional deficits associated with single or multiple mild the brain injury.

Handley, Guy Hartwell, IV (Guy)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Department of Medicine Fellowship
Advisor	Dr. J. Edwin Blalock
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Effects of Cigarette Smoke Condensate on LTA4H Aminopeptidase Activity

Abstract

Chronic pulmonary neutrophilic inflammation is marked by a substantial persistence of neutrophils at the inflammatory site and thought to be due to a deficiency in a self-limiting step of the process. The enzyme Leukotriene A_4 Hydrolase (LTA_4H) is known as a pro-inflammatory mediator that generates Leukotriene B_4 (LTB_4), a potent chemoattractant for neutrophils. In addition, LTA_4H demonstrates an aminopeptidase activity on the peptide motif of proline-glycine-proline (PGP), another potent chemoattractant made even stronger upon its acetylation (AcPGP). Elevated PGP and AcPGP levels have been measured in patients with chronic conditions such as cystic fibrosis and chronic obstructive pulmonary disease (COPD) that maintain a high level of neutrophilic inflammation. Cigarette smoke is known to be a major risk factor of COPD and has been shown to inhibit this aminopeptidase activity of LTA_4H. This not only raises PGP levels, but increases neutrophil infiltration and leads to the progression of chronic neutrophilic inflammation. L-alanine-p-nitroanilide (ALApNA) was used as a substrate for the aminopeptidase activity of LTA_4H in screening assays to predict the enzyme's effect on PGP. Cigarette smoke condensate was shown to inhibit this aminopeptidase reaction similar to its inhibition of PGP cleavage by LTA_4H. The chemicals acrolein and acetaldehyde, both present in cigarette smoke, are potential mediators for inhibiting the aminopeptidase activity of LTA_4H leading to the buildup of PGP and AcPGP. 1mM acrolein does inhibit the aminopeptidase activity on ALApNA but 1mM acetaldehyde does not. In addition, 5mM N-acetylcysteine was shown to restore the aminopeptidase activity of this enzyme on the ALApNA substrate in the presence of acrolein. While this investigation centers on a condition observed in chronic pulmonary neutrophilic inflammatory conditions, it could theoretically apply to any form of such chronic inflammation in the body.

Haritha, Abhishek (Abhishek)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	Dr. Sadis Matalon
Abstract Approved By Advisor	Yes
Co-Authors	James Londino
Title	Influenza M2 alters Cystic Fibrosis Transmembrane Conductance Regulator Activity in Human Bronchial Epithelial Cells

Abstract

Influenza (flu) virus causes more than 30,000 pulmonary and cardiac related deaths per year in the United States alone. It causes up to 250,000-500,000 deaths per year, and millions if it becomes a pandemic. In our research, we are specifically looking at the M2 protein, a homotetrameric protein on the surface of influenza. Influenza M2 protein is activated by the acidic pH of the endosome and facilitates virus uncoating and release of ribonucleoprotein into the cytoplasm for nuclear transport. We are specifically interested in how M2 effects cyclic AMP activated chloride channel (CFTR). CFTR has a prominent role in moving Cl^- across the apical membrane. It helps maintains the amount of fluid in the lungs to promote normal gas exchange. CFTR helps maintain mucus clearance, thus preventing infections by moving pathogens out of the lungs. There are several potential interactions for M2 protein and CFTR. Because Influenza is an airborne virus, some of the first cells M2 will interact with will be epithelial cells in the respiratory tract. CFTR is a prominent ion channel on the apical surface of respiratory epithelial cells. In this study, we wanted to examine how influenza M2 alters CFTR activity in human bronchial epithelial cells expressing endogenous CFTR (16HBE). A Ussing Chamber study was conducted on cells transfected with green florescent protein (GFP) and GFP-M2. We then measured CFTR expression in cells transfected with GFP and GFP-M2. The data we collected shows a decrease in transmembrane current in human bronchial epithelial cells transfected with M2. However, western blot analysis shows that CFTR production is normal in all cell types. This demonstrates that M2 influenza protein does not inhibit CFTR production, but may inhibit its activity.

Honasoge, Avinash Vinayak (Avinash)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Harald Sontheimer
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Expression and function of proton-permeable cation channels in human glioma cells

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. They display striking extracellular pH (pH_e) heterogeneity due to a combination of factors including increased lactic acid production (due to hypoxia) and increased extracellular acidification (via various exchangers and pumps). We wondered if pH_e is purely a metabolic byproduct or if it can serve as a signal for glioma growth and invasion. To this end, we first found via Coulter Counter and BrdU-labeling experiments a marked inhibition in glioma cell proliferation at low pH_e (6.0) and a seemingly unbounded increase in proliferation at high pH_e (up to 8.8). We then hypothesized that ion channels could serve as the transmembrane chemosensor to translate the extracellular pH environment into intracellular changes, leading to pH_e-dependent glioma growth. We discovered large whole-cell pH_e-sensitive changes in both conductance and resting membrane potential (V_m) of human glioma cells. The underlying cation currents are tonically active, quinine- and 2-aminoethoxydiphenyl borate (2-APB)-sensitive, and reversibly abolished by acidic pH_e (6.0). From here, we speculated that it was these pH_e-dependent changes in ion flux and V_m that could be causing the changes in glioma growth. In this vein, both quinine and 2-APB affected glioma cell proliferation in a pH_e-dependent manner, implicating this cation conductance in cell physiology. In higher pH_e (and with larger cation conductance) the cells displayed greater drug sensitivity. Interestingly, in nominally Na^+- and K^+-free conditions, there exists a residual current that is pH_e- and 2-APB-sensitive and follows the reversal potential for protons, suggesting a direct proton permeability that is pH_e-dependent, with larger fluxes from lower external proton concentrations (higher pH_e). Hence we show evidence for a hitherto unrecognized cation conductance in glioma cells with properties that exploit the unique pH environment around these tumors.

Hughes, Jacob Tyler (Tyler)

Project Length	Long
Prior Research Experience	No
Funding Source	Other
Advisor	Marjorie Lee White, MD
Abstract Approved By Advisor	Yes
Co-Authors	Nancy Tofil, Kathy Harrington, Lynn Zinkan, Amber Youngblood, Dawn Taylor Peterson, Alfred Bartolucci, Brian Perrin
Title	Teaching Fellows to Teach Through the Use of Simulation

Abstract

Doctors are teachers. They teach patients, nurses, parents, medical students, residents, and peers. Despite this fact, few have any formal education in teaching and even fewer receive feedback on their teaching skills. Our hypothesis was that instructional activities utilizing simulation could expose Pediatric Fellows to a teaching opportunity with immediate feedback while improving their knowledge and attitudes towards teaching skills.

From July 2009 - June 2011, pediatric subspecialty fellows whose fellowships were more than one year in duration were included in this study. A pre-survey on teaching knowledge, skills and attitudes was completed by each Fellow prior to attending a teaching seminar on adult learning principles and active learning techniques. The Fellow then developed a case related to their subspecialty, which the simulation center transformed into a simulation scenario. After the learners experienced the case, the Fellow utilized active learning techniques to teach. This session was videotaped and immediate feedback was given to the Fellow concerning their teaching technique. Learners anonymously evaluated the Fellow concerning the effectiveness of their teaching using a structured evaluation tool.

Statistical analysis of the surveys was done with a paired T-test, Analysis of Variance and appropriate agreement statistics utilizing SAS v9.2. There was a significant increase in the number of participants who recognized that demonstration is a more effective teaching strategy for retention of knowledge than discussion, didactic lecture, or lecture with audiovisual aids (p=.006).

Most pediatric Fellows reported not having prior education on techniques of effective teaching de a common requirement by the Accreditation Council on Graduate Medical Education. Simulation offers a tool to simultaneously and directly observe Fellows teaching with structured, timely, and specific feedback. Simulation is also an ideal instructional strategy for Fellows to use when teacl residents and medical students about a subspecialty case that is important for a general pediatric

Hull, Travis David (Travis)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	James George and Anupam Agarwal
Abstract Approved By Advisor	Yes
Co-Authors	Subhashini Bolisetty, Angela DeAlmeida, Amie Traylor, Sumanth D. Prabhu
Title	Heme Oxygenase-1 Expression Protects the Myocardium from Cre-Induced Systolic Dysfunction

Abstract

Background: Heme oxygenase-1 (HO-1) is an enzyme that catalyzes the breakdown of pro-oxidant heme into carbon monoxide, biliverdin, and iron. Our laboratory has shown that HO-1 is tissue-protective due to its antiapoptotic, cytoprotective, and immunomodulatory functions. Using Cre/LoxP technology, we generated a novel transgenic mouse with cardiac-specific, tamoxifen-inducible HO-1 overexpression (MHC-HO-1 mice) to investigate the tissue-specific requirement for the cardioprotective function of HO-1. However, it was recently shown that Cre expression in the myocardium causes transient systolic dysfunction.
Hypothesis: We hypothesize that, relative to mice only expressing cardiac-specific Cre Recombinase (MHC-Cre mice), MHC-HO-1 mice, which over express Cre and HO-1 in a cardiac specific manner, are protected from Cre-induced cardiac toxicity.
Methods/Results: We injected MHC-HO-1, MHC-Cre, and CBA (transgenic mice containing a floxed β-gal-stop-codon cassette upstream of the *hmox1* gene) with tamoxifen (TAM) to induce Cre Recombinase activity, and monitored HO-1 induction, survival, cardiac function by echocardiography, and the process of cardiomyocyte death by apoptosis. We compared MHC-HO-1 mice with single transgenic MHC-Cre mice to determine the effect of HO-1 overexpression on Cre-induced toxicity. We also included CBA single transgenic control groups to determine if TAM administration by itself had an effect on the heart. We determined that in MHC-HO-1 mice, maximal HO-1 induction occurred by three days after TAM administration (~60-fold increase in HO-1 mRNA message), but decreased thereafter due to Cre-induced toxicity. HO-1 induction prevented the nearly 85% mortality rate observed in MHC-Cre mice three days after TAM administration. By echocardiography, we observed that cardiac HO-1 induction in MHC-HO-1 mice protected against the severe systolic dysfunction caused by Cre activation in MHC-Cre mice (22.84% versus 42% decline in ejection fraction, respectively). TAM in CBA mice resulted in no significant changes relative to untreated mice.
Conclusion: HO-1 overexpression in the myocardium protects the heart from Cre-induced toxicity.

Hunt, Raymond Bryce (Bryce)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Dr. Pauline Jolly
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Aflatoxin effects in liver cancer and liver disease in Ghana

Abstract

Pupose: The study has been designed to determine aflatoxin biomarker levels in hepatitis B (HBV) and hepatitis C (HCV) positive patients and the association between aflatoxin biomarker levels and liver disease or liver cancer. Predictors of high aflatoxin biomarker levels were investigated in study participants. This study provides data that can be used to formulate educational and other interventions to decrease aflatoxin intake, improve the quality of life, and reduce the high morbidity and mortality associated with liver disease and liver cancer in Ghana.
Method: The participants were divided into three populations: cases, control positives, and control negatives. Cases are HBV and/or HCV positive and also have measurable liver damage (ALT readings greater than 60, ultrasound findings, or physical symptoms). Control positives are HBV and/or HCV positive without measurable liver damage. Control negatives are HBV and HCV negative and without liver damage. All participants were interviewed to complete a questionnaire of demographic, health, family health, and dietary intake questions. When available, chart review was performed for all participants. Urine (30mL) and blood samples (10mL) were obtained. The blood was separated into plasma and PBMCs (peripheral blood mononuclear cells) at the KCCR laboratory in Kumasi, Ghana. The case participants were recruited by Dr. Opare-Sem or Dr. Yaw Boakye from the wards or from the hepatitis clinic. The control participants were recruited from the hepatitis clinic or from the Blood Donor Clinic.
Results: Of the 118 participants interviewed, 31 were cases, 31 were control positives, and 57 were control negatives. The urine and blood samples are still frozen at the KCCR laboratory in Kumasi, Ghana and await shipment to UAB for analysis.
Conclusion: No conclusions can be reached at this time while awaiting blood and urine analysis.

Huynh, Thy Nhat (Thy)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Other
Advisor	Bruce Korf, MD, PhD
Abstract Approved By Advisor	Yes
Co-Authors	Bruce Korf, MD, PhD and Steven Carroll, MD, PhD
Title	Health Flow Care of Neurofibromatosis Type 1 Patients with Plexiform Neurofibromas (PN) or Malignant Peripheral Nerve Sheath Tumors (MPNST)

Abstract

Neurofibromatosis type 1 (NF1) is autosomal dominant, neurocutaneous disorder caused by genetic alteration of NF1 gene that encodes for neurofibromin, a tumor suppressor protein located on chromosome 17q11.2. This disease is characterized by growth abnormalities in a wide variety of tissues derived from embryonic neural crest, including plexiform neurofibroma (PN) and malignant peripheral nerve sheath tumors (MPNST). We investigated the flow of care for patients with either PN or MPNST to gain insight on the clinical presentation and outcome of patients who require surgery for either PN or MPNST at the University of Alabama (UAB) Health System. We also assessed if these patients were referred to our NF Clinic. Medical record review was used to screen patients with NF1 who had tumors surgically removed at UAB during 2005-2010 to assess patient management and outcomes. In both sets of patients with PN or MPNST, care is usually referred from a primary care physician (PCP) to UAB Surgery or Neurosurgery Clinic for evaluation and/or surgery after long-standing observation of NF1 progression by the PCP. A limited number of patients were also referred and managed in NF Clinic at UAB. Patients with PN presented to UAB for a variety of complaints that include pain, bleeding, numbness, etc. Patients with PN entered the UAB Health System via PCP referral for pain or other complaints, undergo surgery, and follow-up with surgery briefly before returning to PCP. In contrast, the majority of patients with MPNST generally presented with chief complaint of visible mass or pain. Due to the aggressive nature of MPNST, patients undergoing surgery for MPNST were more likely to be compliant with medical advice and follow-up management than patients treated for PN. Notably, patients with MPNST were more prone to resection and metastasis, and thus underwent radiation oncology treatment than patients with PN. Our study revealed a difference in extent of care, presentation, and outcome for NF1 patients with PN or MPNST. These findings also indicated that outreach to surgical specialties will be necessary to identify patients in order to facilitate care in NF Clinic and collect tissue samples for research in the future.

Jarrell, Seth Adam (Seth)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Dr. Nancy Tofil
Abstract Approved By Advisor	Yes
Co-Authors	Nancy Tofil, MD, Collin King, MD, 3. Jennifer Dollar, MD2, 4. Seth Jarrell, MS6, 5. Jerri Zinkan, MPH, RN4, 6. Amber Youngblood, BSN, RN 3, 7. Dawn Taylor Peterson, PhD5, Marjorie Lee White
Title	Simulated Ventricular Fibrillation in an Anesthetized Pediatric Patient

Abstract

Backgound:
Pediatric emergencies in anesthesia are rare, and exposure to critical events depends on the residency program. Literature shows that simulation of critical intraoperative events improves performance of anesthesia residents in the attainment of event specific skills. The purpose of this study was to evaluate time to recognition of cardiac arrest in pediatric prone patients and to expose all learners to the management of emergencies in prone patients.

Methods:
Simulations designed for anesthesia residents were conducted monthly for 13 months. Each team participated in a scripted scenario in which a patient undergoing posterior spinal fusion experiences hypotension, metabolic acidosis, hypothermia and hyperkalemia from blood products. The patient was prone and hyperkalemia resulted in ventricular fibrillation three minutes into the case. The simulations were viewed by staff, and times to critical events were recorded. The teams were debriefed with a checklist of expected actions after each case.

Results:
Thirteen groups totaling 24 anesthesia residents participated in this study. Although the average time to recognize ventricular fibrillation was one minute and 15 seconds, defibrillation was not requested for another 40 seconds. Only five out of 13 groups (38%) recognized hyperkalemia as the cause of arrest. Ten of the 13 groups (76%) ordered an arterial blood gas showing hyperkalemia and only 31% of these gave calcium.

Conclusions:
Pediatric dysrhythmias are rare. Thus, anesthesia residents should consider hyperkalemia in an intraoperative arrest and treatment initiated. Based on the results of our study, the average time to recognition of ventricular fibrillation was one minute and 15 seconds and 38% recognized hyperkalemia as the cause. Therefore time to defibrillation and recognition of hyperkalemia by anesthesia residents could be improved. Exposure to critical events through simulation is an effective and safe means of providing anesthesia residents with the skills needed to respond effectively in these rare events.

Kadish, Robert (Robert)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	Steven M. Rowe
Abstract Approved By Advisor	Yes
Co-Authors	Sammeta V. Raju, Clifford A. Courville
Title	Recovery of CFTR Function in vitro and in vivo after Smoking Cessation

Abstract

Recovery of CFTR Function in vitro and in vivo after Smoking Cessation

BACKGROUND: Functional cystic fibrosis transmembrane conductance regulator (CFTR) is essential to prevent CF, a disease characterized by recurrent bronchitis. Similar characteristics are found in chronic obstructive pulmonary disease (COPD) due to smoking. Data from our laboratory indicates that cigarette smoke causes CFTR dysfunction in vitro, but whether CFTR dysfunction occurs in vivo and can recover following smoking cessation is unknown. Our objective was to determine the contribution of cigarette smoke exposure to CFTR dysfunction in vivo, and how reversible this abnormality is with smoking cessation.

METHODS: Nine week old A/J mice were exposed to cigarette smoke for 4 weeks after which a nasal potential difference (NPD) reading was obtained on day 0, 7, 14, and 21 in order to monitor recovery of CFTR. To compliment in vivo studies, HBE (Human Bronchial Epithelial) cells were exposed to cigarette smoke and then subjected to a transient short-circuit current experiment (I_{SC}) on day 0, 3, and 7.

RESULTS: Cigarette-smoke exposed mice had reduced nasal potential difference, a measure of CFTR function in vivo, after 4 weeks (low Cl^- + forskolin response on day 0 (-11.5 ± 2.0 $\mu A/cm^2$, -5.6 ± 1.3 $\mu A/cm^2$, respectively, $P<0.05$), but not after 7 days of smoking cessation (-12.7 ± 1.8 $\mu A/cm^2$, -10.7 ± 3.6 $\mu A/cm^2$, respectively). Similarly, after smoke exposure, smoke exposed cells exhibited significantly reduced forskolin currents (17.9 ± 3.7 $\mu A/cm^2$, 4.5 ± 1.8, respectively, $P<0.05$), while 7 days later we observed no significant reduction (9.6 ± 2.7 $\mu A/cm^2$, 8.9 ± 2.0 $\mu A/cm^2$).

CONCLUSION: Both HBE cells and mice exhibited reduced CFTR activity after smoke exposure compared to air control, and fully recovered 7 days later. These results suggest that airway epithelia exposed to cigarette smoke can recover CFTR function and provide further confirmation as to the causal link between cigarette smoking and CFTR dysfunction.

Keith, Charles Joseph, Jr. (Charles)

Project Length	Short
Prior Research Experience	Yes
Funding Source	
Advisor	Marc A. Passman, MD
Abstract Approved By Advisor	Yes
Co-Authors	Michael J Gaffud, Zdenek Novak, Marjan U Mujib, Thomas C Matthews, Mark A Patterson, William D Jordan, Jr
Title	Comparison of Long-term Outcomes following Endovascular Repair of Abdominal Aortic Aneurysms Based on Size Threshold

Abstract

PURPOSE: To determine the effect of abdominal aortic aneurysm (AAA) diameter on long-term outcomes following endovascular repair (EVAR).
METHODS: Patients undergoing EVAR with modular stent grafts from 2000-2011 were identified from a prospectively maintained database and stratified by maximum aortic diameter at time of repair: small (4.0-4.9 cm), medium (5.0-5.9 cm), and large (>/=6.0 cm). Comparisons of demographics, indications for repair, peri-operative complications, and long-term outcomes were made using ANOVA, chi square, and Kaplan-Meier plots.
RESULTS: Seven hundred forty patients were identified: 157 (21.2%) small, 374 (50.5%) medium, and 209 (28.2%) large. Patients differed by mean age (69.3±8.09, 71.7±8.55, and 73.6±8.77 years for small, medium, and large, respectively; P<0.001), coronary artery disease (42% small, 57% medium, 51.2% large; P=0.01), prior coronary angioplasty (14.6% small, 18.2% medium, 9.6% large; P=0.02), congestive heart failure (5.7% small, 15.2% medium, 19.6% large; P=0.01), prior vascular surgery (7% small, 15.8% medium, 10% large; P=0.016), and COPD (21% small, 27% medium, 33% large; P=0.038). Small AAAs were more frequently symptomatic (19.7% small, 7.5% medium, 8.1% large; P<0.001). There was no difference in peri-operative complication rates (P=0.399), expansion >/=5 mm (2.6% small, 5.6% medium, 7.2% large; P=0.148), or all-type endoleak (40.8% small, 41.7% medium, 44.5% large; P=0.73). However, small AAAs developed fewer type I endoleaks (5.1% versus 6.95% medium and 14.8% large; P=0.001). Compared with small AAAs, both medium (P=0.39) and large (P<0.001) required secondary intervention more frequently, with hazard ratios of 2.32 (95% CI: 1.045-5.156) and 4.74 (95% CI: 2.115-10.637), respectively. Ten-year survival was 72%, 63.1%, and 49.8% in the small, medium, and large groups, respectively (P<0.001) with no known AAA-related deaths. All-cause mortality differed among the 75-84 year-old patients (30.4% small, 51.6% medium, 55.7% large; P=0.017).
CONCLUSIONS: EVAR for small AAAs shows improved long-term outcomes than for age-matched patients with larger aneurysms.

Kezar, Carolyn Elise (Carolyn)

Project Length	Long
Prior Research Experience	Yes
Funding Source	
Advisor	Dr Gustavo Heudebert
Abstract Approved By Advisor	Yes
Co-Authors	Dr Gustavo Heudebert
Title	Survey of United States Medical Schools Basic Clinical Skills Curricula

Abstract

This project examines the education methods employed at United States medical schools for teaching basic clinical skills training to medical students during the first two years. We hope to determine the scope of educational tools employed in clinical skill instruction and to collect information on particularly innovative and successful approaches. The project is a web-based survey of clinical curricula components for every United States medical school, administered via AAMC email contacts to be completed by faculty members responsible for clinical courses such as an Associate or Assistant Dean. An iterative process was utilized to develop the content of this survey instrument; input from seasoned educators was sought to choose the original questions and refine the content. The survey questions address topics such as: school size, school funding, curricula type, instructional session frequency, small group size (if utilized), course duration, course instructors, type of patients utilized, setting, and course evaluation method.

