

MEDICAL STUDENT RESEARCH DAY 2010



Forward

Medical Student Research Day provides an opportunity for medical and MSTP students to present their research to faculty and students. One hundred and fifty-three abstracts were submitted for presentation at the 2010 Medical Student Research Day. Vijal Patel, Class of 2013, designed the cover for this year's abstract booklet using a photograph from DeviantArt. Funding for Medical Student Research Day was generously provided through the Office of Dr. Hughes Evans, Senior Associate Dean for Medical Education.

Acknowledgements

JUDGES

Dr. Namasivayam Ambalavanan
Dept. of Pediatrics - Neonatology

Dr. Joycelyn A Atchison
Dept. of Endocrinology

Dr. Laura Cotlin
Dept. of Cell Biology

Dr. Derek A DuBay
Dept. of Surgery

Dr. Carrie Elzie
Dept. of Cell Biology

Dr. Candace Floyd
Dept. of Physical Medicine & Rehabilitation

Dr. Gregory Kane Friedman
Dept. of Pediatrics

Dr. Andrey Frolov
Dept. of Surgery

Dr. Catherine Fuller
Dept. of Physiology & Biophysics

Dr. F Shawn Galin
Dept. of Medicine

Dr. W Timothy Garvey
Dept. of Nutrition Sciences

Dr. Shawn R Gilbert
Dept. of Surgery

Dr. Clyde Guidry
Dept. of Ophthalmology

Dr. Fadi G Hage
Dept. of Medicine

Dr. Hyunki Kim
Dept. of Radiology

Dr. Kenneth L McCormick
Dept. of Pediatrics – Endocrinology

Dr. Carmel McNicholas
Dept. of Physiology & Biophysics

Dr. Michael Mugavero
Dept. of Medicine

Dr. Michelle Olsen
Dept. of Physiology & Biophysics

Dr. Cynthia Owsley
Dept. of Ophthalmology

Dr. Brent Ponce
Dept. of Surgery

Dr. Raghavan Raju
Dept. of Surgery

Dr. Sasanka Ramanadham
Dept. of Physiology & Biophysics

Dr. Brian Sims
Dept. of Pediatrics – Neonatology

Dr. Peter Smith
Dept. of Physiology & Biophysics

Dr. Ryan C Splittgerber
Dept. of Cell Biology

Dr. John M Straughn
Dept. of Obstetrics and Gynecology

Dr. Kristina Visscher
Dept. of Neurobiology

Dr. Qin Wang
Dept. of Physiology and Biophysics

Dr. John Waterbor
Dept. of Epidemiology

Dr. Douglas Weigent
Dept. of Physiology & Biophysics

Dr. James Willig
Dept. of Medicine

Dr. Bradford Woodworth
Dept. of Surgery

Dr. Martin E Young
Dept. of Medicine

ORAL PRESENTATIONS
Lecture Room E

Short-term Research

- 10:00 – 10:15 am **David Doo, MS2**
“IGFBP-3 is degraded in pig vitreous in the presence of serum”
Mentor: Dr. Clyde Guidry
- 10:15 – 10:30 am **Grace Flowers, MS2**
“The impact of depression on cardiac rehab outcomes in ischemic heart disease patients”
Mentor: Dr. Vera Bittner
- 10:30 – 10:45 am **Zachary Griffith, MS2**
“A novel humanized monoclonal anti-ErbB3 receptor antibody (MM-121) slows tumor growth and reduces ligand-activated intracellular signaling in a murine model of pancreatic cancer”
Mentor: Dr. Andrey Frolov
- 10:45 – 11:00 am **Travis Hull, MSTP (year – MS2)**
“Heme Oxygenase-1 expression affects dendritic cell development and localization”
Mentor: Dr. James George
- 11:00 - 11:15 am **Jennifer Kirkman, MS2**
“When can we not screen infants for tethered spinal cord? An analysis of presenting factors in 1141 infants”
Mentor: Dr. John Wellons
- 11:15 – 11:30 am **Adam Scott, MS2**
“Pediatric injury prevention: baby safety showers to bring safe May flowers”
Mentors: Dr. Teresa Coco and Dr. Kathy Monroe
- 11:30 – 11:45 am **Jason Skelley, MS2**
“Diabetes in Alabama school systems: a survey of parental satisfaction with student care ”
Mentor: Dr. Joycelyn Atchison

ORAL PRESENTATIONS
Lecture Room A

Long-term Research

10:00 – 10:15 am

Asher Albertson, MSTP (year – graduate 3)

“HCN channels constrain network activity”

Mentor: Dr. John Hablitz

10:15 – 10:30 am

Travis Lewis, MSTP (year – graduate 5)

“Transduction of brain dopamine neurons by adenoviral vectors is modulated by CAR expression: rationale for tropism modified vectors in PD gene therapy”

Mentors: Dr. David Standaert and Dr. David Curiel.

10:30 – 10:45 am

Aimee Merino, MSTP (year – graduate 4)

“Killer immunoglobulin-like receptor genes and heterosexual HIV-1 transmission”

Mentor: Dr. Richard Kaslow

Intermediate-term Research

10:45 – 11:00 am

Neal Hatch, MS4

“Resveratrol inhibits LPS-induced IL-8 secretion in vitro: implications for chronic rhinosinusitis”

Mentor: Dr. Bradford Woodworth

11:00 - 11:15 am

John Jarboe, MSTP (year – graduate 2)

“MARCKS can regulate glioma cell migration, proliferation, and radiation sensitivity”

Mentor: Dr. Christopher