Medical curricula are required to include clinical skills training during the first two years. There is currently no standardized format for instructional method, and minimal information is available about approach efficacy. These survey results will describe the scope of clinical medicine instructional methods and compare novel approaches to traditional curricula. Preliminary findings include use of residents and fellows as educators, as well as the different approaches to standardized patients for teaching and testing.

Khan, Farah Naz (Farah)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Andrea Cherrington
Abstract Approved By Advisor	Yes
Co-Authors	April Agne, Sandeep Buttan, Andrea Cherrington
Title	Assessing barriers to uptake of available services and diabetes education amongst patients with diabetes: A qualitative study in Delhi, India.

Abstract

Assessing barriers to uptake of available services and diabetes education amongst patients with diabetes: A qualitative study in Delhi, India.

Farah Naz Khan[1], BS; April A. Agne[2], MPH; Sandeep Buttan[3], MBBS, MS; Andrea L. Cherrington[2], MD, MPH

1. UAB School of Medicine; 2. UAB Division of Preventive Medicine; 3. Dr. Shroff's Charity Eye Hospital

Background: Diabetes is a growing problem in India, yet little is known about the awareness levels and barriers to care amongst patients with diabetes. The purpose of this qualitative study was to investigate patients' knowledge related to diabetes and its complications as well as barriers to care.

Methods: Semi-structured interviews were conducted with patients with diabetes seen at Dr. Shroff's Charity Eye Hospital (SCEH) in Delhi. The moderator's guide incorporated constructs from the Health Belief Model. Interviews were recorded and transcribed. Two independent reviewers used a combined inductive-deductive approach to identify themes.

Results: Twenty-three participants were interviewed; the mean age was 59, nearly half were men (42%), most were married (83%), and 48% had less than 10 years of education. Participants had general knowledge about the severity of diabetes, but did not necessarily perceive personal susceptibility to the complications of diabetes. Cues to action were typically symptom-related. Most patients recognized exercise and diet as key components of diabetes management, but self-efficacy for these behaviors was low. Often patients had difficulty identifying their diabetes related needs based on limited knowledge; when identified, limited education and financial constraints were the main barriers reported.

Conclusions: This study suggests there is a need for accessible diabetes education programs in India. Further research is needed to elucidate specific barriers to uptake of available healthcare services amongst patients with diabetes in India.

Keywords: Endocrinology/metabolism, global health, qualitative research, chronic disease management

Submission Category: Qualitative Research

Kukkamalla, Rene (Meghana)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center Fellowship
Advisor	Dr. Gareth Dutton
Abstract Approved By Advisor	Yes
Co-Authors	
Title	The Impact of Group Size on Weight Loss Interventions

Abstract

Obesity is a pressing public health concern especially because it is a risk factor for Type 2 diabetes. Many weight loss interventions are administered in a group setting; however, the ideal number of participants optimal to gain the greatest reduction in weight has not been determined. This study hypothesized that interventions administered via a small group (~12 members) would not produce larger weight loss percentages than those of a large group (~33 members). The intervention included weekly group sessions for the first six months and monthly group meetings for the last six months. The primary outcome variables were percent weight loss at baseline, 6 months, and 12 months, while the secondary outcomes were session attendance, patient satisfaction, and group climate. Participants in the small groups lost more weight than those in the large group at month 6 (M6) and month 12 (M12); however, the difference was significant only at M12. Based on the pattern of continued weight loss in the small groups and weight regain in the large group from M6 to M12, participating in a small group may confer the greatest benefits at extended follow-ups. The small groups had a higher mean number of session attendance than the large groups, raising the question of whether treatment attendance may mediate the association between group size and weight loss outcomes. In regards to patient satisfaction ratings, at M6 there was not a significant difference between the two groups; however, the mean satisfaction ratings of the small group were significantly greater than those of the large group at M12. There was a significant difference in the group climate scale between the two groups at both follow-ups, with the small groups reporting significantly stronger group climate scores, suggesting that this may be an important factor for the success of the small group environment.

Laufer, Vincent Albert (Vincent)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Harald Sontheimer
Abstract Approved By Advisor	Yes
Co-Authors	Vishnu Cuddapah
Title	Characterization of Astrocytes Co-Cultured with Human Glioblastoma Multiforme Cells

Abstract

Glioblastoma multiforme (GBM) is the most common and deadly primary brain cancer, with a mean survival of only 14 months. This dismal prognosis stems in part from the resistance of GBM to standard cancer regimens, including chemotherapy, surgical resection, and radiation. Since glioma cells are resistant to standard therapies, new treatment options are needed. One promising target is astrocytes, which carry out a number of cellular processes believed to be altered by gliomas. We hypothesize that human gliomas induce reactive gliosis in astrocytes, and propose that targeting this more homogenous population of cells may allow for decreases in morbidity and mortality that standard regimens have been unable to provide. Specifically, a common presenting symptom for GBM is seizure, which results from neuronal hyperexcitability. This hyperexcitability can be caused by an accumulation of K^+ in the extracellular space. Therefore we hypothesized that there was a disruption of astrocytic Kir4.1 channels, which are responsible for clearing K^+ from the extracellular space. Using whole-cell patch clamp electrophysiology, we measured Kir4.1 current by blocking it with Barium. However, we saw no significant difference between naïve and gliotic astrocytes. Instead, we found that magnitude of currents of naive and gliotic astrocytes is different before the application of Barium. This likely means that another channel or transporter is upregulated, and characterizing this current will be one of our goals for the future. To further characterize the nature of astrocyte-glioma interaction we also present data regarding the gap junction coupling between astrocytes and glioma cells, as well as time-lapse studies of glioma.

Le, Phuong Thanh To (Thanh)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Ambika Ashraf, Children's of Alabama, Department of Endocrinology
Abstract Approved By Advisor	Yes
Co-Authors	Carrie Huisingh, Ambika Ashraf
Title	Early Insulin Therapy Improves Glycemic Control and Diabetic Dyslipidemia in Adolescents with Type 2 Diabetes Mellitus

Abstract

Background: Type 2 diabetes (T2DM) is increasing at an alarming rate especially in ethnic minorities and is associated with significant co-morbidities. The optimal management of T2DM in children remains elusive.

Objective: The primary objective of this study was to identify ethnic discrepancies in outcome of T2DM in European Americans (EA) and African American (AA) children, and whether initiating insulin at diagnosis would be more beneficial for glycemic control and cardiovascular risk outcomes, compared to starting with oral hypoglycemic drugs alone.

Hypothesis: We hypothesize that there are ethnic differences in co-morbidities in children with T2DM, with more ominous cardiovascular disease risk profile in AA. We also hypothesize that insulin therapy will have beneficial effects on outcomes compared to oral hypoglycemic agents alone.

Methods: Retrospective electronic chart review of obese, EA and AA children diagnosed with T2DM over 10 years, in a tertiary care university hospital. Data was collected and analyzed on demographic, clinical and outcome measures at initial presentation, and follow-up at 3-6 months and 8-16 months.

Results: A total of 120 patients, 67.5% females and 80% AA with T2DM were included. Of the 43.3% who were started on insulin at diagnosis, there were 44.8% of AA (43/96) and 37.5% of EA (9/24). Overall, significant improvement in glycemic outcomes (P= <0.0001 in insulin + metformin treated vs. P= 0.02 in metformin alone) and in dyslipidemia in those started on insulin + metformin at diagnosis [improvement in total cholesterol (P= 0.001), LDL (P=0.02), HDL (P=0.01), non-HDL (P= 0.0002), TC/HDL (P= 0.005) in insulin + metformin treated group vs. no significant change in metformin alone group]. Significant improvements in lipid profiles were observed in AA at follow up [total cholesterol (P=0.01), triglycerides (P= 0.01), LDL (P=0.02), HDL (P=0.01), non-HDL (P=0.003), TC/HDL (P= 0.003)].

Conclusion: Insulin along with metformin therapy at onset has significant beneficial effects on T2DM outcomes. AA children may benefit from insulin therapy early on.

LeGrand, Jason Nathaniel (Jason)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Christopher Klug
Abstract Approved By Advisor	Yes
Co-Authors	Heidi Nick, C. Scott Swindle
Title	A Mouse Model of inv(16) and Kras Acute Myeloid Leukemia

Abstract

The inv(16) chromosomal inversion is one of the most frequent cytogenetic abnormalities found in adult patients with acute myeloid leukemia (AML). The resulting fusion protein between core binding factor β and smooth muscle myosin heavy chain, *MYH11,* (CBFβ-SMMHC) has been shown to be insufficient for leukemogenesis without additional genetic changes. Clinical studies of AML patient samples have shown that *K-RAS* mutations are over-represented in inv(16) AML versus other AML subtypes. This finding suggests that *K-RAS* mutations may contribute to the leukemogenesis of inv(16) AML and may have implications for therapy. To address this question and to evaluate potential therapeutic approaches, we created a mouse model to explore CBFβ-SMMHC and *K-RAS* cooperativity in leukemogenesis. To create this model, we transduced bone marrow from Cre^{ERT} inducible LSL $K\text{-}ras^{G12D}$ mice with a CBFβ-SMMHC-IRES-GFP retrovirus and transplanted GFP+ FACS-sorted cells into C57BL/6 congenic recipients. After engraftment, $K\text{-}ras^{G12D}$ expression was induced by tamoxifen injection and leukemia development was followed over time by monitoring peripheral blood. The initial results have been complicated by an aggressive GFP- T-cell leukemia that developed in the majority of both the control and CBFβ-SMMHC recipients 2-3 months after transplant. The lack of GFP expression by these T-cell leukemias indicates that they are derived either from contaminating GFP- cells in the transplant or from a portion of the transplant that has silenced the expression of the CBFβ-SMMHC retrovirus.

Lin, Erica (Erica)

Project Length	Short
Prior Research Experience	Yes
Funding Source	O'Brien Center Fellowship
Advisor	Scott Ballinger
Abstract Approved By Advisor	Yes
Co-Authors	Erica Lin, Melissa Sammy
Title	Role of mitochondrial oxidant production in insulin secretion

Abstract

Diabetes mellitus (DM) affects almost 24 million people in the US, and type 2 DM accounts for 90-95% of all its diagnosed cases. Type 2 DM, characterized by hyperglycemia due to failure of glucose-stimulated insulin secretion and insulin resistance by pancreatic β-cells, is thought to be a polygenic disease. While nuclear genetics cannot account for its differences in ethnic susceptibility, we hypothesize that mitochondrial mutations, which were evolutionarily advantageous during Northern migration out of Africa, can. Specifically, we hypothesize that production of mitochondrial reactive oxidant species (mROS) in pancreatic β-cells influences insulin secretion. Therefore, individuals with mitochondrial haplogroups, characterized by greater mitochondrial "economy," will have increased mROS production in response to the same level of substrate (e.g. glucose), and increased basal levels of oxidant stress, due to long-term excess caloric intake, is hypothesized to stimulate insulin secretion and result in insulin resistance, an event in the development of type 2 DM. To test this hypothesis, insulin secretion from pancreatic islets, under conditions of basal levels of glucose with and without oligomycin will be quantified in wild-type C3H/HeN and C57BL/6J mice strains, which, like humans, have differential susceptibility to dietary-induced insulin resistance: C3H/HeN mice are resistant while C57BL/6J mice are susceptible. These two strains also have distinct mtDNA sequences. Both mice exhibit increases in secreted insulin in the presence of oligomycin, despite the inhibited ATP production, suggesting that oligomycin-induced mROS generation stimulates insulin secretion; however, C57 mice reported a considerably lower change in insulin secretion compared to C3H mice likely due to differences in mitochondrial coupling. Specifically, this study provides insight into the role of mitochondrial oxidant production and genetics in caloric utilization. Moreover, it will potentially have significant impact in our understanding of the association between mitochondrial DNA and pancreatic function as well as differential susceptibility to type 2 DM.

Luker, Austin Malory (Austin)

Project Length	Short
Prior Research Experience	Yes
Funding Source	HSF Community and Rural Health Fellowship
Advisor	Lee Ascherman, MD and Tolu Aduroja, MD
Abstract Approved By Advisor	Yes
Co-Authors	Lisle Hites, PhD; Jessica Wakelee, MPH
Title	Perceptions of Rural vs. Urban Primary Care Physicians Regarding Telepsychiatry

Abstract

Background:
There is currently a shortage of practicing psychiatrists in Alabama, with the deficit exacerbated by inequitable geographic distribution of psychiatrists toward larger, more metropolitan areas. The purpose of this study was to assess the perceptions and interests of primary care physicians in Alabama in using telepsychiary to meet their patients' mental health needs.
Hypothesis:
It was predicted that rural primary care physicians will have a greater perceived need of psychiatric services than urban and suburban physicians, and rural physicians will have greater interest in telepsychiatry.
Method:
A 15-minute web survey was offered to practicing Alabama internists, pediatricians, and family physicians. Perceptions were assessed in 4 areas using a numeric scale: comfort level in treating psychiatric illness, current satisfaction with psychiatric services, current perceptions related to telepsychiatry, and level of interest in using telepsychiatry.
Results:
Out of 40 respondents, 20 described themselves as "rural;" 5 as "suburban," and 13 as "urban." Comfort levels in treating mental illness were similar across geographic groups; with high average comfort for mild psychiatric illness (8.3/10)—which diminished with increasing severity. Satisfaction with psychiatric services was low across all groups, with rural physicians noting a lower satisfaction with availability of services (2.8/10), compared to urban responders (3.8/10). Rural responders reported greater familiarity with telepsychiatry than urban responders (5.0 vs. 3.1/10). Overall interest in using telepsychiatry was high, with rural physicians expressing greater interest than urban responders for patient assessment (8.3 vs. 7.1/10 and patient management (7.6 vs. 6.6/10).
Conclusions:
Preliminary findings suggest that there may be a greater perceived need for psychiatric services, and a greater interest in telepsychiatry among rural physicians. These differences appear to be modest, and the data may reflect a state-wide deficit in mental health care. It is anticipated that further data collection and analysis will provide additional clarity.

Ma, Elizabeth Yean (Elizabeth)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Tim Townes, PhD
Abstract Approved By Advisor	Yes
Co-Authors	Chia-Wei Chang, Dewang Zhou, Tim Townes
Title	Potential Role of Kinases in Fetal to Adult Globin Gene-switching

Abstract

Sickle cell disease (SCD) is an autosomal recessive disorder caused by an A to T transversion in the adult, human β-globin gene, resulting in rigid, "sickled" red blood cells that can occlude small capillaries, leading to stroke, kidney failure, and other painful crises. SCD is not a major problem until after the first couple months of birth, when the anti-sickling human fetal hemoglobin (γ-globin) has switched almost completely to adult Hb (β-globin). Knockdowns of Klf1, an erythroid-specific transcription factor, increases the γ-globin:β-globin ratio in adult red blood cells suggesting it is a key player in this switch. Environmental signal transducers may help regulate Klf1, so 2000 kinases in human adult bone marrow progenitor cells were knocked down with lenti/shRNA and assayed to test this hypothesis. Some were found to increase the γ-globin:β-globin ratio to 3:1 or higher, suggesting that they are involved in gene-switching. Our goal was to confirm this by doing the opposite experiment – determining whether upregulating these kinases in cord blood progenitors or in embryonic stem (hES) cell-derived CD34+ hematopoetic progenitor cells, would switch them from ~50% γ-globin into 98% β-globin.

METHODS: 4 target kinase cDNAs were used for this study. Each was subcloned into a lentiviral expression vector via restriction enzyme digestion, purification, and ligation into the vector plasmid. Vectors were then transformed into DHα-competent *E. coli* cells and expanded overnight. Kinase cDNA insertion was verified with mini-prep, PCR, and DNA sequencing. *In vitro* CD34+ cells were generated by co-culturing H1 hES cells onto a modified, primary human cell for differentiation into hematopoetic progenitor cells for 20-24 days. CD34+ cells were purified from the culture via immunomagnetic beads and verified via FACS.

RESULTS: One kinase was confirmed to be inserted with correct orientation into the target vector. FACS analysis on cell culture showed CD34+ cells were present in the hES-derived cells, as well as double-positive CD34+ and CD43+ cells.

CONCLUSION: We were able to subclone one of the potentially regulatory kinases into a vector, which will then be used to create a virus to transduce the cells. On the cellular side, we have shown that it is possible to generate CD34+ cells *in vitro* by co-culturing human ES cells on human primary cell lines, helping move the field towards using less animal products and therefore less chance of rejection during transplantation. This has significant implications on future gene therapies derived from this system.

Martin, Morgan Sparks (Morgan)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Sherry Collawn
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Successful treatment combination for refractory keloid scars on the upper back

Abstract

Keloids and hypertrophic scars are common lesions, which typically present as a cosmetic concern; however, they also can cause significant pruritus and pain. These lesions pose as a particular therapeutic challenge among clinicians due to a lack of complete knowledge of the formation of keloids and hypertrophic scars. Multiple treatments are widely accepted, yet all have shown limited benefit. In this case, we describe the treatment combination of CO_2 fractional laser (10 600 nm, Cynosure), Pulsed dye laser (585 nm, Cynosure), and topical application of triamcinolone diacetate for keloids refractory to solitary treatments of triamcinolone diacetate injection and other laser modalities.

Mays, Melissa Ann (Melissa)

Project Length	Short
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Dr. Elizabeth Sztul
Abstract Approved By Advisor	Yes
Co-Authors	Jason Lowery, John Wright, Elizabeth Sztul
Title	Progress Toward a Crystal Structure of the GBF1-ARF Interface for Therapeutic Drug Design

Abstract

GBF1 is a Golgi-localized guanine nucleotide exchange factor (GEF) that catalyzes GDP to GTP exchange on the ADP-ribosylation factor (ARF) family of GTPases. ARFs are regulators of vesicle formation in intracellular traffic and are only active in the GTP-bound state. GBF1-mediated ARF activation is essential for Golgi biogenesis and for ER-Golgi trafficking of lipids and proteins. All GEFs associated with ARFs share a Sec7 domain (Sec7d) that catalyzes the exchange of GDP and GTP. The activity of GBF1 is inhibited by Brefeldin A, a drug that binds the GBF1-ARF complex and has potent anti-tumor activity. It appears that the GEF GBF1 can be targeted for potential anticancer therapy. Development of optimized drugs requires structural information on the ARF-GBF1 interface. We hypothesize that by generating recombinant GBF1 Sec7d, we will be able to solve its structure. Such structural information will be used to generate models of the GBF1-ARF interface, which will then be used to design drugs with more specificity. We have cloned a fragment of GBF1 containing the Sec7d (amino acids 667-1280) into the pET28b vector and expressed in *E. coli*. We were unable to purify the protein via affinity purification suggesting that the protein was insoluble. We also cloned the same insert into the mammalian expression pcDNA4 vector. This plasmid was transfected into HeLa cells. We were unable to detect the protein by immunofluorescence indicating that the protein was not expressed in mammalian cells, likely because of a long 5' UTR. Alternative expression systems or source DNA will be required for subsequent investigation.

McCormick, Don Earl, III (Don)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Other
Advisor	Candace Floyd
Abstract Approved By Advisor	Yes
Co-Authors	Tracy Niedzielko
Title	Antidepressant Therapy Following Spinal Cord Injury Inhibits Functional Recovery

Abstract

Spinal cord injury (SCI) can significantly alter a person's physical and psychological health. Depression in persons with SCI is often treated with antidepressants which alter serotonergic and adrenergic signaling, both regulators of plasticity. However, the effects of antidepressants functional recovery after SCI have never been evaluated. Therefore, we hypothesize that antidepressant therapy would alter functional recovery and neuropathic pain behaviors in a SCI rodent model.

The aim of this study was to evaluate the effects of venlafaxine (VEN) administration on functional recovery using a SCI rodent model. Adult male Sprague-Dawley rats received a moderate contusion T10 SCI. Therapeutic intervention began at day 31 post-SCI and continued for 30 days. Animals were randomly assigned to receive either VEN, rehabilitation (REHAB), both (VEN/REHAB), or neither as a control (CTRL). Functional recovery was evaluated with the Basso, Beattie, and Bresnahan open-field test, the CatWalk® kinematic analysis, and the Louisville swim scale. Neuropathic pain was assessed using both the tail-flick test and von Frey filaments. Depression was evaluated with the Porsolt forced swim test prior to and following therapeutic interventions.

We found that the group receiving the REHAB intervention alone had significantly increased hind limb function and decreased pain when compared to CTRL, and the benefits of REHAB on motor function were not seen in the VEN/REHAB group. VEN alone had no effect on either pain or functional recovery. These data suggest that VEN treatment hinders the functional recovery gained from REHAB. Another interesting finding seen in groups receiving VEN is a significant increase in the incidence of priapism. Finally, the Porsolt forced swim test showed no differences in depressive behaviors between groups. Therefore, our findings suggest that antidepressant therapy in an SCI model fails to alter depressive behaviors, while preventing functional gains from rehabilitation and causing the untoward side effect of priapism.

Supported by W81XWH-10-1-0839.

McKay, Jack Edward (Jack)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Shawn Gilbert
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Increasing Vascularity to Improve Healing of Segmental Defects

Abstract

Sufficient blood supply is imperative to proper bone healing. Hypoperfused fracture sites are at higher risk for nonunion and infection than well-vascularized sites. Our hypothesis is that application of a substance, Desferrioxamine (DFO), used to induce the Hypoxia Inducible Factor (HIF) Pathway can promote angiogenesis and subsequent bone formation in a rat segmental defect model. In our study, the femur was exposed on Brown Norway rats under anesthesia to allow a 8mm defect to be created. The defect was then fixed either with an external fixator or internally with a 1.6mm Kirschner wire. The animals were then inoculated with a gram-negative / gram-positive bacterial combination to recreate the setting of severe contaminated open fractures. The gram-negative strain was *Acinetobacter Baumannii Complex* (ABC). The gram-positive strain was *Methicillin Resistant Staphylococcus Aureus* (MRSA). This bacteria combination was chosen to simulate an infection resulting from a contaminated battle wound. Depending on the study group, the animals were then treated at different time points with either normal saline, antibiotics, DFO, or a combination of DFO and antibiotics. The extent of infection, angiogenesis, and subsequent healing was then evaluated. Our evaluation methods include radiograph, microCT angiography, bone culture, vascular perfusion study, histological examination, PCR, and biomechanical strength testing. We found that over the course of the injury, the infection became predominantly gram-positive (MRSA) in nature. Also, we found that DFO is capable of increasing angiogenesis and improving the strength of newly healed bone. It is our hope that therapeutic angiogenesis can alter the standard of care for severe open contaminated fractures.

Meadows, Jarrod Phillip (Jarrod)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	John J Hablitz
Abstract Approved By Advisor	Yes
Co-Authors	David Sweatt
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. We also aim to investigate the types of epigenetic changes involved in synaptic scaling. Through the use of techniques such as high pressure liquid chromatography/mass spectrometry, western blotting, chromatin immunoprecipitation, methylation-dependent immunoprecipitation, and RT-PCR we will be able to measure the epigenetic changes at the global and individual gene levels and also assess how those changes effect gene expression.

Meehan, Margaret Janice (Maggie)

Project Length	Short
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Allan Zajac
Abstract Approved By Advisor	Yes
Co-Authors	Rakesh K Bakshi, Allan Zajac
Title	The CD200/CD200R interaction is a potential target for relieving T cell exhaustion

Abstract

Effective cell mediated immune responses are essential for restricting tumor outgrowth and controlling intracellular pathogens. Although these responses potently control malignancies and infections, tumor progression does occur and chronic infections do become established. Both of these scenarios represent the presence of a persistent antigenic burden, which is difficult for the host immune response to eradicate. Under these conditions it has been shown that T cells succumb to exhaustion, which is associated with a progressive loss of effector functions. A hallmark of the exhausted state is the expression of constellations of inhibitory receptors such as PD-1 and LAG3, which limit the ability of the T cells to respond to stimulation. The CD200 cell surface glycoprotein is known to be expressed on a wide range of cells including neurons, endothelium, B cells, and activated T cells. The CD200 receptor (CD200R) has been shown to be expressed on cells of the myeloid lineage, and CD200-CD200R interaction is known to result in contact mediated inhibition of myeloid cell activity. The role of CD200 and its receptor in the exhaustion process is undefined. We examined CD200 and CD200R expression in C57BL/6 mice and CD4 depleted mice infected with Lymphocytic choriomeningitis virus (LCMV) clone 13, a well-established model of chronic infection. Here we show that CD200 and CD200R are upregulated on virus–specific T cells as they succumb to exhaustion in chronically infected hosts. Moreover, other cell types including NK cells, macrophages, and dendritic cells also express CD200R as the infection ensues. Our findings provide rational for tactically blocking the CD200-CD200R axis as a potential stand-alone or combination therapy to boost ineffective immune responses to tumors or chronic viral infections.

Mitchell, Chase Matthew (Chase)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Elizabeth Sztul
Abstract Approved By Advisor	Yes
Co-Authors	Jason Lowery, John Wright, & Elizabeth Sztul
Title	Regulation of Catalytic Activity of the ARF GEF GBF1 by Non-catalytic Domains and its Role in Cancer Cell Survival

Abstract

After proteins are synthesized in the endoplastic reticulum, they must cross the Golgi network before they begin their journey to their intended destination. Transport to and within the Golgi requires vesicle formation, a process that is controlled by Golgi-specific brefeldin A-resistance factor 1 (GBF1). GBF1 is a guanine nucleotide exchange factor (GEF) that localizes to early Golgi compartments and functions to activate ADP-ribosylation factors (ARFs). ARFs facilitate vesicle formation by recruiting coat proteins that participate in sorting proteins into vesicles. Before ARFs can initiate vesicle formation, they must be activated by a GEF. All GEFs share a common catalytic site known as the Sec-7 domain. Our hypothesis is that other domains adjacent to Sec-7 play crucial roles in structural stabilization and regulation of catalytic activity. Our area of interest includes the HUS, HDS1, and HDS2 domains that flank the Sec-7 domain. We cloned a DNA insert encoding HUS-Sec-7-HDS1-HDS2 domains into expression vectors for bacterial and mammalian cells, and attempted to express proteins in both systems. We were unable to express the fragment in bacteria because of its large size (>100,000 kDa). We didn't detect expression in mammalian cells probably due to the long 5' UTR of the construct. The next step in our research is to attempt protein expression using shorter constructs or genes from other organisms such as *Rattus norvegicus* or *Mus musculus.*

Moseley, Carson Edward (Carson)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Casey T. Weaver
Abstract Approved By Advisor	Yes
Co-Authors	Craig L. Maynard, Theresa Ramos, Scott R. Barnum, Robin D. Hatton, Casey T. Weaver
Title	Functional characterization of transcription factors in CD4+ T cell development and autoimmunity

Abstract

The immune system is capable of recognition and clearance of diverse types of pathogens from the body. Effector CD4+ (Helper) T Cells are a principal component of the immune system that directs these varied responses, which ultimately result in pathogen clearance. Helper T Cells differentiate from naïve precursors in response to antigen and inflammatory signals along several developmental pathways (e.g. Th1, Th2, and Th17) that allow for optimal immune responses to invading microbes. For example Th1 cells develop in response to IL-12, up-regulate the transcription factor T-bet, and secrete Interferon-γ in order to promote clearance of intracellular bacteria and viruses. Although the signaling cascades, transcription factors, and secreted cytokines characteristic of each CD4+ T cell lineage have been well defined, precisely how these differentiation programs act to reorganize chromatin and alter gene transcription remains in its infancy. While attempting to develop methods to assess lineage-relevant loci in CD4+ T cells, we focused on a transcription factor predicted to bind in several critical cytokine genes—including in the *Il17a/f* intergenic region—and thought to be involved in human autoimmune disease. In addition to *in vitro* T cell differentiation and Chromatin Immunoprecipitation (ChIP) assays, we also performed *in vivo* experiments to evaluate the function of this transcription factor in mouse models of autoimmunity. Thus, we have utilized a multi-modal approach to assess the function of transcription factors in T cell differentiation that should have relevance for other cells types as well as for preliminary investigations of human disease.

Mwakalindile, Edwin (Edwin)

Project Length	Short
Prior Research Experience	No
Funding Source	
Advisor	Henry E. Wang, MD, MS
Abstract Approved By Advisor	Yes
Co-Authors	Su Q. Nguyen, Edwin Mwakalindile
Title	The Accuracy of Automated Sepsis Detection in the Emergency Department

Abstract

Sepsis poses a major health burden in the US, resulting in 200,000 deaths annually. While often first treated in the Emergency Department (ED), identification of sepsis in this setting is very difficult since clinicians may not recognize the patterns of signs, symptoms, and laboratory results that constitute sepsis. Electronic medical record (EMR) clinical decision tools offer a novel strategy for identifying patients with critical illness such as sepsis. We tested the accuracy of an EMR-based automated sepsis identification system.

We tested an EMR-based sepsis identification tool at a major academic urban tertiary care ED with 70,000 annual visits. The ED EMR system collected vital sign and laboratory test information on all ED patients, triggering a “sepsis alert” for all ED patients with ≥2 SIRS criteria (fever, tachycardia, tachypnea, leukocytosis) plus ≥1 major organ dysfunction (SBP≤90 mm Hg, lactic acid>1.9). We determined the “gold-standard” presence of sepsis through manual review of ED physician, nursing and laboratory records. We also reviewed a random matched selection of non-sepsis alert ED records, confirming the presence or absence of sepsis. We evaluated the diagnostic accuracy of the sepsis identification tool by calculating sensitivity, specificity, positive and negative predictive value, and area under the ROC curve.

From January 1 – March 31, 2012, we analyzed 794 automated sepsis alerts and 301 non-alerts. “Gold-standard” prevalence of sepsis was 355/784 (45%) among alerts and 0/301 (0%) among non-alerts. Sensitivity and specificity of automated sepsis alerts were 100.0% (95% CI: 98.6-100.0%) and 40.7% (37.1-44.3%). Positive and negative predictive values were 44.7% (95% CI: 41.2-48.3%). Area under the ROC curve was 0.71 (95% CI 0.69-0.72). Along false-positive sepsis alerts, the most common medical conditions were gastrointestinal (26.6), traumatic (26.1%) and cardiovascular (20.3%) conditions.

This ED EMR-based automated sepsis identification system demonstrated high sensitivity but low specificity. Automated EMR-based detection may provide a viable strategy for identifying sepsis.

Nevin, Christa Renee (Christa)

Project Length	Short
Prior Research Experience	Yes
Funding Source	O'Brien Center Fellowship
Advisor	James H. Willig, MD, MSPH
Abstract Approved By Advisor	Yes
Co-Authors	Donald Dempsey, Martin Rodriguez, Andrea Cherrington, Mukesh Patel, Niveditha Thota, Erin D. Snyder, Angelo L. Gaffo, Joseph Barney, Matthew Wyatt, Brita Roy, David Daly, James H. Willig
Title	New Graduate Medical Education teaching strategies in a post-ACGME work-hour mandated environment.

Abstract

Background: In 2003 and 2011, the Accreditation Council of Graduate Medical Education (ACGME) introduced guidelines limiting resident duty hours, resulting in a decrease in educational opportunities for residents. We explored resident attitudes regarding the educational impact of ACGME guidelines and openness to new educational strategies. With these data, and applying principles of Gamification (the use of game elements in non-game applications), we developed a web-based application to supplement medical resident training.

Methods: Eight focus groups of internal medicine residents at the University of Alabama at Birmingham (UAB) were conducted between 6/2012-7/2012 to explore attitudes towards the 2011 ACGME duty hour guidelines. Focus group transcripts were reviewed and common themes identified using a deductive/inductive approach. Participants also completed a survey on openness to new teaching strategies. Using Gamification principles, we developed an online software application (Kaizen-IM), accessed via desktop or mobile device, to improve medical knowledge by allowing residents to compete with their peers to answer clinically relevant questions in structured multispecialty-focused seasons throughout the academic year.

Results: 34 residents participated in focus groups (16 PGY-1, 12 PGY-2, 6 PGY-3). Residents reported a decline in teaching by attending physicians and by PGY-2/PGY-3 residents to interns since implementation of the ACGME guidelines. 79% reported that they would use an application that allowed them to compete with peers to improve medical knowledge. Kaizen-IM, named after the Japanese business principle of continuous improvement, was launched on 8/20/12. After 10 days, 20 questions (2/day) developed by UAB faculty were administered to 73 residents who provided 1082 total responses.
Conclusions: Residents are concerned about the educational impact of the ACGME work-hour restrictions and are open to new learning strategies. Novel educational methodologies, like Kaizen-IM, may provide additional learning opportunities for residents. Kaizen-IM is actively being used and has been enthusiastically embraced by UAB Internal Medicine residents.

Nguyen, Su Quoc (Su)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Dr. Henry Wang
Abstract Approved By Advisor	Yes
Co-Authors	Edwin Mwakalindile
Title	The Accuracy of Automated Sepsis Detection in the Emergency Department

Abstract

Sepsis poses a major health burden in the US, resulting in 200,000 deaths annually. While often first treated in the Emergency Department (ED), identification of sepsis in this setting is very difficult since clinicians may not recognize the patterns of signs, symptoms, and laboratory results that constitute sepsis. Electronic medical record (EMR) clinical decision tools offer a novel strategy for identifying patients with critical illness such as sepsis. We tested the accuracy of an EMR-based automated sepsis identification system.

We tested an EMR-based sepsis identification tool at a major academic urban tertiary care ED with 70,000 annual visits. The ED EMR system collected vital sign and laboratory test information on all ED patients, triggering a “sepsis alert” for all ED patients with ≥2 SIRS criteria (fever, tachycardia, tachypnea, leukocytosis) plus ≥1 major organ dysfunction (SBP≤90 mm Hg, lactic acid>1.9). We determined the “gold-standard” presence of sepsis through manual review of ED physician, nursing and laboratory records. We also reviewed a random matched selection of non-sepsis alert ED records, confirming the presence or absence of sepsis. We evaluated the diagnostic accuracy of the sepsis identification tool by calculating sensitivity, specificity, positive and negative predictive value, and area under the ROC curve.

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This ED EMR-based automated sepsis identification system demonstrated high sensitivity but low specificity. Automated EMR-based detection may provide a viable strategy for identifying sepsis.

Novack, Andrew Scott (Scott)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	Dr. Reed Estes
Abstract Approved By Advisor	Yes
Co-Authors	Dr. Reed Estes
Title	Iliotibial Band Stretching and Vastus Medialis Strengthening for the Prevention of Patellofemoral Syndrome and Iliotibial Band Syndrome in Track and Field Athletes: A Randomized Controlled Trial

Abstract

Background:

The purpose of this research is to test a hypothesis that adding two iliotibial band stretches and a vastus medialis strengthening exercise to the normal routine of a track and field athlete will help to reduce the incidence of patellofemoral syndrome (PFS) and/or iliotibial band syndrome (ITBS). Due to suggestion that the vastus medialis, a stabilizing muscle for the patella, is overpowered in a person suffering from PFS, the routine focuses on stabilizing the patella through stretching of the iliotibial band and strengthening of the vastus medialis.

Methods:
Members of the Women's Track and Field team at UAB will be invited to participate. Following voluntary enrollment, the team will be divided into two groups in each of three different areas: distance, sprints, and field events. The control and prevention groups will be randomized by coin flip, with the control group continuing routine training without adding new modalities and the prevention group adding two iliotibial band stretches and a vastus medialis strengthening exercise to the warm up. Evaluation by the team physician will be made at pre, mid, and post season, as well as whenever the participant has complaints indicating possible PFS or ITBS.

Results and Conclusions:
The additions to the typical warmup routine are expected to help decrease the incidence of PFS and ITBS by decreasing the adduction of the knee and stabilizing the patella during running and jumping to improve patellofemoral tracking and decrease patellofemoral contact forces. The trial will be in progress at the time of medical student research day, yet formal conclusive data will not be available until conclusion of the track season in June 2013, at which time the initial trial will end. At this juncture, there is a goal of expanding to other track and field teams in the state.

Nwaobi, Sinifunanya Elvee (Sini)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Michelle Olsen
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Epigenetic Regulation of Kir4.1 During Normal Astrocytic Development

Abstract

Astrocytes are the most numerous cells in the brain and play a critical role in maintaining homeostatic extracellular potassium ([K+]e) in the CNS. This process is largely mediated by an astrocyte-specific, inwardly rectifying potassium Kir4.1. Pharmacological inhibition, knock down or complete knock out of this channel results in astrocytes with increased membrane resistance, depolarized resting membrane potential and altered extracellular potassium dynamics. Subsequent to the dysregulation of [K^+]e, Kir4.1 KO animals suffer from ataxia, seizures, and early postnatal death. Kir4.1 has long been characterized as a seizure susceptibility gene. The importance of Kir4.1 is further underscored by studies that link mutations in the gene to developmental disorders which are characterized by early onset seizures, ataxia, epilepsy, and severe cognitive impairments. Multiple lines of evidence demonstrate consistent loss of Kir4.1 coincident with reactive gliosis, a hallmark of several CNS pathologies. Kir4.1 exhibits robust developmental upregulation. Despite the essential role of Kir4.1 in normal and pathologic states, there is no information regarding the regulation of Kir4.1. **We hypothesize that normal developmental upregulation of Kir4.1 expression occurs via altered DNA methylation states of the Kir4.1 gene.** To assess the DNA methylation status of Kir4.1 we utilized **M**ethylation-**S**ensitive **H**igh **R**esolution **M**elt (MS-HRM) analysis followed by pyrosequencing. Our data demonstrate that the robust developmental upregulation of Kir4.1 is paralleled by decreased DNA methylation of the Kir4.1 gene. Additionally, DNA methyltransferase inhibitors which decrease the methylation state of Kir4.1 were sufficient to drive expression of Kir4.1 *in vitro.* Overall, our studies suggest that developmental increases in Kir4.1 are mediated by decreases in DNA methylation of the Kir4.1 gene. Given the broad clinical implications for both acute and chronic dysregulation of [K+]e in a variety of CNS pathologies, understanding the regulation of Kir4.1 expression will prove to be useful in developing therapies for a diverse clinical subset.

Oliver, James Caleb (James)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	
Advisor	Marisa Marques
Abstract Approved By Advisor	Yes
Co-Authors	Russell L. Griffin, Marisa B. Marques
Title	The success of blood management programs depends on an institution-wide change in transfusion practices.

Abstract

Blood management programs aim at packed red blood cell (PRBC) conservation and, most importantly, patient safety. Since our tertiary care institution embarked in a blood management program, we have achieved a decrease in PRBC utilization greater than 25% at 5 years. In this study, we sought to determine how the change occurred.

We analyzed PRBC transfusions for the first 6 months of fiscal year 2007 (pre-blood management) compared with the same months of 2011 by reviewing Transfusion Services' and hospital's electronic records. Medical records of patients admitted for nonsurgical reasons were reviewed for the indication for transfusion, while transfusions for surgical patients were assigned to the surgical specialty.

Transfusion episodes decreased slightly from 9,519 in 2007 to 9,261 in 2011 ($p=0.4358$), while the number of units per transfusion episode had a marked decrease from 2 to 1.5 ($p<0.0001$). This change is probably due to the fact that the percentage of patients who received 1 or 2 units in 2007 (22% and 48%, respectively) was significantly lower than in 2011(51% and 33%, respectively) ($p < 0.0001$). Overall, we classified indications for transfusion in 41 categories. Cardiovascular (CV) surgery, malignancy, and multifactorial anemia accounted for significantly more transfusions in 2011; trauma, gastrointestinal bleed, and vascular surgery significantly decreased, and orthopedic surgery's contribution remained stable. In addition, the mean number of PRBC units per transfusion decreased significantly for all top indications except for vascular surgery. The biggest drop was noted for CV surgery, which went from 3.3 to 1.8 units/transfusion from 2007 to 2011. Indeed, the mean number of units per transfusion decreased for 90% of the 41 indications between the two time-periods, leading to a total reduction in the total number of PRBC units transfused from 19,714 in 2007 to 14,020 in 2011.

This analysis of our blood management program helps explain its success. We hope our results may encourage others to consider blood management programs at their institutions for improved patient outcomes and future blood conservation. Our data confirm that success is only possible through hospital-wide physician buy-in and changes in transfusion practice.

Oliver, James Caleb (James)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	
Advisor	Marisa Marques
Abstract Approved By Advisor	Yes
Co-Authors	L. Griffin, Marisa B. Marques
Title	Can we predict the need for PRBC transfusions based on current utilization?

Abstract

There is a paucity of literature on the demographics of red blood cell (PRBC) transfusions in the United States from the last two decades. This is critically important with the potential shortfall of PRBC units due an aging population. Therefore, a study of PRBC transfusion demographics is necessary to estimate future needs.

Data from our institution's Transfusion Services were obtained for all PRBC transfusions for a period of one year (October 1, 2010 to September 30, 2011). Small volume transfusions given to newborns were excluded. Patients were divided into 4 age brackets: children and adolescents (i.e., 0-13 years), young adults (i.e., 14-39 years), middle aged adults (i.e., 40-64 years), and elderly adults (i.e., 65+ years). Reasons for transfusions of surgical patients were assigned to the ordering physician's surgical specialty (e.g., vascular, gynecological). Indications for transfusion for nonsurgical patients were collected from the electronic medical records. All indications were grouped into one of 41 categories for analysis. Chi-square test was used to compare transfusion proportion by age group, and a Poisson regression was used to compare the number of units per transfusion among age groups. In the 0-13 age group, 90% of transfusions were for repair of congenital heart disease; as a result, this age group was dropped from statistical analysis, though was kept for descriptive purposes.

During the study period, 5,917 patients received 19,393 transfusions. Their mean age was 51 ± 23 years, and the gender distribution was 47.5% males and 52.5% females. Most indications were surgical (59%) ($p < 0.0001$) and 97% of patients were hospitalized. Overall, the number of units transfused was higher for middle aged adults ($p=0.0259$). Additionally, middle aged adults received almost half (44%) of all the transfusions, followed by elderly (26%) and young adults (22%). The most common indications for 14-39 years of age were Trauma (29.4%), Burns (8.2%), Malignancy (6.2%), Hemoglobinopathy (5.8%), and CV Surgery (5.3%). The most common indications for 40-64 years of age were Trauma (10.7%), Malignancy (10.5%), Multifactorial (8.8%), CV Surgery (8.1%), and Ortho Surgery (6.9%). The most common indications for the elderly age group were CV Surgery (13.8%), GI Bleed (9.9%), Ortho Surgery (9.9%,) Trauma (8.9%), and Malignancy (8.1%).

These results help establish a baseline for future reference in terms of PRBC needs assessment. In light of the impending PRBC shortage in industrialized nations, it is essential to define on a larger scale, which patients are more likely to require transfusions. Since the study was performed in a regional medical center, the results may generalizable to the population of the United States.

Osula, Daniel Oluwatomidimu (Daniel)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	Fadi Hage M.D.
Abstract Approved By Advisor	Yes
Co-Authors	Meaghan Bowling, MD, Suzanne Oparil, MD, Dongqi Xing, MD, Mark McCrory, BSc, Alexander Szalai, PhD, Yiu-Fai Chen, PhD, Fadi Hage, MD
Title	Age and Hormone Status Dependence of Anti-Inflammatory Effect of Estrogen in Macrophages Derived from Pre- and Post-menopausal Women

Abstract

Objective: 17beta-estradiol (E2) is known to be protective against the acute vascular injury response in rodent models. Randomized controlled trials have shown increased cardiovascular risk in women treated with hormone therapy (HT), calling into question the concept of estrogenic vasoprotection. One explanation for these discrepant findings is the 'timing hypothesis' which speculates that E2 is protective in young but not old women. This study tested the hypothesis that E2 signaling in human macrophages is age and hormone-status dependent.
Methods: Peripheral blood was obtained via venipuncture from premenopausal (<40 y, n=4) and postmenopausal (>60 y) women both on (n=2) and off HT (n=3). Monocytes were isolated and grown in culture. After 7 days, the cells were treated with E2 (10-7 M) or vehicle for 24 hrs, then incubated with CRP (50 mcg/ml) or vehicle for 4hrs. RNA was extracted and analyzed using real-time RT-PCR reaction to measure the expression of inflammatory mediators chemokine C-C motif ligand 3 (CCL3) and complement component 3 (C3).
Results: CRP resulted in increased expression of CCL3 (4.5-fold) and C3 (2.6-fold) in the macrophages derived from pre- and post-menopausal women. Pre-treatment with E2 attenuated CRP-induced expression of CCL3 and C3 in the premenopausal group. In postmenopausal women off HT, E2 had no effect (CCL3) or had a trend towards paradoxically increased expression (C3) of these mediators when compared to CRP treatment alone. The attenuating effect of CRP-induced expression of CCL3 and C3 was regained in macrophages derived from the postmenopausal women on HT.
Conclusions: E2 attenuates CRP-induced expression of CCL3 and C3 in human macrophages derived from premenopausal women and postmenopausal women on HT, but not in postmenopausal women off HT. This data supports the anti-inflammatory and vasoprotective effects of E2 in young women, and may explain the vasotoxic effects of E2 seen in clinical studies.

Outlaw, Darryl Alan, Jr. (Darryl)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	John Hartman IV, M.D.
Abstract Approved By Advisor	Yes
Co-Authors	
Title	How Gene-Drug Interaction Networks Modulate the Anti-Proliferative Effects of Cancer Therapeutics

Abstract

Much remains unknown about the mechanisms of action of chemotherapy drugs, and even more so how variation among the cancer genomes of different patients influences individual tumor responsiveness to these drugs. *Saccharomyces cerevisiae* serves as an ideal organism for studying effects of mutation on eukaryotic cellular drug responses, due to a genome-wide collection of gene deletion strains used to assess gene-drug interaction.

Optimization of experimental parameters (assay development) is key for successful high throughput genetic screening. In this regard, the goal of my project was to assess the relative growth inhibitory effect of chemotherapy drugs of interest across a concentration gradient to determine which drug concentration, media, and yeast deletion library optimally manifest the effects of each drug. This optimization will facilitate efficient testing of the role of individual yeast genes in chemotherapy response, which predict homologous human genes having similar influence in drug response.

For each of 24 drugs, we systematically tested yeast strains having defects in drug efflux on different media recipes. We employed drug gradients to ascertain relative growth inhibitory effects by Quantitative High Throughput Cell Array Phenotyping, a method developed in the Hartman laboratory.

As hypothesized, media and genetic background significantly affected cellular resistance of yeast to some of the chemotherapy drugs. Non-fermentable media rendered cells least resistant to most drugs, and it was the only media revealing sensitivity to bendamustine, the platin family, and topotecan at the concentrations tested. We also noted that mechanistically related chemotherapy agents showed similar patterns of media influence. Thus, the use of different media in yeast drug screening may provide additional resolution for classifying potential chemotherapy agents of unknown mechanisms of action based on gene-drug interaction profiles.

Ozaki, Masayo (Masayo)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Peter Smith, PhD
Abstract Approved By Advisor	Yes
Co-Authors	Lauren Pring, Evelin Rivero, Michelle Kaplinski, Keith Fischer, Jessica Salama, Eva Clark, Gerson Galdos-Cardenas, Robert Gilman, Caryn Bern
Title	Identification of sudden deaths due to Chagas disease in an indigenous community in Bolivia

Abstract

Chagas' disease (American trypanosomiasis) causes a chronic, progressive heart disease characterized by conduction delays, ventricular arrhythmias, and a dilated cardiomyopathy with congestive heart failure. A primary cause of death due to Chagas' disease is sudden death, most commonly due to ventricular fibrillation. However, it is difficult to ascertain such deaths in the field where deaths are often unreported to local health authorities. In this study, we utilized epidemiologic and qualitative studies to identify and characterize sudden deaths in a Bolivian indigenous community where more than 95% of adults above 30 years of age are infected. Of 180 randomly selected households in the study area, 81% identified the triatomine vector as a source of Chagas' disease and 75% answered that Chagas' disease affects the heart. There were 24 deaths of family members between ages 35 and 60 in the past 5 years. Of those, 10 were reported to have died in a sudden, unexpected manner. Sudden deaths in the community occurred at home when the deceased were engaged in daily activities such as walking back from a well and cooking. When the deceased showed any signs of an illness prior to his or her deaths, family members reported symptoms ranging from palpitation, syncope, dizziness, headache, stomachache, to fatigue. Despite the reported symptoms, deaths were unexpected and few sought medical attention. Some deaths occurred without any prior signs or symptoms reported to family members by the deceased. The families attributed sudden deaths to a number of causes including Chagas' disease and witchcraft. Our findings suggest that knowledge and awareness of Chagas' disease are high within the community. While several deaths followed events that were likely to be of cardiac origin, the lack or paucity of reported symptoms characteristic to Chagas' heart disease limit our ability to attribute a sudden death to Chagas' in a field setting without prior medical diagnosis.

Parris, Tyler Christian (Tyler)

Project Length	Short
Prior Research Experience	No
Funding Source	Departmental or Mentor Funds
Advisor	Carlos Estrada M.D, M.S.
Abstract Approved By Advisor	Yes
Co-Authors	Ryan Kraemer MD, Jeremiah Newsom MD, Carlos A. Estrada MD MS, Lisa L. Willett MD, Jason Morris MD
Title	Selecting the Best Clinical Vignettes for Academic Meetings: Further Modification of a Scoring Tool

Abstract

Background: A recently proposed evidence-based approach to selection of vignettes for presentation at academic meetings suggested a simplified scoring tool could be used with success.
Objective: To further validate and simplify clinical vignettes scoring tools within a multi-institutional setting. Validity and simplification will allow institution of a more efficient externally validated selection system of clinical vignettes. We also propose, pending our results, SGIM use this knowledge as an approach to plausibly decrease the burden on volunteer reviewers.
Design: Prospective descriptive study
Participants: Submittees and reviewers of clinical vignettes to the Southern Society Of General Internal Medicine annual meetings. (2011-2012)
Main Measures: A 5 item scoring tool consisting of items a) *clarity, b) relevance to clinical practice, c)relevance to general internal medicine, d) teaching value,* and *e) overall assessment*. A 3 item tool consisting of *a) relevance to general internal medicine, b) teaching value, c)overall assessment.* A single item tool consisting of *overall assessment*. All tools contained detailed descriptors.
Key Results: The internal consistency of Chronbach's alpha was 0.94 (95% confidence interval [CI]) for the 5-item tool and 0.92 (95% CI) for the 3-item tool, suggesting excellent internal consistency.
The 5 item versus 3 item tool acceptance data was compiled for 2011 and 2012 totaling 70 versus 64 accepted respectfully. The 5 item versus 1 item data was compiled for 2011 giving 40 versus 34 respectfully. The simplification of the scoring tool demonstrated similar Kappa values of 5 item versus 3 item and 5 item versus 1 item, 0.90 and 0.83 respectfully.
Conclusions: Our study shows the 3 item tool to be an externally valid independently verified tool to select the best clinical vignettes for academic meetings and a single item tool can give similar results.

Provided our research and externally validated tools, we suggest on a cautionary note use of the modified 3 item clinical vignette scoring tool.

Future research on selection of clinical vignettes should focus on further validation of the 3 item and single item tool.

Patel, Pratik Prafulchandra (Pratik)

Project Length	Long
Prior Research Experience	Yes
Funding Source	
Advisor	Dr. Steven G. Lloyd
Abstract Approved By Advisor	Yes
Co-Authors	Dr. Steven G. Lloyd, Dr. Bassem Abazid , Dr. Hosakote Nagaraj, Dr. Ravi Desai, Dr. Vijay Misra, Dr. Himanshu Gupta
Title	Quantification of Pulmonary/Systemic Shunt Ratio by Single-Acquisition Phase-Contrast Cardiovascular Magnetic Resonance

Abstract

Purpose: Phase contrast cardiovascular Magnetic Resonance (PC-CMR) quantification of intracardiac shunt (measuring the Pulmonary to systemic flow ratio, Qp/Qs) is typically determined by measuring flow through planes perpendicular the pulmonary trunk (PA) and ascending aorta (Ao). This method is subject to error from presence of background velocity offsets and requires two scan acquisitions. We evaluated an alternate PC-CMR technique for quantifying Qp/Qs using a single modified plane that encompasses both the PA and Ao.

Material and Methods: In 45 patients evaluated for intracardiac shunting, PC-CMR measurement in the individual Ao and PA planes and also in a single acquisition plane were obtained and Qp/Qs calculated by each method. Bland -Altman analysis was performed to evaluate the agreement between the two methods.

Results: The 95% confidence limits of agreement ranged from -0.51 to +0.33 indicating excellent agreement between the two methods. There was excellent agreement on the clinically relevant threshold value of Qp/Qs ratio of 1.5 (representing criteria for surgical correction of shunt).

Conclusions: Qp/Qs determined from the single-acquisition approach agrees well with that of the individual PA and Ao method, and offers potential improved accuracy (due to background velocity offset).

Key Words: Intracardiac Shunt; atrial septal defect; ventricular septal defect; partial anomalous pulmonary venous return; congenital heart disease; cardiovascular magnetic resonance.

Patel, Shaan Suresh (Shaan)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Dr. Meredith Kilgore
Abstract Approved By Advisor	Yes
Co-Authors	Meredith Kilgore
Title	Cost-effectiveness of colorectal cancer screening tests

Abstract

Colorectal cancer is one of the leading causes of cancer-related deaths. Several screening tests are currently available that help reduce the incidence and mortality of colorectal cancer. The purpose of this review was to analyze the cost-effectiveness of each screening test and determine if an optimal screening strategy exists. The screening tests evaluated in this review included fecal occult blood test (Hemoccult II and Hemoccult SENSA), fecal immunochemical test, sigmoidoscopy, combination of sigmoidoscopy and a fecal occult blood test or fecal immunochemical test, colonoscopy, CT colonography, and stool DNA test. Each screening test had a specific time interval associated with it (e.g. colonoscopy every 10 years). Two databases (PubMed and the Cost-Effectiveness Analysis Registry) were searched for cost-effectiveness analyses published in English between January 2007 and June 2012 and conducted with a U.S. population. Fifteen publications were identified. All publications found that each screening strategy was cost-effective compared with no screening. However, the results among the publications were inconsistent as to which screening strategy was optimal. We conducted a meta-analysis on the cost and effectiveness of each screening strategy across the publications in order to provide a more definitive answer as to which screening strategy was optimal. Our results are pending.

Patel, Shweta Naran (Shweta)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Julie Locher
Abstract Approved By Advisor	Yes
Co-Authors	Shweta N. Patel, Tim R. Nagy, Julie L. Locher
Title	Calorie Restriction and Cancer Progression: From Mice to Men

Abstract

Calorie Restriction (CR), a reduction in calories consumed while still obtaining appropriate essential nutrients, has been linked to improving health and lifespan in different species, from yeast to fruit flies to monkeys. Human trials, as exemplified by the multicenter Comprehensive Assessment of Long Term Effects of Reducing Caloric Intake (CALERIE) program, have shown health benefits as well. Of particular significance, CR in mammals has been found to not only increase longevity but also protect against cancer. Various mice studies have demonstrated that CR decreases both tumor growth and cancer progression. Based on a systematic literature review of mice studies, existing evidence suggests potential translational applications in humans. For instance and contrary to conventional thinking, physicians who provide supplemental nutritional support to cancer patients during treatment could be potentially causing harm because the extra nutrition in essence “feeds the tumor” as well. This thought is supported by epidemiologic studies that reveal an association between increased adiposity with an increase oxidative stress and inflammatory mediators, leading to increase incidence of cancer. In addition, long-term studies in humans demonstrate that similar changes in metabolic and physiologic response to CR are seen in humans as observed in the animal studies, suggesting the potential benefits of CR in cancer progression. Randomized controlled trials in non-humans combined with epidemiologic and retrospective evidence in humans call for randomized control trials in humans indicating the benefits of CR and slowing cancer progression. Such studies would contribute data-based evidence regarding consideration of supplemental nutrition in treatment of cancer patients.

Patel, Toral Rohit (Toral)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Frederick Goldman
Abstract Approved By Advisor	Yes
Co-Authors	Larisa Pereboeva, Erik Westin, Lawrence Lamb, Frederick Goldman
Title	The Effect of the Antioxidant N-Acetylcysteine (NAC) on Proliferative Defects in Dyskeratosis Congenita

Abstract

Dyskeratosis congenita (DC) is a premature aging disorder consisting of marrow failure, cancer predisposition, and the characteristic triad of mucosal leukoplakia, skin dyspigmentation and nail dystrophy. Gene mutations affecting telomerase activity that induce telomere shortening have been found in DC. Bone marrow transplantation, the cure for marrow failure, is associated with significantly greater morbidity in DC patients. Dr. Goldman's lab has previously identified elevated levels of apoptosis, oxidative stress, and DNA damage responses (DDR) in DC cells. We hypothesize that antioxidant intervention to alleviate oxidative stress may impart a protective effect in DC cells, including those challenged with DNA chelating agents. Lymphocytes from DC subjects with hTERC mutations and age-matched controls were cultured and expanded *in vitro*, then subjected to irradiation in the presence or absence of NAC. Cellular proliferation and apoptosis were monitored by cell counting and flow cytometry using Annexin V. Western blotting was used to measure basal and radiation-induced expression of DDR proteins including total levels of p53, p53s15, $p21^{WAF}$, and γ-H2AX. Comparison of growth kinetics demonstrated a significant decrease in proliferation of DC versus control lymphocytes that was more pronounced following exposure to 500 cGy radiation. DC lymphocytes had higher basal levels of apoptosis, as well as increased expression of p53 and p53S15 that was further heightened upon irradiation. In a dose-dependent manner, NAC partially ameliorated the growth disadvantage of DC cells. Importantly NAC also decreased radiation-induced apoptosis and oxidative stress in DC cells, coincident with its effect on p53 down-modulation. Our findings confirmed elevated basal levels of apoptosis and DDR proteins in DC lymphocytes which may explain the increased sensitivity of DC cells to irradiation. Furthermore, our data suggests that antioxidants may provide a potential pharmaceutical means to mitigate hypersensitivity to DNA damage and increase the safety of myeloablative therapy and transplantation for DC patients.

Peden, Bradley Wilson (Brad)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	Martin Young
Abstract Approved By Advisor	Yes
Co-Authors	Billy J. Ammons, William F. Ratcliffe, Rachel A. Brewer, Martin E. Young
Title	The Cardiac Circadian Clock Regulates Myocardial Glycogen Metabolism

Abstract

Background: Cardiovascular disease remains the leading cause of death in the United States, despite significant improvements in treatment strategies. Time of day dramatically impacts a host of cardiovascular parameters, including both physiologic (e.g., heart rate) and pathologic (e.g., myocardial infarction) cardiovascular events. Recent studies suggest that the cardiomyocyte circadian clock may impact heart function/dysfunction in a time-of-day-dependent manner, through modulation of myocardial metabolism. **Hypothesis:** We hypothesized that the cardiomyocyte circadian clock allows the heart to anticipate energetic demands associated with daily sleep/wake and feeding/fasting cycles by regulating myocardial glycogen levels. **Methods and Results:** Wild-type and cardiomyocyte-specific BMAL1 knockout (CBK) mouse hearts were isolated from fed and fasted mice at distinct times of the day, after which myocardial glycogen levels were determined through use of a spectrophotometric assay. Myocardial glycogen levels were elevated in CBK mice independent of feeding status. Consistent with previous observations, fasting increased myocardial glycogen levels in wild-type hearts. In contrast, fasting had no effect of myocardial glycogen levels in CBK hearts. **Conclusions:** These data are consistent with the hypothesis that the cardiomyocyte circadian clock influences myocardial glycogen levels, and modulates the metabolic responsiveness of the heart to fasting.

Pierce, Caleb Andrew (Caleb)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Marjorie Lee White
Abstract Approved By Advisor	Yes
Co-Authors	Marjorie Lee White, Nancy Tofel, Dawn Taylor Peterson
Title	Interprofessional high-fidelity simulation training improves knowledge and teamwork in nursing and medical students during internal medicine third year clerkship

Abstract

Introduction – Previous studies have confirmed the effectiveness of high-fidelity simulation in improving nursing and medical students' knowledge and communication. However, most studies have demonstrated these effects in isolation. We hypothesized that interprofessional simulation training will improve each profession's knowledge, communication, and understanding of roles in patient care.

Methods – Over 10 months, 78 third-year medical students (SOM) and 30 senior nursing students (SON) participated in four every-other-week one-hour simulation sessions. Knowledge was assessed with multiple-choice pre- and post-tests. Attitudes toward professional roles and communication practices were assessed before and after the course. All students completed an evaluation survey consisting of 9 questions on a 5-point Likert scale. The survey also included open-ended questions about areas for improvement. Qualitative data was coded and analyzed for emergent themes. Quantitative statistical analysis was performed using SPSS (Chicago, IL) with paired t-tests and chi square tests.

Results – There was a significant improvement in correct responses for both SOM and SON students from pre- and post-tests on the knowledge questions (SOM 53±19% pre vs. 63± 20% post test $p<0.0001$; SON 32±15% pre vs. 43±16% post test $p=0.05$). Results of the post-simulation evaluations indicated that students felt the activity was applicable to their field (4.93/5 SOM, 4.99/5 SON) and a beneficial educational experience (4.90/5 SOM, 4.95/5 SON). Among the open-ended responses, the most frequent positive responses were increased medical knowledge, improved teamwork, and enhanced communication.

Conclusions – The results support our hypothesis that interprofessional simulation training for nursing and medical students can increase knowledge and improve communication and team role understanding as indicated by attitudes. By instituting a high fidelity simulation curriculum similar to the one used in this study, students can be exposed to other disciplines in a safe and realistic environment. Further research is needed to demonstrate the efficacy of interprofessional training in other fields.

Poholek, Catherine Helen (Katie)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Dr. Laurie E. Harrington
Abstract Approved By Advisor	Yes
Co-Authors	
Title	The Pathogenicity of Interleukin-21 in Inflammatory Bowel Disease

Abstract

Th17 CD4 T cells are necessary for protection against pathogens but have also been cast as pathogenic in the context of many autoimmune diseases, including Inflammatory Bowel Disease (IBD). Th17 cells produce several inflammatory cytokines, including IL-17A, IL-17F, IL-21, and IL-22. Although these cytokines may act in concert to induce inflammation during colitis, IL-21 is a strong candidate for further scrutiny since other groups have shown IL-17 and IL-22 to be dispensable for disease. IL-21 expression is increased in biopsies from patients with ulcerative colitis compared to healthy controls, and recent Genome Wide Association Studies have shown an association between the locus containing *il2/il21* and IBD. We have shown that a large number of IL-21-producing CD4 T cells are present in the intestines in mice with colitis. Further, our data suggests that IL-21 production is required for the full induction of IBD in multiple murine models of disease. While others have shown *in vitro* that exogenous IL-21 acts to induce IL-17 production by CD4 T cells, our *in vivo* data suggests that IL-21-deficient cells are capable of producing IL-17A and IL-17F to a greater degree than IL-21-competent cells in the intestine. In addition, our data disputes the previous finding that IL-21 suppresses the transcription factor Foxp3 as we have shown that IL-21 deficient T-regulatory cells express equal or less Foxp3 both *in vitro* and *in vivo*. Moreover, our data indicate that CD4 T cells deficient in the IL-21 receptor are capable of inducing IBD, suggesting that IL-21's role in the intestine may be independent of its action on CD4 T cells. Taken together, our data indicate that IL-21 plays an essential role in the induction of chronic intestinal inflammation that is independent of IL-17 production and T regulatory cell induction, highlighting a previously unrecognized function for IL-21 in the pathogenesis of IBD.

Powell, Stephen Lee (Stephen)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	
Advisor	Henry E. Wang MD
Abstract Approved By Advisor	Yes
Co-Authors	Bryant K. Allen MD, Jordan Morgan MPH, David G. Warnock MD, Henry E. Wang MD
Title	Biomarkers of Inflammation, Endothelial Cell Activation, and Chronic Kidney Function and Risk of Acute Kidney Injury After Sepsis

Abstract

Introduction

Acute kidney injury (AKI) is an important sequelae of sepsis and associated with increased morbidity and mortality. Only limited data describe associations between baseline biomarkers and risk of future AKI after sepsis.

Hypothesis

Patients with elevated baseline markers of inflammation, endothelial cell activation and chronic kidney function are at increased risk of future AKI after sepsis.

Methods

We conducted a nested case-control analysis using the national 30,239 subject REGARDS cohort. From an 8-year observation period, we identified sepsis cases (hospitalization for serious infection with ≥2 systemic inflammatory response syndrome criteria) with ≥2 serum creatinine (sCr) measurements during hospitalization. We excluded patients with prior dialysis or kidney transplantation. We defined AKI as sCr increase ≥0.3 mg/dL or initiation of hemodialysis. Biomarkers measured at the beginning of the observation period included C-reactive protein (CRP) interleukin-6 (IL-6), tumor necrosis factor (TNF-α), E-selectin, inter-cellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), cystatin C (CysC), sCr and urinary albumin-to-creatinine ratio (ACR). Using logistic regression, we evaluated associations between sepsis and biomarker quartiles, adjusted for comorbidities.

Results

We identified 212 sepsis cases encompassing 41 (19.3%) AKI. Compared with non-AKI, AKI had higher TNF-α (9.4 vs. 6.2 pg/mL, p=0.003), E-selectin (60.6 vs 49.1, p=0.01), sCr (1.5 vs. 1.0 mg/dL, p<0.001), cystatin C (1.7 vs. 1.2, p<0.001), and ACR (504 vs. 62 µg/mg, p<0.001). CRP, IL-6, ICAM-1 and VCAM-1 were similar between AKI and non-AKI. AKI was more likely in those with higher TNF-α (adjusted OR for each quartile 0.80-2.36, p-trend=0.04), E-selectin (OR 1.99-4.01, p-trend=0.04), sCr (OR 1.21-2.94, p-trend=0.04), cystatin C (OR 0.55-3.82, p-trend=0.001) and ACR (OR 2.29-10.67, p-trend <0.001). CRP, IL-6, VCAM-1 and ICAM-1 were not associated with AKI.

Conclusion

Elevated baseline TNF-α, E-Selectin, sCr, cystatin-C and ACR were associated with future AKI after sepsis. Biomarkers at stable baseline may predict future risk of AKI.

Powell, Thomas Clark (Clark)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Elizabeth Brown PhD, MPH
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Differences in the SLE Clinical Phenotype by Age of Diagnosis

Abstract

Background: Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease that is characterized by the presence of antinuclear autoantibodies, complement activation and the formation and deposition of immune complexes resulting in multisystem organ damage. Trends in SLE vary by age, with pediatric SLE (pedSLE) patients presenting with more active, severe and rapidly progressive disease than adult SLE patients. However, the basis for this variation is unknown. In this investigation, we sought to characterize the clinical phenotype associated with the age of diagnosis including pedSLE, adult SLE and late onset SLE in a large multiethnic cohort. **Methods:** We evaluated clinical manifestations, disease course and severity (per the Systemic Lupus International Collaborating Clinics/ACR Damage Index) and autoantibody profiles using a total of 2,564 SLE patients with a cumulative presence of at least 4 of 11 revised and updated ACR classification criteria for SLE, self-defined race/ethnicity (African American, EuropeanAmerican, Hispanic), disease duration ≤10 years at enrollment and with at least 2 years follow up included in the PROFILE longitudinal cohort. Patients were stratified by age of onset including pedSLE (≤16 years), adult SLE (17-49 years) and late onset SLE (≥ 50 years). Risk estimates were calculated using multivariable logistic regression, although frequencies are provided herein. **Results:** A total of 2,564 SLE patients were evaluated. The mean (±standard deviation, SD) age at diagnosis in each of three age strata was 14±3 years, 32±9 years and 58±7 years for pedSLE, adult SLE and late onset SLE, respectively and the mean (±SD) disease duration was 10.9±8.7 years, 5.7±5.8 years and 3.8±3.4 years for each of the respective groups. Across each age of onset group, the majority were female (≥86%) and slightly more pedSLE patients were of African American (38%) or Hispanic (13%) ancestry. We confirm that compared to SLE patients with adult onset, pedSLE patients are more likely to present with acute and severe disease features including discoid rash (27% vs. 18%), serositis (48% vs. 44%), renal involvement (62% vs. 41%), neurologic involvement (18% vs. 10%), hematologic involvement (73% vs. 68%) and immunological involvement (89% vs. 79%). In contrast, SLE patients with late onset were significantly less likely to present with serositis (34%), renal involvement (20%), neurological involvement (8%) and immunological involvement (67%) compared to each of the pedSLE and adult onset SLE groups. Consistent with increasing age, the late onset SLE group demonstrated more damage associated with ocular, neuropsychiatric, pulmonary, cardiovascular, musculoskeletal, diabetes and malignancy domains than did the pedSLE or adult SLE groups, whereas the pedSLE group had significantly more renal damage. **Conclusion:** These findings confirm more aggressive disease, particularly renal involvement, in SLE patients presenting in childhood. They further suggest SLE disease manifestations decrease with age of onset throughout adulthood. These results will inform future studies aimed at delineating the etiology and natural history of the more aggressive clinical phenotype observed in children.

Prater, Ginnie (Ginnie)

Project Length	Short
Prior Research Experience	
Funding Source	
Advisor	Cynthia Brown, M.D.
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Recognition of At-risk Nutritional Status in Hospitalized Geriatric Patients

Abstract

Background: Geriatric patients hospitalized for acute illness are subjected to periods of low mobility, contributing to decreased muscle protein synthesis, loss of strength and wasting of whole body mass, particularly lower extremity mass. Undernutrition exacerbates such adverse effects of bedrest, accelerating the process of sarcopenia and the onset of frailty. Understanding patterns of clinician recognition of at-risk nutritional status and implementation of appropriate interventions in hospitalized geriatric patients will assist in the identification of potential barriers to optimizing nutritional status in this population.
Purpose: To examine the frequency of accurate recognition of at-risk nutritional status in hospitalized geriatric patients as a component of usual care.
Methods: A secondary data analysis of an open study is currently underway. The study was designed as a randomized controlled trial to determine the impact of a hospital walking program on functional status and community mobility.100 patients who were ≥ 65 years of age, newly admitted to the medical ward of the Birmingham VAMC, with a Mini Cognitive Assessment Score and Confusion Assessment Method score = 0, and able to walk in the 2 weeks prior to admission were enrolled. The Mini-Nutritional Assessment-Short Form (MNA) and the Short Nutritional Assessment Questionnaire (SNAQ) were administered at baseline. Secondary analysis involved selection of two subgroups based on MNA scores of 8-11, indicating at-risk nutritional status, and SNAQ scores of ≤ 14, indicating significant risk of at least 5% weight loss within six months. We plan to undertake a chart review to examine nutrition, occupational therapy (OT) and social work (SW) consults for recommendations involving protein-calorie supplementation (PCS), other dietary interventions, feeding assistance and home care. Patient factors included in the existing data that may be associated with receiving recommendations or services will be explored.
Results: There was a higher percentage of black patients in the MNA at-risk subgroup as compared to the study group (24% vs. 19%). Other baseline characteristics did not differ significantly between the MNA at-risk subgroup and the study group as a whole. Of 100 patients (mean age 73.9 years; 97% male; 81% white; 19% black), ten did not complete the study. Three of these ten patients expired; five were withdrawn due to medical complications or patient wishes; two patients dropped out secondary to inability to contact post-hospitalization or patient refusal. 53 participants were identified as at-risk per MNA score (8-11); three of these patients were withdrawn secondary to medical complications. The remaining 50 patients comprising the MNA at-risk subgroup were determined to have the following baseline characteristics: mean age 73.6 years; 98% male; 76% white; 24% black. Median length of stay for this subgroup as well as for the entire study group was 3 days. 32% of patients in the at-risk subgroup received OT services vs. 27% of the study group; 54% received SW services vs. 49% in the study group.
Conclusions: Available results indicate a slightly higher percentage of black patients in the at-

risk subgroup; however, it is yet unknown how baseline characteristics of patients in the normal status and malnourished status categories compare. Patients in the at-risk group were more likely to receive both OT and SW services compared to the entire study group. We will report further conclusions pending completion of our chart review and data analysis.

Raborn, Joel (Joel)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Gregory K Friedman, MD
Abstract Approved By Advisor	Yes
Co-Authors	Virginia Kelly, James M Markert, G Yancey Gillespie
Title	Pediatric Medulloblastoma Cells from a Patient-Derived Xenograft Contain a Stem Cell Fraction that is Sensitive to Engineered Herpes Simplex Virus Therapy

Abstract

BACKGROUND: Medulloblastoma (MDB) is the most common malignant pediatric brain tumor, and survival in patients with high-risk disease only approaches 50%, despite surgery, chemotherapy, and radiation. Recently, a subpopulation of radiation- and chemotherapy resistant cells termed 'MDB stem cells' (MSC) has been identified. These cells retain the properties of multipotency and self-renewal and are driven by the hypoxic microenvironment. A novel therapy like engineered herpes simplex virotherapy (oHSV), which targets tumors cells while sparing normal cells, may improve outcomes for children with resistant MDB. We hypothesized that oHSV would target and kill MSC.

METHODS: A pediatric MDB xenograft, BT45, was disaggregated and cultured as neurospheres in serumless, growth factor defined medium to promote the MSC-phenotype. Expression of CD133 and CD15, putative MSC markers, were determined by fluorescence-activated cell sorting analysis. Neurosphere cytotoxicity to oHSV M002, which produces interleukin-12 thereby enlisting an immune response through T-cell and natural killer cell activation, was measured by the AlmarBlue Assay 72 hours after infection. *In vivo* survival was measured in BT-45 bearing nude mice after intracerebellar injection of saline or M002.

RESULTS: CD133 and CD15 expression in BT-45 cells were 21.9 ± 3.7% and 16.6 ± 2.4%, respectively. Neurospheres were highly sensitive to killing by M002 (LD_{50} 0.58 PFU/cell) with 100% cell death at 3.3 PFU/cell. *In vivo*, M002 significantly improved survival in mice (15.0 ± 1.1 days versus 11.0 ± 1.2) including 30% long-term survivors compared to saline.

CONCLUSIONS: MDB cells from a patient-derived xenograft contain a fraction of MSC when grown as neurospheres. These cells were sensitive to killing by oHSV *in vitro* and *in vivo*, suggesting that MDB may be an excellent target for oHSV.

Raines, Benjamin Todd (Todd)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Mary T Hawn, MD
Abstract Approved By Advisor	Yes
Co-Authors	Ponce B, Vick C, Richman J, Hawn M.
Title	Comparative effectiveness of prophylactic antibiotic choice and surgical infection in arthroplasty

Abstract

Introduction: Prophylactic antibiotics (PA) decrease surgical site infections (SSI). Recent studies have failed to show improved SSI rates with adherence to the Surgical Care Improvement Project (SCIP) measures. The aim of this study is to identify the comparative effectiveness of the SCIP approved antibiotics for SSI prevention.
Methods: This is a retrospective cohort study using national Veteran's Administration (VA) data on patients undergoing elective primary or revision hip or knee arthroplasty from 2005 to 2009. Data on the type of PA used was merged with VA Surgical Quality Improvement Program data to identify SSI as well as patient and procedure risk factors. Patients were stratified by documented penicillin (PEN) allergy, and SSI rates were compared among patients receiving vancomycin (VANC) alone versus other SCIP-approved PA using chi-square tests. The overall low event rate precluded reliable adjustment for covariates.
Results: A total of 16,568 arthroplasties were included in the cohort. PA use distribution: 81.2% received a 1st generation cephalosporin (CF1), 8.3% VANC, 5.8% VANC + CF1, 4.7% clindamycin (CLINDA). A documented PEN allergy accounted for 52.9% of patients receiving VANC, and 95.0% of those receiving CLINDA. The overall 30-day observed SSI rate was 1.5%. Unadjusted SSI rates by PA were: 2.6% with VANC alone, 1.5% with VANC + CF1, 1.4% with CF1, and 1.0% with CLINDA. Unadjusted analysis among patients with documented PEN allergy revealed an SSI frequency of 2.1% with VANC prophylaxis compared to 1.0% for CLINDA (Chi-square p=0.12). For patients without PEN allergy, SSI rate of 3.3% for VANC prophylaxis compared to 1.6% for VANC + CF1 (p=0.04) and 1.4% for CF1 alone (p<0.001).
Conclusion: Factors other than PEN allergy, such as concern for MRSA or practice style, significantly influence the choice of VANC administration. Higher SSI rates observed with VANC as the sole PA suggest that VANC may not be an optimal PA. These data suggest that CLINDA is more effective in patients with PEN allergy and when there is concern for MRSA, VANC should be used in conjunction with a CF1**.**

Raines, Benjamin Todd (Todd)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Mary Hawn, MD.
Abstract Approved By Advisor	Yes
Co-Authors	Ponce B, Deierhoi R, Richman J, Hawn M.
Title	Determinants of readmission: An analysis of 28,041 elective arthroplasty procedures

Abstract

Introduction: All-cause hospital readmission has been proposed as a metric of hospital quality. Reducing readmissions represent an opportunity to improve care and reduce costs. However, little is known about what factors influence or potentially predict hospital readmissions in orthopedic surgery patients. Our aim is to identify variables associated with readmissions following knee or hip arthroplasty.

Methods: This is a retrospective cohort study using national Veterans' Affairs (VA) data from 2005 to 2009 for total, partial, and revision knee or hip arthroplasties. Patients were identified from the Surgical Care Improvement Project and matched to outcomes from the VA Surgical Quality Improvement Program. Risk factors for readmission within 30 days of hospital discharge were identified using chi-square tests. Logistic regression models assessed independent predictors of 30-day readmission at the patient level, and linear regression was used to estimate correlation with readmission rates at the hospital level.

Results: A total of 2,044 (7.3%) readmissions occurred within 30 days following 28,041 elective arthroplasties (6.6% for 17,471 knee and 8.4% for 10,570 hip procedures, $p< 0.0001$). Overall, 12.8% of patients experienced at least one post-operative complication and were more likely to be readmitted than those without a complication (25.2% vs 4.6%, $p < 0.0001$). Hospital acquired conditions (HAC) accounted for 42.2% (1,516 patients) of all complications. These conditions consisted of UTI (35.6%), surgical site infection (28.8%), VTE (23.9%), and pneumonia (19.1%).HACs were the strongest predictor of readmission for both knee (OR 7.76, 95% CI 6.45-9.34) and hip arthroplasties (OR 7.55, 95% CI 6.07-9.37). Readmission rates at the hospital level showed a weak correlation with facility HAC rates ($R^2= 0.15$, $p< 0.0001$).

Conclusion(s): Hospital acquired conditions are strongly associated with 30-day readmission rates at both patient and hospital levels following elective knee or hip arthroplasty. Efforts aimed at reducing these events will reduce costs and improve the safety of arthroplasty. Further research is needed to develop interventions reducing HAC's.

Ramaker, Ryne (Ryne)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Dr. Stephen Barnes
Abstract Approved By Advisor	Yes
Co-Authors	Kyle Floyd, Alan Crockett, Gloria Robinson, Landon Wilson and Stephen Barnes
Title	Analysis of UV-Light Induced Modifications of the Lens Protein αB - crystallin and Potential Protective Agents

Abstract

Age-related cataracts represent nearly half of the world's blindness. Long-term exposure to UV light may increase risk of age-related cataract formation via protein modifications and cross-linking. The lens is an avascular tissue containing high concentrations of protein complexes (crystallins) which maintain transparency. Lens α-crystallin is particularly important because it has both chaperone and structural functions. The lens relies on α-crystallin and the nutrients supplied through the aqueous humor to maintain its integrity for the lifetime of the organism. The chaperone functions of α-crystallin can be overwhelmed since it cannot be replaced if damaged, resulting in protein aggregation and precipitation and eventually cataract formation. Antioxidants naturally present in the aqueous humor or lens tissue (ascorbic acid, AA, and glutathione, GSH) and those supplemented in the diet may reduce UV-light induced damage. The goal of this project is to analyze UV-induced modifications to human lens αB-crystallin and identify compounds that reduce or enhance UV-induced modifications.

Purified, recombinant human αB-crystallin, with and without antioxidant supplementation, was exposed to 50 J/cm^2 of UV-A (320-340nm) light via a modified DNA cross-linker. After induction, UV-A exposed samples were compared to dark control samples using both one- and two-dimensional SDS-PAGE analysis along with mass spectrometry analysis to identify UV-light induced modifications. Preliminary results suggested UV-A light introduced crosslinks and potentially other modifications to αB-crystallin. AA limited cross-linking, while its oxidized product, dehydroascorbic acid (DHA), increased cross-linking. GSH lessened crosslinking, especially in the presence of AA and DHA, while oxidized glutathione dimer (GSSG) didn't affect levels of crosslinking in the presence of AA and DHA. Putative dietary antioxidants, catechin, epicatechin, and whole grape seed extract, all increased levels of protein crosslinking suggesting that these flavanols may have pro-oxidant effects. Overall, these findings suggest that UV-light causes crosslinking of αB-crystallin and supplementation with dietary antioxidants may produce unanticipated outcomes.

Ranganath, Neel Kiran (Neel)

Project Length	Short
Prior Research Experience	Yes
Funding Source	O'Brien Center Fellowship
Advisor	Dr. Bradford Woodworth
Abstract Approved By Advisor	Yes
Co-Authors	Shaoyan Zhang, Dan Skinner, Eric Sorscher
Title	CFTR activation by the solvent ethanol: Implications for CF drug testing and delivery

Abstract

CFTR activating molecules identified through high throughput drug screening may exhibit limited solubility in water and are therefore dissolved in solvents such as DMSO or ethanol for experimental testing. During evaluation of novel compounds obtained in this fashion, we serendipitously discovered that agents solubilized in low concentrations of ethanol produce robust activation of wild type CFTR-mediated Cl^- transport in well characterized primary cell culture models of murine nasal septal (MNSE) and human sinonasal respiratory epithelium (HSNE). Dysfunctional mucociliary clearance (MCC) is a hallmark of many airway diseases, including cystic fibrosis (CF), chronic obstructive pulmonary disease, and chronic rhinosinusitis (CRS). The objectives of the current study were to investigate ethanol for effects on transepithelial Cl^- secretion and characterize the mechanism that underlies this form of CFTR modulation. Primary MNSE [wild type (wt) and transgenic $CFTR^{-/-}$] and HSNE cultures were subjected to transepithelial ion transport measurements using pharmacologic manipulation in Ussing chambers. CFTR R-domain phosphorylation and cAMP levels were examined as a test of PKA-dependent activation. Time-dependent and dose-dependent toxicity were also measured using LDH based protocols. A strong increase in CFTR-mediated Cl^- transport (change in short-circuit current,DI_{SC}) was demonstrated with activation stable at 0.5% ethanol. Effects of ethanol were completely abrogated by INH-172 and CFTR dependence confirmed by lack of stimulation in transgenic $CFTR^{-/-}$ MNSE. There was no increase in cellular cAMP attributable to ethanol at the concentrations studied. R-domain phosphorylation, as judged by a biochemical gel shift assay of recombinant R-domain, was also unchanged. Incubations up to 24 hours were performed using all concentrations tested and no cellular toxicity noted. The same intervention could be useful to activate residual CFTR (e.g. in the setting of F508del-CFTR pharmacologic correction) and ameliorate underlying mucus obstruction in CF-associated sinusitis. In addition, it should be noted that CFTR activation by potentiators dissolved in ethanol may overestimate potency, and our findings emphasize the need for stringent vehicle controls during experimental testing of CFTR modulators in vitro and in vivo.

Raper, Jaron Drew (Jaron)

Project Length	Short
Prior Research Experience	Yes
Funding Source	O'Brien Center Fellowship
Advisor	Henry E. Wang, MD, MS
Abstract Approved By Advisor	Yes
Co-Authors	Katherine R. Lai
Title	Urine Output Changes Associated with Post-Cardiac Arrest Therapeutic Hypothermia

Abstract

Introduction: Therapeutic hypothermia (TH) is an important treatment for survivors of cardiac arrest. While commonly described, no studies have characterized urine output changes ("cold diuresis" or re-warm anti-diuresis") during TH delivery, which is essential because of concurrent hypovolemia, shock, pulmonary edema or electrolyte abnormalities. We sought to determine urine output changes during delivery of TH.

Methods: We studied consecutive patients receiving post-cardiac arrest TH at an urban tertiary care center. TH was provided to comatose adult survivors of out-of-hospital and in-hospital cardiac arrest using cold intravenous saline, external cooling pads (Arctic Sun) and ice packs. We excluded patients <18 years old, with end stage renal disease, who received hemodialysis, or those who died before completing ≥12 hours of TH. For each TH treatment phase (induction, maintenance, re-warm, and post-TH), we determined fluid input and urine output rates (mL/hr). Using Generalized Estimating Equations and defining post-TH urine output as the baseline, we examined the differences in urine output rates between TH phases, adjusting for fluid input rate, age, sex, location of cardiac arrest, initial arrest ECG rhythm, and vasopressor use.

Results: Among 33 patients with complete fluid input and urine output data, mean treatment phase durations were: 1) induction 4.9 hrs (95% CI 4.5-5.4), 2) maintenance 23.1 hrs (22.5-23.6), 3) re-warm 11.1 hrs (10.5-11.7), and 4) post-rewarm 12 hrs (12-12). Mean urine output rates were: 1) induction 162 mL/hr (95% CI: 106-218), 2) maintenance 100 mL/hr (79-121), 3) re-warm 66 mL/hr (50-83), and post-TH 97 mL/hr (70-123). Urine output rate was higher during TH induction than post-TH (p=0.004). There were no differences in urine output rates between post-TH and TH maintenance (p=0.88) or TH re-warm (p=0.19).

Conclusion: Compared with baseline, urine output rate increases during TH induction. Urine output rates do not change during TH maintenance or re-warming.

Reish, Nicholas Joseph (Nicholas)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Other
Advisor	Alecia Gross
Abstract Approved By Advisor	Yes
Co-Authors	Xiaogang Cheng
Title	Rab11a Directs Rhodopsin Trafficking in Rod Photoreceptors

Abstract

Precise vectorial transport of rhodopsin is essential for rod photoreceptor health and function. Mutations that truncate or extend the carboxy terminus of rhodopsin disrupt essential transport and lead to retinal degeneration in human patients and in mouse models. We hypothesize that these mutations disrupt an essential intermolecular interaction of rhodopsin with trafficking proteins. To test this hypothesis, we conducted pull-down assays using native rhodopsin from wild-type mice and mice homozygous for gene mutations encoding defective rhodopsin carboxy termini. Using this method, we show the novel finding that such mutations disrupt the binding interaction between rhodopsin and the small GTPase rab11a. To confirm this result in intact rod cells, we used the proximity ligation assay (PLA) to verify the rhodopsin-rab11a interaction in sections from wild-type mouse retina. In accordance with our *in vitro* data, the rhodopsin-rab11a interaction was severely diminished in sections from mice with homozygous mutations in the carboxy terminus of rhodopsin. To expand on these studies we conducted binding assays between GST-fusions of rab11a mutants and purified rhodopsin. These assays show the rhodopsin-rab11a binding is direct and does not depend on the nucleotide binding status of rab11a. To investigate whether the nucleotide binding status of rab11a is important *in vivo*, we expressed EGFP-tagged mutants of rab11a in *Xenopus laevis* tadpole photoreceptors. Expression of EGFP-rab11a or the constitutively active mutant Q70L rab11a did not cause rhodopsin mislocalization or photoreceptor degeneration. While the expression of the dominant-negative mutant S25N rab11a did not cause degeneration, the mutant rab11a ectopically accumulated in the OS. Expression of a different dominant-negative mutation N124I rab11a did cause rhodopsin mislocalization and photoreceptor degeneration. Taken together our results show the critical importance of rhodopsin-rab11a interactions to support the formation and maintenance of vertebrate photoreceptors.

Robert, Stephanie Marie (Stephanie)

Project Length	Long
Prior Research Experience	Yes
Funding Source	T35
Advisor	Harald Sontheimer, PhD
Abstract Approved By Advisor	Yes
Co-Authors	Susan Buckingham, Toyin Ogunrinu, Michael Berens, Neils Danbolt, Harald Sontheimer
Title	Two classes of gliomas defined by the expression and function of distinct Cystine/Glutamate Transporters

Abstract

Glioblastoma multiforme is the most prevalent and aggressive malignant brain tumor. Past research has identified a role for the cystine/glutamate exchanger, system xc- (SXC) in the growth of these tumors. SXC is an important pathway for cellular cystine uptake and glutathione (GSH) synthesis; furthermore, glutamate released in exchange causes excitotoxic neuronal death and peritumoral seizures. Since these findings are based on data from glioma cell lines, we examined patient tissue samples and used a xenograft model, whereby glioma tissue from patients is propagated in mice, to study patient-derived tissues. Immunohistological evaluation of tissue micro-arrays from 37 patients suggests the existence of two subpopulations of gliomas; 64% expressed increased levels of SXC whereas 34% expressed low to undetectable levels. This heterogeneity was confirmed by Western blot, where 5/9 xenograft samples showed prominent SXC expression, while 4/9 expressed low to undetectable levels. However, the latter expressed Na+ dependent glutamate transporters (EAAT) previously found nonfunctional in cell lines. We examined GSH levels and cystine transport in tumors with high and low SXC levels, but found no significant difference. This finding can be explained by 35S-cystine uptake studies showing low SXC tumors rely on TBOA-sensitive EAAT1/3 transporters for cystine uptake, suggesting EAAT1/3 act as alternate pathways for cystine uptake and GSH synthesis. Cystine uptake through SXC and EAAT1/3 differs in regard to their glutamate gradient, with only SXC mediating excitotoxic glutamate release. In agreement with this directional difference, cortical neurons co-cultured with high SXC gliomas showed marked glutamate excitotoxicity. Upon implantation of high SXC cells into animals, 92.8% of mice exhibited seizures; whereas, only 12-25% of low SXC gliomas had seizures, which agreed with the lack of toxicity seen in vitro. These findings suggest high SXC gliomas may be associated with poorer prognosis and increased incidence of glioma-associated seizures than gliomas with lower SXC expression.

Roddy, Ryan Rebekah (Ryan)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Connie Kohler
Abstract Approved By Advisor	Yes
Co-Authors	Katie J. Work, Shermetria D. Massingale MPH
Title	Living the Story: The Evaluation of Translating Plot to Policy

Abstract

Background: In Jefferson County, Ala., 21% of adults smoke cigarettes, compared with the national median of 18.4%. Environmental tobacco smoke contains more than 7,000 chemicals, more than 200 of which are poisonous and 69 are known carcinogens. In 2010, Jefferson County received $13.3 million to address tobacco use and obesity through the *Communities Putting Prevention to Work* grant. An African-American radio drama was conceived out of this media campaign to influence residents to advocate for smoke-free policies. Media for Health produced a 48-episode program entitled *Camberwell* that was broadcast on two local radio stations, and the episodes were embedded in an hour-long radio magazine show.

Goal: The purpose of this study is to evaluate individuals' knowledge, attitudes, and behavior change and to assess interpersonal influence that *Camberwell* had on the greater Birmingham area.

Methods: We administered a 19-question survey to a convenience sample of 100 participants that were among the target audience. The participants were African-American church members in Jefferson County. The survey included questions about listening habits, interpersonal influence, campaign slogan recognition, and perceived second-hand smoke exposure risk.

Results: Birmingham became a smoke-free city in June 2012. We expect to see a correlation between listenership and engagement with campaign objectives, including advocating for smoke-free public environments.

Conclusion: We recommend that an effective evaluation plan should be developed for implementation immediately after the production of a radio drama. Additionally, funding should be allocated during the planning process in order to serve this purpose.

Roszczynialski, Kelly Nicole (Kelly)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Eben Rosenthal
Abstract Approved By Advisor	Yes
Co-Authors	Alexandra E Kejner, Mary T Hawn, Lisa K Clemmons, William R Carroll, and Eben L Rosenthal
Title	Repair of osteoradionecrosis using microvascular free tissue transfer is associated with worsened quality indicators

Abstract

Objective: To investigate the relationship between surgical indications for microvascular-free tissue transfer reconstruction and patient outcomes using established quality indicators.

Design: Retrospective cohort review.

Setting: Academic tertiary care medical center.

Patients: A total of 555 surgical patients were reviewed for microvascular-free tissue transfer procedures between 2005 and 2008.

Main Outcome Measures: Previously established quality indicators were examined, including length of stay, return to the operating room within 7 days of surgery, number of transfusions, flap viability, diet at 3 month post-operative visit, surgical site infection within 30 days, 30-day readmission, and 30-day mortality. The standards for transfusions and length of stay were based on previous investigations. Non-oncologic reconstructions were classified as those performed for osteoradionecrosis and for functional reconstructions. Oncologic reconstructions were classified as those performed subsequent to resections of primary or recurrent disease.

Results: Overall flap viability was 97.5%. Non-oncologic reconstructions had lower viability (95.1%) than oncologic cases (97.9%, p=0.04). Patients who underwent reconstruction for osteoradionecrosis had an increased hospital stay when utilizing the 10 day standard (50%, p=0.0003).Non-oncologic reconstructive cases showed a similar trend (30.5%, p=0.0003). Osteoradionecrosis patients had a higher rate of re-operation within seven days of the original procedure (45%, p=0.0008). This was also seen in combined non-oncologic reconstructive patients (24.4%, p=0.01). Excluding osteoradionecrosis patients, non-oncologic reconstructions had a higher proportion of patients hospitalized over ten days (24.2%, p=0.03).

Conclusions: Osteoradionecrosis cases are associated with negative quality indicators of longer hospitalization and higher incidence of re-operation. Cases of non-oncologic revision have higher rates of returning to the operating room and longer hospitalizations, but the relationship is lost for return to the OR once osteoradionecrosis cases are excluded.

Rutherford, John Matthew (Matt)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Lucas Pozzo-Miller
Abstract Approved By Advisor	Yes
Co-Authors	Gaston Calfa, John Hablitz
Title	Hyperexcitability in hippocampus with loss of MeCP2: Pathophysiology of Rett syndrome

Abstract

Rett syndrome is a debilitating X-linked autism-spectrum disorder characterized by seizures, autonomic dysregulation, and dysfunctional movement and intellectual ability. Seemingly normal growth for 6-18 months precedes failure to meet, and often regression from, developmental milestones. More than 90% of clinically defined cases of Rett syndrome are associated with mutations in the gene for the transcriptional regulator methyl-CpG-binding protein (MeCP2). This regression in development, along with the seizures that often begin after regression initiates, interested us in the role of MeCP2 in development of the hippocampus, which consists of a relatively simple neuronal network and is associated with seizure.

This presentation describes network hyperexcitability in region CA3 of the hippocampus in a *Mecp2* loss-of-function mouse and underlying physiological differences. These include greater principal neuron activity per excitatory input and the inverse (a reduced "return on investment") for inhibitory input to the same cell type. Wild-type CA3 networks are in the same sense highly reactive until postnatal day 20-40, when the local network matures and stabilizes, but *Mecp2* mutant mice exhibit comparatively less reduction of excitability by symptom onset at 50-60 days of age. However, this excitability is not explained by a change in number or subtype of local inhibitory neurons in symptomatic *Mecp2* mutant mice, as might be expected from the input-output relation of interneuron to principal cells. The apparent necessity of MeCP2 for this maturation and eventual stability hints at the epigenetic regulatory mechanisms - at the level of the individual neuron - involved in such a coordinated physiologic shift in a neuronal network highly interconnected by excitatory synapses, like the CA3 region of the hippocampus.

Salisbury, Charles Drew (Charles)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Thomas Matthews
Abstract Approved By Advisor	Yes
Co-Authors	Dr. Thomas Matthews, Dr. William Jordan
Title	Comparison of long-term survival for surveillance, open repair, and endovascular repair of abdominal aortic aneurysms

Abstract

Infrarenal abdominal aortic aneurysm (AAA) repair is indicated for symptomatic aneurysms or aneurysms that meet specific size criteria to prevent aneurysm rupture. Surveillance is sometimes chosen over repair as a management option for AAA > 5cm for various reasons. In this retrospective analysis, mortality profiles of surveillance are compared to open repair and endovascular repair (EVAR). We sought to determine which patients will receive a survival benefit from AAA repair.

All patients referred with AAA who either underwent surveillance, open, or endovascular repair for AAA (symptomatic or > 5cm in size) between 1985 and 2012 were identified from a prospectively maintained vascular registry. Health system charts, medical communication, and national death indexes were reviewed. Chi-squared data analysis was performed and Kaplan-Meier survival curves were calculated.

Between January 1996 and June 2012, 180 AAA patients were followed in a surveillance protocol. From July 1985 to September 2009, 1908 patients underwent 1986 AAA repair procedures (EVAR 1066; open 920). Surveillance was selected secondary to patient specific clinical factors (n=76, 42.8%), high risk patients who were not endovascular candidates (n=67, 37.2%), and patient preference (n=36, 20%). Patients were followed up to 290 months and the average length of surveillance for surveillance patients was 40.9 months (range: 0.1 - 161.1). Through 100 months, all-cause mortality rate was 69.4% with surveillance, 25.2% after EVAR, and 39.1% after open repair (SE = 3.63%). Six patients (4.8%) from the surveillance group died from known AAA rupture.

In patients with AAA > 5cm selected for surveillance over aneurysm repair the long term mortality was higher than EVAR and open repair. This data suggest that risk assessment of AAA patients can help in selecting the patients who will gain a survival benefit from AAA repair.

Salisbury, Charles Drew (Charles)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Thomas Matthews
Abstract Approved By Advisor	Yes
Co-Authors	Dr. Thomas Matthews, Dr. William Jordan
Title	Long-term outcomes for non-operative surveillance of abdominal aortic aneurysms

Abstract

Aortic aneurysms are often managed conservatively through a surveillance program rather than electing to undergo open or endovascular repair. Reasons for choosing to manage non-operatively include small-sized aneurysms, patient factors, patient preference, and aneurysms that are unable to be repaired via an endovascular approach. In this study, long-term outcomes for patients with aortic aneurysms that have never undergone surgical repair are evaluated.

All patients who have undergone non-operative surveillance for aortic aneurysms between 1996 and 2012 were identified from a prospectively maintained vascular registry. Health system charts, medical communication, and national death indexes were reviewed. Chi-squared data analysis was performed and Kaplan-Meier survival curves were calculated.

Between January 1996 and June 2012, there were 885 patients evaluated for aortic aneurysms that have never undergone an aortic operation. Patients were followed up to 190 months and the average length of surveillance was 29 months (range: 0.1 - 189.9). There were 81 thoracic aneurysms (TAA, 8.8%), 78 thoracoabdominal aortic aneurysms (TAAA, 9.2%), and 726 abdominal aortic aneurysms (AAA, 82.0%). Mean time of survival was 70.3, 51.8, and 43.4 months for AAA, TAA, and TAAA respectively. The reasons for not undergoing repair include small-sized aneurysms (n=624), patient factors (n=104), not endovascular candidates (93), and patient preference (64) and the mean survival was 85.1, 21.1, 32.9, and 43.1 months, respectively.

Long-term survival is greater for AAA compared to TAA and TAAA. There were various reasons for choosing to forego operative repair of aortic aneurysms and patient factors showed the highest long-term mortality while small-sized aneurysms showed the lowest long-term mortality compared to patient preference and not endovascular candidates. 4.2% of the patients died from aortic ruptures or dissections proving that there is a significant risk taken when non-operative management is chosen although the majority of patients will die of other causes.

Shah, Nishi M. (Nishi)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Chirstopher Willey
Abstract Approved By Advisor	Yes
Co-Authors	John S. Jarboe, Samantha Scanlon, Robert Gish
Title	Myristoylated Alanine Rich C-Kinase Substrate (MARCKS) is a Key Regulator of

Abstract

Background: Glioblastoma multiforme (GBM) represents the most common and deadly form of glioma, with the median post-diagnosis survival being 12 months. In xenograft models, GBM has been shown to be more radiation resistant when the phosphatidylinositol-3-kinase (PI3K)/Akt pathway is active; the PI3K/Akt pathway promotes increased cell growth, DNA damage repair, and survival. In this pathway, phosphatidyl inositol bisphosphate (PIP2) is converted to the triphosphate (PIP3) by PI3K, which leads to Akt activation. Myristoylated Alanine Rich C-Kinase Substrate (MARCKS) is a potential regulator for the availability of PIP2 to the PI3K/Akt pathway as it is capable of sequestering PIP2 at the membrane via electrostatic interactions.

Objective: Our main objectives are to further elucidate the mechanism of this regulation, which is anticipated to occur through a reversible sequestration of PIP2 at the cell membrane by MARCKS, and to show that over-expression of MARCKS will lead to decreased cell survival after radiation through decreased signaling of the PI3K/Akt pathway.

Methods: This will be investigated through the over-expression of various MARCKS mutants in three glioma cell lines (U87, U373, and U251) and subsequent observation of its effects on the PI3K/Akt pathway, proliferation, radiation sensitivity, DNA damage repair, and apoptosis. The mutant protein will contain a V5 tag, which will be used to probe only for the presence of the mutant MARCKS protein in the cells.

Results: As compared to the control, proliferation was significantly decreased while radiation sensitivity was increased in MARCKS overexpressing cells (WT) cells. Decreased DNA damage repair was observed in wild type mutants as compared to control as indicated by decreased levels of phospho-DNA-PK. Apoptosis was also increased as indicated by elevated levels of cleaved caspase-3 in WT. Further experiments are ongoing to potentially draw further conclusions about the mechanistic relationship between MARCKS and the PI3K/Akt pathway.

Simanyi, Eva (Eva)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Nabiha Yusuf
Abstract Approved By Advisor	Yes
Co-Authors	Iman A Tamimi, Hillary DelaRosa, Israr Ahmad, Craig A Elmets, Nabiha Yusuf
Title	Toll-Like Receptor-4 augments ultraviolet radiation induced cutaneous tumor development by DNA damage mechanism

Abstract

Ultraviolet (UV) B radiation (290-320 nm) induced DNA damage is an important trigger for suppression of immune responses and for the initiation of non-melanoma skin cancers. UVB causes DNA damage, predominantly in the form of cyclobutane pyrimidine dimers (CPD). Reactive oxygen species (ROS), which are generated endogenously by cellular oxygen metabolism or exogenously by UV, also produce various types of DNA damage. 8-Oxo-2'-deoxyguanosine (8-Oxo-dG) is one type of oxidative DNA damage that can result in stable mutations. Toll-like receptor 4 (TLR4), a component of innate immunity, has been shown to play an important role in cancer. Previous studies from our laboratory indicate that TLR4 deficient mice developed significantly fewer CPD ($p<0.05$) in their skin upon UVB exposure. Our recent experiments indicate that when mice are exposed to single dose of UVB (200 mJ/cm^2), UVB-induced DNA damage mediated by ROS is greatly reduced in TLR4 deficient mice, indicated by significantly fewer 8-Oxo-dG lesions ($p<0.05$) in the skin of these mice. We also found that when mice were exposed to multiple doses of UVB radiation (200 mJ/cm^2), cutaneous carcinogenesis was inhibited in terms of tumor incidence and tumor latency in mice deficient in TLR4 compared to TLR4 competent mice, with significantly greater ($p<0.05$) number of tumors occurring in TLR4 competent mice. Together, our data indicate that TLR4-mediated UVB-induced DNA damage in the form of CPD and 8-oxo-dG lesions may be a molecular trigger for development of UVB-induced skin cancers. Thus, strategies to inhibit TLR4 may allow us to develop immunopreventive and immunotherapeutic approaches for management of UVB-induced cutaneous DNA damage and skin cancer.

Singer, Jeffrey Robert (Jeff)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Casey Weaver
Abstract Approved By Advisor	Yes
Co-Authors	Matthew T. Palmer and Karen M. Janowski
Title	Using the HAT-BAC mouse model to define cis-regulatory elements in the Human Interferon gamma locus

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*.

Sloan, Meagan Elizabeth (Meagan)

Project Length	Short
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Dr. Julia Gohlke
Abstract Approved By Advisor	Yes
Co-Authors	Mary Evans, Molly Bernhard, Shia Kent
Title	A Pilot Project to Assess Individual temperature and light exposures in urban and rural populations

Abstract

Individuals in Alabama are often exposed to a great deal of sunlight and high temperatures during the summer months. However, little is known about the effects that such exposures can have on these individuals' activity levels and BMI. Besides that, over-exposure to sunlight can lead to melanoma and other skin cancers. This pilot study seeks to quantify the temperature exposures and time spent outdoors among urban and rural Alabamians using the HOBO temperature and sunlight monitor. Participants were asked to wear the monitors for one week, while also recording daily logs of their indoor and outdoor activities. The participants also had their height, weight, and body composition measured; completed a demographic questionnaire; and had an infrared picture taken in order to estimate core and peripheral temperature. Data analyzed thus far indicates that individuals in rural Alabama may have higher daily mean heat exposure, but urban residents may be exposed to higher daily maximum temperatures. In comparison to community members, City of Birmingham groundskeepers had significantly higher heat and sunlight exposure, suggesting the use of this personal data logging monitor is able to track different exposures across geographic regions and occupations. Results from the exit survey conducted suggest participants found wearing the monitor and keeping a daily log useful in raising awareness regarding time spent outdoors and physical activity during their daily lives.

Smith, Cody Brian (Cody)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Jeffrey P. Blount and Robert Knowlton
Abstract Approved By Advisor	Yes
Co-Authors	C. B. Smith, MS4; R. Knowlton, MD; C. J. Rozzelle, MD; M. Goyal, MD; H. Kim, PhD; P. Kankirawatana, MD; C.N. Shannon; K. Riley, MD; J.P. Blount, MD, FAAP, FAANS
Title	MEG Contributes to Surgical Management in Lesional Epilepsy

Abstract

Rationale: Focal surgical resection of an abnormality, lesionectomy, has been the conventional approach; however, simple removal may lead to failure rates as high as 30%. This study aims to characterize the contribution of magnetoencephalography (MEG) imaging to the management of a contemporary series of surgical epilepsy patients.

Methods: Following IRB approval, a retrospective review of surgeon and epilepsy center databases (UAB or Children's Hospital of Alabama, 1995-2011) was performed to identify patients (adult and pediatric) who had epilepsy arising from a region of brain with an MRI evident lesion. Clinical data included MRI findings, video-EEG, operation performed, intraoperative frameless navigation, histopathology, and seizure outcome. Imaging data included MRI, MEG, ictal SPECT/SISCOM, and PET findings.

Results: We identified 116 patients (73 children and 43 adults) who had lesional epilepsy surgery. Lesions included 40 tumors, 38 FCD, 13 gliosis/encephalomalacia, 10 phakamatoses, and 6 vascular lesions. Forty-seven patients underwent MEG studies, 13 extraoperative and 34 intraoperative with co-registration of frameless navigation systems. MEG contributed in the tumor cases by directing/expanding electrode placement for IC-EEG (n= 3), defining adjacent eloquent cortex (n=3), and in aiding pre-operative localization of dipoles. MEG indicated remote dipoles in one cavernoma case, contributing to a grid based resection and confirming an extensive epileptogenic region. MEG demonstrated dipoles in regions that could not be studied by other functional imaging modalities (IS, PET) (n=4) and expanded the implicated region of ictal onset to prompt more widespread electrode coverage (n=2). Regression analysis studies are ongoing.

Conclusions: MEG studies can significantly contribute to the assessment of lesional epilepsy. Extraoperative utilization can include conventional localization of dipoles to localize ictal onset, implicate areas beyond the lesion in epileptogenesis, map adjacent eloquent function, guide IC-EEG electrode placement, and allow study of tissue that is difficult or impossible to study with other functional imaging modalities.

Snead, Benjamin Ross (Ben)

Project Length	Short
Prior Research Experience	No
Funding Source	Other
Advisor	Dr. Desiree Morgan
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Dual-Energy CT Analysis of Ablation Therapy for Hepatocellular Carcinoma

Abstract

Background: Although the concept of dual-energy CT (DECT) was developed over 3 decades ago, it has only recently begun to be considered for widespread clinical use. Technological developments have allowed the same object to be scanned once with two different energies, rather than capturing sequential images with a polychromatic x-ray beam. This results in reduced radiation exposure to the patient with enhanced contrast. The efficacy of DECT in analyzing the ablation response in hepatocellular carcinoma patients has not been established.

Hypothesis: When analyzing DECT exams of hepatocellular carcinoma lesions that were treated with ablation, an energy level of 52 keV is superior to 70 keV in visualizing changes in lesions between pre-ablation and post-ablation scans.

Methods: Retrospective study involving 14 patients and 22 ablated hepatocellular carcinoma lesions that had both pre- and post-ablation DECT scans. Arterial phase scans were analyzed using an independent DECT workstation and compared using t-test. Hounsfield Units of the lesion and normal liver were measured. Standard deviation of the Hounsfield Units of an area of paraspinal muscle was also measured for each image in order to account for image noise levels.

Results: At 70 keV, the average of the difference between post- and pre-ablation measurements recorded for absolute contrast (lesion HU–normal liver HU), enhancement index (absolute contrast/normal liver HU), and conspicuity (absolute contrast/standard deviation of HU of paraspinal muscle) were: -47.00 ($p = 0.0089$), -0.65 ($p = 0.0044$), -3.60 ($p = 0.0013$), respectively. At 52 keV, differences were: -102.49 ($p < 0.0001$), -1.03 ($p < 0.0001$), -4.88 ($p < 0.0001$).

Conclusion: The greater average difference between the post-ablation and pre-ablation values in absolute contrast, enhancement index, and conspicuity in the 52 keV group appears to indicate that 52 keV is superior to 70 keV in visualizing the changes in appearance in scans following ablation.

Sollie, Rebecca Susan (Rebecca)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Yang Yang
Abstract Approved By Advisor	Yes
Co-Authors	Rebecca S Sollie1, Li Nan1, Jian Ruan1, and Yang Yang1,2
Title	Runx2 Transcription Factor Regulates Heparanase-Induced Bone Resorption in Multiple Myeloma

Abstract

Background. Despite advances in treatment strategies, myeloma remains incurable, and bone destruction is a major cause of morbidity in myeloma patients. Dr. Yang's lab has documented in earlier studies that heparanase enzyme is preferentially expressed in myeloma cells and induces severe bone destruction in myeloma. They also discovered that heparanase increases the production of two major bone-resorbing factors named Receptor Activator of NF-κB Ligand (RANKL) and Matrix Metalloproteinase 9 (MMP-9) by myeloma cells. Runx2, a member of the runt-related gene family, is a bone-specific transcription factor. Runx2 regulates osteoblast differentiation and is essential for bone tissue development. Interestingly, Runx2 also controls expression of RANKL and MMP-9 genes in osteoblasts. Recent evidence indicates that ectopic induction and overexpression of Runx2 in breast, uterine and prostate cancer cells is associated with bone-metastasis, and osteolytic bone disease in these cancers. However, very little is known about the function of Runx2 in myeloma cells. In the present study, I investigated the role of Runx2 in heparanase -induced expression of RANKL and MMP-9 in myeloma cells.
Methods. Molecular, biochemical and cellular approaches were used to assess the role of Runx2 in heparanase-induced expression of RANKL and MMP-9. These included: (1) Western blot analysis to monitor Runx2 levels in CAG myeloma cells expressing high level of heparanase (HPSE-high cells) or with knockdown of endogenous heparanase (HPSE k/d cells), and the corresponding control cells. (2) Knockdown of Runx2 in human myeloma MM1.S and CAG (HPSE-high cells, using Runx2 shRNA (Sigma), non-targeting shRNA was used as control. (3) Confirm the knockdown of Runx2 in above cells by real-time PCR and Western blot. (4) Real-time PCR to determine changes in RANKL and MMP-9 gene expression in Runx2 knockdown CAG-HPSE and MM1.S myeloma cells.
Results. Runx2 expression is significantly increased in CAG myeloma cells expressing a high level of heparanase and dramatically reduced in HPSE k/d cells. Increased Runx2 in HPSE-high myeloma cells results in an increase in expression of RANKL and MMP-9 mRNA as well as MMP-9 activity. In sharp contrast, knockdown of Runx2 in human myeloma CAG-HPSE and MM1.S cells results in a significant reduction of RANKL, MMP-9 gene expression and MMP-9 activity. Thus heparanase promotes RANKL and MMP-9 expression via Runx2. These results demonstrate that Runx2 is a positive regulator of RANKL and MMP-9 gene expression in myeloma cells.
Conclusions. Runx2 transcription factor upregulates heparanase-induced myeloma bone disease by promoting RANKL and MMP-9 expression in myeloma cells. Our discoveries provide new insight into the mechanism of myeloma-induced bone disease and identify Runx2 as a novel target to block myeloma bone disease.

Spann, Ashley Ladana (Ashley)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Andra Frost
Abstract Approved By Advisor	Yes
Co-Authors	Kun Yuan
Title	Primary Cilia Dependent GLI-1 Expression in Cancer

Abstract

Primary cilia (PC) are single, microtubule-based, non-motile organelles that can promote cellular processes in response to changes in the extracellular environment. PC are also important for regulation of canonical Hedgehog signaling. In some cancer types, Hedgehog signaling is often up-regulated and is a possible therapeutic target. However, less PC are found in malignant tissues in comparison to their non-malignant counterparts. Therefore, the presence or absence of PC may be relevant to the effectiveness of therapeutic interventions targeting different steps of Hedgehog pathway. Cancer cell lines with (SKOV3) and without (MCF7, MDA-MB-231) PC and a non-malignant, ciliated, Hedgehog ligand responsive cell line (NIH3T3, Light cells) were treated at varying nM concentrations with Smoothened agonist (SAG), a cilia-dependent activator of Hedgehog signaling. mRNA expression levels of the downstream protein product GLI-1 were measured by RT-qPCR and Gli1 activity was measured by luciferase assays (Promega Dual Luciferase Assay Kit; Lipofectamine 2000). PC counts were also obtained for each cell line using immunofluorescence for acetylated α-tubulin as a primary cilia marker. In non-malignant, cilia positive cell lines, after 30 hours of SAG treatment, a 6-fold increase in GLI-1 expression was observed with a 16-fold increase in GLI-1 activity after 60 hours as determined by luciferase assay. In malignant, cilia negative cell lines (MCF-7; MDA-MB-231) no appreciable GLI-1 expression or activity was observed after SAG. In malignant, cilia positive cell lines (SKOV3), there was also no significant change in GLI-1 expression or activity with SAG treatment. These data suggest that primary cilia may be necessary for canonical Hedgehog signaling, but are not sufficient. In cancer, there may be ciliary dysfunction that prevents canonical HH signaling, even in the presence of PC. Therefore, in malignancies without PC or with PC dysfunction, there may be no canonical Hedgehog signaling thereby rendering inhibition of Smoothened to be ineffective.

Sriram, Neeraj (Neeraj)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Diabetes Research and Training Center Fellowship
Advisor	Dr. Gary Hunter, PhD
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Changes in resting energy expenditure effect changes in blood pressure over time in premenopausal women

Abstract

Recent studies have reported a strong association between blood pressure (BP) and resting energy expenditure (REE). Therefore, we examined the relationship between REE and BP over time after adjusting for potential confounders such as sympathetic tone and anthropometric variables. Subjects were premenopausal women aged 20 to 42 years old, and testing was performed over 4 years (5 time points) in the General Clinical Research Center. Resting energy expenditure was measured by indirect calorimetry, body composition was determined by dual-energy x-ray absorptiometry, intra-abdominal adipose tissue by CT, 24-hour fractionated urinary catecholamine measurements of norepinephrine and epinephrine were determined by high-performance liquid chromatography, and blood pressure was measured with automatic auscultation while lying in the supine position. Repeated measures mixed-models revealed, after adjusting for time, REE as a significant predictor of mean systolic blood pressure (β=0.0155, P<0.0001), independent of catecholamines (β=0.0268, P=0.6328), percent body fat (β=0.1853, P=0.0127), activity-related energy expenditure (β=-0.0011, P=0.4950), leg fat (β=0.0003, P=0.2828), intra-abdominal adipose tissue (β=0.0327, P=0.0233), and fat-free mass (β=0.0050, P=0.9707). We conclude that mean systolic blood pressure remains related to REE, independent of anthropometric variables and a marker for sympathetic tone. Additionally, body composition, fat distribution, and intra-abdominal adipose tissue do not explain the relationship between blood pressure and resting energy expenditure.

Stanley, Jennifer Anne (Jennifer)

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Eddy Yang
Abstract Approved By Advisor	Yes
Co-Authors	Somaira Nowsheen, Tiffiny Cooper
Title	Targeting Human Epidermal Growth Factor Receptor Pathways to Render Triple Negative Breast Cancer Cells Susceptible to PARP Inhibition

Abstract

Background/Objectives

Few therapeutic options are effective for the highly aggressive triple negative breast cancers (TNBCs). Inhibitors of the DNA repair protein poly(ADP-ribose) polymerase (PARP), which target homologous recombination (HR) repair deficient cells, are being actively investigated in combination with systemic DNA damaging agents. We previously reported EGFR inhibition (EGFRi) attenuates HR. In this study, we hypothesized that EGFRi can induce a contextual synthetic lethality with PARP inhibition in TNBCs. Additionally, because EGFR activates DNA repair via nuclear translocation, we hypothesized the mechanism of EGFRi-mediated attenuation of HR involves alteration of protein subcellular localization and interaction with key DNA repair proteins, such as BRCA1.

Methods

Human TNBC cells MDA-MB-231, MDA-MB-453, and MDA-MB-468 were used in this study. EGFR and PARP inhibition was achieved using lapatinib and ABT-888, respectively. HR repair was assessed by immunohistochemistry for Rad51 foci and by a chromosomal-based repair assay. Cytotoxicity was assessed by ATPlite and colony formation assays, while cellular apoptosis was determined via annexin staining and assessment for cleaved caspase 3 and 9. Protein-protein interaction was determined by immunoprecipitation. Sub-cellular localization was assessed by cellular fractionation and western blot. Lastly, in vivo tumor growth delay was assessed in mice bearing orthotopic MDA-MB-231 xenografts.

Results

EGFRi induces a contextual synthetic lethality with PARPi both in vitro (70-99% cell kill, $p<0.01$) and in vivo (>3 fold tumor growth delay, $p<0.001$). This enhanced cytotoxicity involves activation of intrinsic apoptosis. Interestingly, EGFR and BRCA1 are in the same protein complex, which is reduced by EGFRi (35-70% reduction, $p<0.01$). EGFRi also increases cytosolic BRCA1 and EGFR, away from their nuclear DNA repair substrates (2-fold reduction, $p<0.01$).

Conclusions

These results reveal a contextual synthetic lethality between combined EGFR and PARP inhibition in TNBC that occurs via novel regulation of HR repair. Importantly, this contextual synthetic lethality may exist in other EGFR-dysregulated tumors.

Stone, Sara Lynn (Sara)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Frances Lund
Abstract Approved By Advisor	Yes
Co-Authors	Betty Mousseau
Title	T-bet supports differentiation of B-effectors into antibody secreting cells

Abstract

Memory B cells (Bmem) and long-lived plasma cells (LLPC) arise from germinal center B cells (GCB). The transcription factor BCL6 is required for GCB cell survival and the development of Bmem. By contrast, BCL6 inhibits LLPC development by repressing the transcription factor Blimp1 which normally controls LLPC development. To date, it is not clear how these opposing transcription factors are regulated in GCB cells. Interestingly, in T lymphocytes, the transcription factor T-bet modulates the balance between Blimp1 and BCL6 and controls their subsequent differentiation into memory and effector cells. We recently defined a B-cell subset, referred to as B-effector 1 cells (Be-1 cells), that express high levels of T-bet and secrete IFNg. We showed that IFNg or T-bet deficient Be-1 cells inefficiently seed the LLPC compartment, leading us to suspect that the Be-1 cells may be precursors to LLPCs and Bmem. We therefore hypothesized that T-bet expression by Be-1 cells promotes cytokine production and supports their differential development into antibody secreting cells (ASCs). To test this hypothesis, we co-cultured naïve splenic Bcells from T-bet-/-, IFNγ-/-, or C57BL/6 mice with Th1 or Th2 cells. After 4 days, we sort purified total B-cells and the IFNg producing CXCR3+ CCR6+ Be-1 cell subset. We evaluated the transcription profile of the cells and measured cytokine and antibody secretion. We found that the CXCR3+ CCR6+ Be1s expressed higher levels of BCL6 and T-bet but lower levels of Blimp1, Ig J-chain, and XBP1 compared to the non-Be1 cells. T-bet-/- Be1s expressed lower Blimp1, XBP1, and J-chain expression, but higher BCL6 compared to B6 Be1s. T-bet-/- and IFNγ-/- Be1s had attenuated IFNγ production and antibody secretion compared to B6 Be1s. These results support a role for T-bet in determining Blimp1 and BCL6 levels in Beffs and modulating their development into ASCs rather than Bmem cells.

Strickland, Leah Ray (Leah)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	W Timothy Garvey, M.D
Abstract Approved By Advisor	Yes
Co-Authors	Fangjian Guo, M.D, Kerry Lok, Ph.D
Title	Type 2 Diabetes with Partial Lipodystrophy of the Limbs: a New Lipodystrophy Phenotype

Abstract

Objective. Lipodystrophies are a rare, heterogeneous group of disorders characterized by loss of subcutaneous adipose tissue and metabolic abnormalities associated with insulin resistance. They are categorized by the extent of fat loss (generalized versus partial) and inheritance (congenital versus acquired). We examined whether a group of patients with partial lipodystrophy of the limbs (PLL), Type 2 Diabetes Mellitus (T2DM), and an absence of family history of lipodystrophy constitute a new clinical subtype.

Research Design and Methods. Ten women with T2DM and PLL were identified in academic diabetes clinics, and were matched by age, gender, BMI, ethnicity, and diabetic status with 10 women with common T2DM without lipodystrophy. All patients were characterized by clinical evaluation and hyperinsulinemic clamp.

Results. Patients with T2DM and PLL exhibited symmetrical loss of subcutaneous fat in forearms, or forearms plus calves, and acanthosis nigricans. Maximally-stimulated glucose disposal rates were markedly reduced by 56% in the T2DM with PLL group when compared with common T2DM whether normalized by body weight or surface area. Most PLL patients exhibited little or no insulin-medicated glucose uptake after subtraction of non-insulin-mediated glucose uptake. The T2DM with PLL group also had greater elevations in hepatic transaminases and triglycerides compared with common T2DM.

Conclusions. The pattern of fat loss and inheritance seen in these patients is dissimilar from known forms of lipodystrophy. T2DM with PLL represents a previously unrecognized phenotype of lipodystrophy and of T2DM. These T2DM patients exhibit symmetrical lipodystrophy of the distal limbs, acanthosis nigricans, marked insulin resistance with little insulin-mediated glucose uptake, hypertriglyceridemia, and hepatic transaminase elevations, which are greater in severity than observed in patients with common T2DM. We believe this subtype of lipodystrophy may not be rare. All T2DM patients with overt hypertriglyceridemia and hepatic transaminase elevations or with high insulin requirements should be examined closely for PLL.

Sultan, Faraz (Faraz)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Dr. J. David Sweatt
Abstract Approved By Advisor	Yes
Co-Authors	Jing Wang, Jennifer Tront, Dan Liebermann, J. David Sweatt
Title	Genetic deletion of gadd45b, a regulator of active DNA demethylation, enhances long-term memory and synaptic plasticity

Abstract

Dynamic epigenetic mechanisms including histone and DNA modifications regulate animal behavior and memory. While numerous enzymes regulating these mechanisms have been linked to memory formation, the regulation of active DNA demethylation (i.e. - cytosine 5 demethylation) has only recently been investigated. New discoveries aim towards the Gadd45 family, particularly Gadd45b, in activity-dependent demethylation in the adult CNS. This study found memory-associated expression of gadd45b in the hippocampus and characterized the behavioral phenotype of gadd45b-/- mice. Results indicate normal baseline behaviors and initial learning but enhanced persisting memory in mutants in tasks of motor performance, aversive conditioning and spatial navigation. Furthermore, we showed facilitation of hippocampal long-term potentiation in mutants. These results implicate Gadd45b as a learning-induced gene and a regulator of memory formation and are consistent with its potential role in active DNA demethylation in memory.

Tagayun, Christine Anne (Christine)

Project Length	Short
Prior Research Experience	Yes
Funding Source	Other
Advisor	Dr. Todd Jenkins
Abstract Approved By Advisor	Yes
Co-Authors	Christine Tagayun, Caroline Juneau, M.D.
Title	Retrospective Analysis of the Effect of Weight on the Levonorgestrel Intrauterine System

Abstract

Scientific Rationale: The levonorgestrel intrauterine system (Mirena®) releases progestin within the endometrial cavity resulting in endometrial atrophy and subsequent menstrual suppression. Previous research has shown that most users experience an 80% reduction in menstrual blood loss after 3 months of usage. In some women, this menstrual reduction results in amenorrhea. However, the majority of the existing research has evaluated women with normal weight and BMI. Therefore, this study is designed to assess the effect of weight on menstrual suppression in Mirena® users.

Specific Aim: To assess the effect of weight on the performance of the levonorgestrel intrauterine system in the control of abnormal uterine bleeding by comparing outcomes in women with a BMI < 30 to those with a BMI $\geq$ 30.

Hypothesis: Amenorrhea at 12 months in levonorgestrel intrauterine system users is not affected by patient obesity.

Experimental Design: The study will be a retrospective cohort study of women utilizing Mirena® in an effort to determine if weight is a factor in control of menstrual bleeding. Patients will be compared in a dichotomous fashion divided by a BMI of 30. Records for patients who received the device will be reviewed from the date of insertion forward one year. Premenopausal females ages 18-49 from 2002 to 2011 who had a Mirena® placed at one of the clinical sites of the Division of Women's Reproductive Healthcare will be reviewed for inclusion. These sites will provide a diverse population consistent with the age, race, socioeconomic, and weight distribution of the local population. 500 women will be needed to establish a significant difference between the two groups. Secondary outcomes include infection, expulsion, continuation, and complication rates.

Anticipated Results: The rate of amenorrhea of patients using the levonorgestrel intrauterine system at 12 months will not be different between those women with a BMI $\geq$ 30 compared to those < 30.

Summary: All of the existing research has evaluated Mirena® in women with a normal BMI. This project is designed as a pilot study for future prospective trials to assess the effect of obesity on menstrual suppression rates with the levonorgestrel intrauterine system.

Thomas, Evan Marshall (Evan)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Other
Advisor	John Fiveash
Abstract Approved By Advisor	Yes
Co-Authors	Matthew Larrison, Richard Popple, John Fiveash
Title	Utilization of Dual Energy CT to Improve Treatment Planning for Patients with Metal Streak Artifact

Abstract

PURPOSE: High-Z objects can compromise the accuracy and visual integrity of CT scans. This artifact hinders radiation treatment planning in two main ways: degradation of visual quality of the images due to photon-starved regions around the high-Z object which prevents proper delineation of both target and organ-at-risk contours in affected CT slices, and adulteration of the Hounsfield Unit (HU) values. If HU values are unreliable, so will the electron density values upon which radiation treatment plans are computed and optimized. We undertook this study to determine whether dual energy CT (DECT) offered a plausible solution to these problems.

METHOD AND MATERIALS: We designed a custom phantom to observe the effects of a variety of metal artifact-causing objects (ACOs). The phantom was first scanned on a radiation therapy CT simulator, w/wo high-Z objects. The phantom was then scanned on a Discovery 750HD 140/80 kVp rapid-switching DECT, w/wo high-Z objects, using a metal- artifact subtraction (MARS) algorithm. We chose HU based auto-contouring and volume computation of ROIs because of its ability to simultaneously illustrate the effect of streak artifact on contour delineation and HU values. Each scan was imported into treatment planning software. The mean differences between each reconstructed volume and the theoretical volume were then statistically compared.

RESULTS: The DECT scans, with and without the MARS algorithm employed, outperformed the traditional scanner in rendering the ROI contours and true HU values. Volume reconstruction data for each ROI is provided in Figure 1 along with each corresponding high-Z object. DECT w/MARS reduced the relative error of volume reconstruction from an average of 18.1% for the traditional scanner to just 4.56%. DECT w/MARS was the only scan whose volume reconstruction was not significantly different from the scans without the presence of high-Z objects ($p = 0.09$ and 0.08 for DECT).

CONCLUSION: DECT w/ MARS represents a promising method of coping with high-Z artifact. Our initial studies reveal that it is a useful tool in improving contouring ability and restoring proper HU values in photon-starved regions of affected CT slices. We are currently undertaking further analysis to verify DECT?s in improving dosimetry for affected patients.

CLINICAL RELEVANCE/APPLICATION
We believe DECT is an effective tool for resolving certain treatment planning difficulties in patients withmetal streak artifact.

Toneva, Galina Dimitrova (Galina)

Project Length	Short
Prior Research Experience	Yes
Funding Source	T35
Advisor	Mary Hawn
Abstract Approved By Advisor	Yes
Co-Authors	Rhiannon Deierhoi, Laura Altom, Jamie Cannon, Melanie Morris
Title	Oral Antibiotic Bowel Prep Reduces Length of Stay and Readmissions Following Colorectal Surgery

Abstract

Oral antibiotic bowel prep (OABP) prior to colorectal resection has been shown to reduce surgical site infections. We examined whether OABP decreases length of stay (LOS) and readmissions for colorectal surgery.

Methods: This retrospective study utilized national Veterans Affairs (VA) Surgical Quality Improvement Program pre-operative risk and outcome data linked to VA administrative and Pharmacy Benefits Management data on patients undergoing elective colorectal resections from 2005 to 2009. Exclusion criteria were pre-operative LOS >2 days, ASA class 5, or death before discharge. Patient and surgery characteristics, bowel preparation use, presence of an ostomy, indication for surgery and indication for readmission using ICD-9 codes were determined. Univariate and multivariable logistic regression analyses modeled post-operative LOS (above or below median) and 30-day readmission.

Results: Of the 8,190 patients, 1,161 (14.2%) were readmitted within 30 days. LOS and readmissions varied significantly by bowel prep, procedure, presence of an ostomy, and ASA class (Table). OABP was associated with a below-median post-operative LOS (adjusted OR=0.61, 95% CI 0.53-0.71) and fewer 30-day readmissions (adjusted OR=0.81, 95% CI 0.68-0.97). Overall, 4.9% were readmitted for infections (ICD-9 codes) and this varied by bowel prep (no prep 6.1%, mechanical 5.4%, OABP 3.9%, p=0.001). The readmission rate for non-infectious reasons was 9.3% and did not differ significantly by bowel prep (no prep 9.9%, mechanical 9.6%, OABP 8.8%, p=0.38).

Conclusion: OABP prior to elective colorectal surgery is associated with shorter post-operative LOS and lower 30-day readmission rates, primarily due to fewer readmissions for infections. Prospective studies are needed to verify these results.

Waits, George Sidney, IV (George)

Project Length	Short
Prior Research Experience	Yes
Funding Source	American Heart Association Fellowship
Advisor	Dr. Ho-wook Jun
Abstract Approved By Advisor	Yes
Co-Authors	Dr. Jeonga Kim, Adi Andukuri
Title	Anti-inflammatory Gene Expression of a Nitric Oxide Releasing Nanomatrix for Cardiovascular Stents.

Abstract

Background: Novel designs for cardiovascular stents are intended to address the shortcomings of existing models including restenosis and late-stent thrombosis. Furthermore, the surface interface between the stent material and the vasculature leads to endothelial injury, which causes a cascade of pro-inflammatory events including monocyte invasion and eventual endothelial dysfunction. To address these limitations, we are developing a nanomatrix polymer based on peptide-amphiphiles (PA) equipped with endothelial-promoting peptide sequences (YK) capable of releasing nitric oxide (NO) at controlled rates. The nanomatrix (termed PA-YK-NO) is designed to mimic the endothelium, reducing inflammatory effects. Numerous proof-of-concept studies are underway to optimize and assess the efficacy of the coating. The purpose of this study is to assess the anti-inflammatory properties of PA-YK-NO under *in vitro* conditions.

Methods: Inflammation was assessed *in vitro* by co-incubating U937 human monocytes with either PA-YK-NO or tissue culture plastic (TCP) as a control. RNA was isolated from each sample, and qRT-PCR was performed to compare relative gene expression of pro-inflammatory cytokines TNF-α, IL-6, and MCP-1. Pro-inflammatory gene expression was reported as a percentage of a gene quantity measured in the PA-YK-NO group relative to the same inflammatory gene measured in TCP samples.

Results: Samples containing the PA-YK-NO nanomatrix showed a reduction in gene expression of TNF-α. Reduced expression of IL-6 and MCP-1 in PA-YK-NO samples were found. However, relative gene expressions of IL-6 and MCP-1 were not statistically significant.

Conclusion: The PA-YK-NO nanomatrix demonstrated marginally less inflammatory expression in human monocytes compared with TCP. Future in vitro studies will seek to demonstrate the anti-inflammatory effect of the nitric-oxide released from PA-YK-NO when presented to a pre-induced inflammatory environment. This effect will be shown in both monocytes and endothelial cells measured at varying time intervals.

Wang, Timothy Adrian (Timmy)

Project Length	Short
Prior Research Experience	Yes
Funding Source	American Heart Association Fellowship
Advisor	Suzanne Oparil, M.D.
Abstract Approved By Advisor	Yes
Co-Authors	Xiangmin Zhao, M.D., Daisy Xing, M.D., Ph.D., Fadi Hage, M.D., Yiu-Fai Chen, Ph.D.
Title	Increased Protein O-GlcNAcylation Inhibits TNF-α--induced Inflammatory Mediator Expression in Rat Aortic Endothelial Cells

Abstract

Objective: Inflammation and endothelial dysfunction play key roles in initiation of many forms of vascular disease. We have previously shown that increasing O-linked-N-acetylglucosamine (O-GlcNAc) protein levels in balloon injured rat carotid arteries inhibited resultant inflammation and neointima formation. The current study tested the hypothesis that increasing protein O-GlcNAcylation can protect endothelial cells (ECs) against inflammatory stress. **Methods and Results:** Quiescent cultured rat aortic ECs (RAECs) were pretreated with glucosamine (GlcN) (5 mM, an amino sugar that increases protein O-GlcNAcylation by increasing flux through the hexosamine biosynthesis pathway), Thiamet-G (0.1 μM, an inhibitor that blocks O-GlcNAcase-mediated removal of O-GlcNAc from proteins) or vehicle for 1 hr and then stimulated with tumor necrosis factor (TNF)-α (10 ng/ml, a primary pro-inflammatory cytokine) or vehicle for another 6 hrs. RNA was extracted for real-time RT-PCR analysis of chemokine and adhesion molecule expression. Nucleocytoplasmic proteins were subjected to Western blot analysis of global O-GlcNAcylated protein levels using the selective CTD110.6 antibody. Treatment with GlcN and Thiamet-G alone significantly enhanced overall O-GlcNAcylated protein levels (increased 60% by GlcN and 150% by Thiamet-G, n=6/group), but did not alter pro-inflammatory chemokine and adhesion molecule expression in RAECs. Treatment with TNF-α alone significantly stimulated VCAM-1, CINC-2β, P-Selectin, and iNOS levels, but did not change O-GlcNAcylated protein levels. Pretreatment with GlcN significantly inhibited TNF-α-stimulated CINC-2β (decreased 22%), P-Selectin (decreased 41%) and VCAM-1 (decreased 27%) mRNA expression; and pretreatment with Thiamet-G also significantly inhibited TNF-α-stimulated CINC-2β (decreased 20%) and P-Selectin (decreased 35%), but not VCAM-1, mRNA expression in RAECs. **Conclusions:** Increased protein O-GlcNAcylation inhibits TNF-α-induced expression of important inflammatory mediators, including CINC-2β and P-Selectin in ECs, consistent with our previous in vivo findings. These results provide evidence that O-GlcNAc protein modification in ECs may protect the vasculature from inflammatory stresses.

Warmus, Brian Andrew (Brian)

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Erik D. Roberson
Abstract Approved By Advisor	Yes
Co-Authors	Dheepa R. Sekar, Gerard D. Schellenberg
Title	Insulostriatal Dysfunction and Repetitive Behavior in a Mouse Model of Frontotemporal Dementia

Abstract

Tau mutations cause behavioral variant frontotemporal dementia (FTD), a progressive and lethal disease commonly presenting with repetitive behaviors. FTD patients have connectivity dysfunction and atrophy in a network of brain regions called the salience network. In this network, FTD patients have insulostriatal abnormalities with neurodegeneration beginning in insular cortex and repetitive behaviors correlating with ventral striatum dysfunction. No mouse model with a tau mutation has yet to demonstrate FTD-relevant behaviors, and it is unknown which brain regions or networks are impaired in a mouse model with FTD-relevant behaviors. We found that transgenic mice with the FTD-associated V337M human tau mutation (hTauV337M mice) have age-dependent repetitive grooming, severe enough to cause facial lesions. In a model demonstrating FTD-relevant behavior, we hypothesized that tau mutations preferentially affect neurons in insulostriatal regions. To test this hypothesis, we compared the biochemistry, anatomy, and physiology in insulostriatal and anatomically similar control regions outside the salience network (motor cortex and dorsal striatum) of non-transgenic and hTauV337M mice. hTauV337M mice have decreased postsynaptic density protein 95 (PSD-95) levels by western blot in insular cortex as early as 2 months of age and in ventral striatum as early as 14 months, but PSD-95 levels are not decreased in either motor cortex or dorsal striatum even by 22 months. hTauV337M mice have dendritic simplification of Golgi-stained neurons in insular cortex and ventral striatum, but not of neurons in motor cortex or dorsal striatum at 24 months of age. Electrophysiological recordings in acute striatal slices show hTauV337M mice have decreased excitatory transmission in ventral but not dorsal striatum as early as 14 months of age. In a model of repetitive behavior, these data suggest that FTD-associated tau mutations preferentially affect the structure and function of neurons in insulostriatal regions, providing a patient-relevant model for future therapeutic intervention.

Watkins, Stacey Michelle (Stacey)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Other
Advisor	Harald Sontheimer
Abstract Approved By Advisor	Yes
Co-Authors	Stefanie Robel, Ian Kimbrough
Title	Invading glioma cells disrupt the neurovascular coupling mediated by astrocytes

Abstract

Neurovascular coupling is the regulation of blood flow in response to neural activity and is mediated by the release of vasoactive molecules including nitric oxide, prostaglandins and arachidonic acid metabolites and K^+. Astrocytes play a vital role in this process, responding to neuronal activity by increasing $[Ca^{2+}]_i$, which in turn regulates the release of these molecules from astrocytic endfeet onto arterial smooth muscle cells.

Malignant gliomas are highly invasive brain tumors, which utilize the abluminal side of blood vessels as a conduit for invasion. *In vivo* imaging studies suggest that invading gliomas are in direct contact with blood vessel endothelial cells and therefore may temporarily or permanently displace astrocytic endfeet. Whether and how this may affect neurovascular coupling is unknown.

To investigate this, we implanted human glioma cells into immuno-deficient (*scid)* mice and studied their interactions with astrocytes and the vasculature in acute brain slices. Application of noradrenaline, which selectively increases intracellular calcium in astrocytes without affecting glioma cells caused a significant vasoconstriction only in those arterioles that lacked perivascular glioma cells (mean 14.65%, n=18). Arterioles in contact with one or more glioma cell failed to respond to noradrenaline (mean 2.60%, n=18). The function of the underlying vascular smooth muscle cells was not altered by the presence of perivascular glioma cells, as they dilated and constricted similarly to vessels not associated with tumor cells when stimulated by U46619, prostaglandin E_2, endothelin-1, and 60 mM K^+. Confocal immunohistochemical analysis shows that glioma cells insert themselves between the endfoot and the blood vessel, hence physically displacing the astrocytic endfoot from the arterioles and explaining the loss of vascular coupling. Arterioles associated with glioma cells were on average 29.55% more dilated than those not associated with glioma cells. Hence invading gliomas, by displacing astrocytic endfeet, cause a loss of vasoregulation and a shunt of blood flow towards the tumor.

Weaver, Alice (Alice)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Dr. Eddy Yang
Abstract Approved By Advisor	Yes
Co-Authors	Tiffiny Cooper, Alex C Whitley, Eben L Rosenthal
Title	Differential Susceptibility of Oropharyngeal Carcinoma to Targeted Therapy Based on Human Papillomavirus Status

Abstract

In recent years, oropharyngeal cancer has changed from a disease of older men with a history of tobacco and alcohol abuse to a cancer occurring in younger adults as a result of human papillomavirus (HPV). HPV oncoproteins are known to disrupt cell signaling pathways, including DNA repair. We previously reported a synthetic lethal interaction between inhibitors of epidermal growth factor receptor (EGFR) and poly (ADP-ribose) polymerase (PARP), two important proteins in DNA repair, in HPV-negative head and neck cancers. In this study, we investigate the susceptibility of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) to two systemic agents, cetuximab and veliparib, which target EGFR and PARP, respectively.

Interestingly, our data support a differential response to these agents based on HPV status. *In vitro*, cetuximab/veliparib combination caused the greatest reduction in HPV-negative OPSCC proliferation (62%), compared to veliparib (32%) or cetuximab (30%) alone. In contrast, the same study in HPV-positive OPSCC cells found that veliparib alone caused the greatest reduction in growth (55%), compared to cetuximab/veliparib combination (40%) and cetuximab alone, which surprisingly stimulated growth in these cells. These results were confirmed *in vivo* by biweekly tumor xenograft volume measurements in mice. Mice bearing orthotopic HPV-negative OPSCC tumors exhibited a 20-day growth delay following combination cetuximab/veliparib treatment, compared to 10 days with cetuximab and no delay with veliparib (*$p<0.01$ vs. control). Conversely, veliparib induced a 15-day tumor growth delay alone and in combination with cetuximab (*$p<0.05$ vs. control) in mice bearing HPV-positive OPSCC human tumor explants, compared to no delay with cetuximab.

These results indicate that different therapeutic strategies may be appropriate for OPSCC depending on HPV status. Additional studies are needed to elucidate the mechanism of enhanced cell death in HPV-positive OPSCC, particularly in response to DNA damaging agents.

Webb, William Mitchell (William)

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program
Advisor	Susan L. Bellis, PhD
Abstract Approved By Advisor	Yes
Co-Authors	Bonnie K. Culpepper
Title	Varying Residue Number of Polyglutamate Domains Facilitates Differential Loading to and Release from Hydroxyapatite and Allograft Bone

Abstract

Bone matrix proteins such as bone sialoprotein (BSP) and osteocalcin contain stretches of negatively-charged amino acids that facilitate their binding to hydroxyapatite (HA), the principle mineral component of bone. Synthetically, heptaglutamate (E7) domains derived from BSP have been employed to facilitate binding and retention of the collagen-mimetic peptide DGEA to HA and allograft bone for the purposes of encouraging osteoblastic differentiation of mesenchymal stem cells. This E7-HA technology could also be exploited to enhance the osteoinductive capacity of HA-coated implants and allograft bone.

Because the negative charge of residues is known to regulate binding of peptide to HA, it was hypothesized that varying the number of glutamate residues attached to a cargo peptide would result in differential binding and adjustable release from HA and allograft bone, paving the way for more adjustable, personalized drug delivery regimens. Furthermore, mixed solutions of different polyglutamate-linked cargo molecules could potentially be combined to facilitate controlled timing and release of a variety of cargo molecules simultaneously, increasing the utility of polyglutamate domains for delivery of a wide range of biomodifiers onto HA-containing materials and allograft bone.

E2, E4, & E7-FITC-tagged peptide solutions were tested for loading to and percent release from both pure HA and allograft bone over time. Fluorometry and qualitative imaging revealed that increasing the number of ‘E’ residues facilitated more rapid binding, experienced greater total loading, and exhibited slower release from the surface of both materials. Solutions of polyglutamate-tagged peptides retained their average propensity to facilitate binding when combined in mixtures; therefore, ratios of E2, E4, and E7-tagged peptides could be adjusted to produce unique, customized release schedules.

These findings suggest a specific but adjustable means for pharmacotherapy delivery to bone as well as for gradual release of bioactive factors from implanted grafts and biomaterials.

Williams, Frank Bernard, III (Will)

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Other
Advisor	Lawrence Ver Hoef
Abstract Approved By Advisor	Yes
Co-Authors	Richard Kennedy
Title	Subtle Hippocampal Asymmetry on Magnetic Resonance Imaging in Temporal Lobe Epilepsy

Abstract

Background:The most commonly identified lesion in medically refractory epilepsy is hippocampal sclerosis (HS), a sign of temporal lobe epilepsy (TLE). Pre-surgically detected HS, identified on MRI by classic hallmarks of hippocampal atrophy and high signal intensity, is a significant predictor of post-surgical seizure-free status. Unfortunately, most TLE patients have normal MRIs.

We evaluated for left-right hippocampal asymmetry on high-resolution MRI in three subtle imaging findings: clarity of hippocampal internal architecture (HIA) defined by visualization of Ammon's horn in the coronal plane, hippocampal head digitation, and prominence of dentation on the undersurface of the hippocampal body. We postulate these signs are independent biomarkers of an epileptogenic hippocampus.

Methods: Retrospective evaluation of patients with video electroencephalogram-proven unilateral TLE and good quality TLE protocol 3T MRI scans identified 54 subjects seen from 2004 to 2008. Four-point subjective scoring scales were developed for HIA and dentation, and a three-point scale was used to grade digitation. Lower scores correlated with less defined hippocampi. Asymmetry scores were calculated by subtracting left hippocampal scores from right.

Results: In 12 patients with previously identified hippocampal sclerosis, 77% had some degree of asymmetry in HIA, 53% had asymmetry in digitation and 84% had asymmetry in dentation. Of the 42 patients without previously identified HS, 59% had asymmetry in HIA, 39% in digitation and 31% in dentation. Logistic regression for single variable models in the total group revealed asymmetry scores correlated with epileptogenic side for HIA ($p=0.001$), digitation ($p=0.001$) and dentation ($p=0.003$). Multivariate modelling among HS-negative subjects revealed significance for only HIA ($p=0.004$). With an HIA asymmetry cut-off value of 0.5, specificity of epileptogenicity was 95% and sensitivity was 40%.

Conclusions:HIA asymmetry is a subtle but specific finding in TLE. Asymmetry in hippocampal digitation and dentation are also significant, though less robust, predictors of TLE laterality.

Witcher, Adam Clarke (Adam)

Project Length	Short
Prior Research Experience	No
Funding Source	T35
Advisor	Dr. Sadis Matalon
Abstract Approved By Advisor	Yes
Co-Authors	Asta Jurkuvenaite
Title	Mitochondrial Membrane Potential and Viability Post-exposure to Cl2 Gas in H441 Cells

Abstract

Exposure to chlorine gas is one of the most common inhalation exposures in the workplace and the environment in the United States.[1] When chlorine gas is inhaled it reacts with low-molecular weight antioxidants. As these antioxidants are depleted, Cl_2 and its hydrolysis products react with proteins, components of the ECM, and unsaturated fatty acids.[2] The products of these reactions mediate chlorine toxicity in the lung. We believe that one of the targets of the reactive oxygen species produced is the mitochondria of bronchial epithelial cells. We hypothesize that post-exposure to Cl_2 gas, mitochondria found in bronchial epithelial cells will have decreased bioenergetic capacity and their function will be compromised. Therefore we will look for a decrease in membrane potential and decreased viability of these mitochondria compared with air controls. H441 cells will be covered in ELF (an artificial epithelial lining fluid) before being exposed to Cl_2 gas. To measure mitochondrial membrane potential we will use a Mito-PT—Trimethylrhodamine methyl ester (TMRM) assay. It will be performed 1 hour after air or chlorine exposure (100ppm/15min). To test mitochondrial viability we will follow the same protocol as for Cl_2 exposure but will measure mitochondrial reductase activity using the MTT assay immediately after chlorine exposure. We found that 1 hour after exposure to Cl_2 gas there was a significant decrease in the mitochondrial membrane potential of human bronchial epithelial cell line (H441 cells) when compared to air control (n=68-72). We also found a significant decrease in mitochondrial viability after Cl_2 exposure in H441 cells when compared to air control (n=36-38). Overall, we have shown that Cl_2 gas adversely affects the mitochondria of H441 cells *in vitro.* Our indices of damage were mitochondrial membrane potential, and mitochondrial viability. Future directions include pre-treating H441 cells with an anti-oxidant targeted to mitochondria (MitoQ) in order to see if scavenging the hydrolysis products of Cl_2 and water can prevent or at least partially alleviate the damage. This experiment would serve as proof of concept that mitochondrial antioxidants do indeed serve as protection from reactive oxygen species, and these antioxidants are depleted before mitochondrial damage takes place.

Wooten, Melanie Susannah (Melanie)

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Dr. Monica Baskin
Abstract Approved By Advisor	Yes
Co-Authors	
Title	Community-Level Barriers and Facilitators to Healthy Eating and Physical Activity Among African Americans Living in Rural Areas in the Deep South

Abstract

Health disparities are a major public health problem in the United States. African Americans have higher incidence and mortality rates for cancer, type 2 diabetes, and cardiovascular diseases compared to other racial/ethnic groups. Trends for obesity are no different. Poor health outcomes are even greater among African Americans living in southern states. A healthy diet and regular physical activity can reduce the risk for obesity, cancer, and other chronic conditions, but African Americans in the Deep South are less likely to engage in these health behaviors. This study utilized a qualitative and participatory approach (i.e., photovoice) to identify community-level barriers and facilitators to healthy eating and physical activity for African Americans in the Deep South. A total of 57 participants (93% female) from eight counties part of the Deep South Network for Cancer Control, an academic-community partnership to reduce cancer disparities in Alabama and Mississippi, were asked to take photographs over a one-week period of things in their communities that impacted their abilities to engage in physical activity and healthy eating. Pictures were discussed in focus group sessions using a standard format to capture what they saw, how it related to healthy behaviors, and potential action steps for community-level supports of healthy behaviors. A total of 171 pictures and notes from 8 focus group sessions were coded and categorized using NVivo, a qualitative data analysis program. Based on participant observation and discussion, the perception was that community members have access to healthy foods and areas for physical activity but barriers exist that hinder the utilization of these resources. This data indicates that community-level interventions in these communities may want to prioritize utilization and maintenance of existing resources prior to investing in new resources. The study also highlights the importance of community-based participatory research methods, such as photovoice, when considering interventions.

Yuan, Yih Ying (Yih Ying)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Other
Advisor	Marjorie Lee White, MD, MPPM, MEd
Abstract Approved By Advisor	Yes
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Title	A Simulation Course Focusing on Forensic Evidence Collection Improves Pediatric Knowledge and Standardizes Curriculum for Child Abuse

Abstract

According to the American Academy of Pediatrics, pediatricians must be prepared to provide care for sexual abuse victims. Forensic evidence collection is often a necessary part of the workup for these patients. Studies indicate an overall lack of knowledge regarding child abuse among pediatric residents, general pediatricians, and pediatric emergency physicians.[1] Our hypothesis was that pediatric residents and medical students who participated in a structured forensic evidence collection course would have improved knowledge of prepubertal evidence collection practices and pubertal genital anatomy.

The course curriculum included a 20-minute introductory forensic evidence collection video created by the SANE Program Director and the SANE Medical Director. A hybrid simulation setting was created using a simulator. After watching the video, the participants simulated forensic evidence collection utilizing state-approved forensic evidence collection kits. Prior to the course, evidence was staged on the simulator such as hair, a bite mark, and other debris that had to be collected during the simulation. The simulator also verbally expressed fear and embarrassment to the participants. All sessions were led by a pediatric SANE nurse. The participants completed a multiple-choice test and an eight item fill-in the blank anatomical diagram test before and after the sixty-minute course.

There was significant improvement in knowledge with the average pre-test score of 62 ± 20% and the average post-test score of 86 ± 9% ($p<0.001$). Anatomic labeling also improved; the average number of correctly identified parts on the pre-test was 5.2 + 1.3 and 5.8 + 1.1 post-test ($p=0.008$). Qualitative evaluations were also overwhelmingly positive.

In conclusion, a simulation course focusing on child abuse and the forensic collection process improves knowledge of pubertal genital anatomy and management of abused victims. This study introduced the concept of using the simulated setting to improve pediatricians' knowledge of forensic evidence collection.

Zelickson, Adam Mendel (Adam)

Project Length	Short
Prior Research Experience	Yes
Funding Source	
Advisor	Dr. Shawn Gilbert
Abstract Approved By Advisor	Yes
Co-Authors	Ken Waites MD, Xiao LI PhD
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. This model allows us to investigate both the early prevention and treatment of established infections in reproducible open fractures. An important outcome in this model is bacterial load and the progression of osteomyelitis. A quantitative PCR protocol has been developed to supplement standard microbiological culture procedures in examining this endpoint. Primers and probes specific for *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 *S. aureus* and rat RBL cells for sensitivity assays. Cycling parameters were optimized to achieve appropriate specificity, and sensitivity assays confirmed our detection threshold. This qPCR model will continue to serve as a simple method for directly quantifying bacterial involvement in test subjects 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 receive 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.

Zimmerman, Jacquelyn Winifred (Jackie)

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Boris Pasche, MD/PhD
Abstract Approved By Advisor	Yes
Co-Authors	Michael J. Pennison, Ivan Brezovich, Nengjun Yi, Celeste T. Yang, Ryne Ramaker, Devin Absher, Richard M. Myers, Niels Kuster, Frederico P. Costa, Alexandre Barbault, Boris Pasche
Title	Specific modulation frequencies inhibit cancer cell proliferation in vitro and in vivo

Abstract

Background: Hepatocellular carcinoma (HCC) incidence in the US is dramatically increasing. Five-year survival remains 3-5%, demonstrating urgent need for additional therapies. Intrabuccal administration of amplitude modulated electromagnetic fields (RF EMF) is a novel, minimally invasive treatment modality. Clinical evidence demonstrates this treatment approach elicits therapeutic responses in cancer patients. *In vitro* we described a phenotype in HCC cells following RF EMF exposure that included proliferative inhibition, modulation of gene expression, and disruption of the mitotic spindle. This phenotype was specific for HCC cells exposed to HCC-specific RF EMF. We hypothesize modulation frequencies affect intracellular calcium release in cancer cells, resulting in our *in vitro* phenotype and *in vivo* efficacy.

Methods: HCC cells were exposed to radiofrequency electromagnetic fields modulated at specific frequencies previously identified in HCC patients. MicroRNA arrays compared exposed and control groups of HCC cells, with validation followed by Western blot. NOD SCID mice received HCC subcutaneous cellular xenografts. Following palpable tumor establishment, mice were exposed to HCC-specific RF EMF, euthanized following excessive tumor burden, and evaluated by immunohistochemistry.

Results: We identified increased levels of miRNAs that target mRNAs used to synthesize proteins important in the PI3K pathway, specifically IP3/DAG signaling and intracellular calcium release. This pathway is frequently disrupted in HCC, making it an excellent candidate for modulation by RF EMF; furthermore, downstream effects include: cell cycle progression, proliferation, inhibition of apoptosis, and cell migration, each of which were implicated in our *in vitro* phenotype. *In vivo,* normal tissue architecture was preserved and xenograft tumors were seen infiltrated with fibrous tissue. Xenograft tumors in RF EMF treated mice also showed significantly decreased growth rate as compared to controls.

Conclusion: These findings uncover a novel mechanism that controls cancer cell growth at specific modulation frequencies, possibly through modulation of PI3K signaling and downstream release of intracellular calcium.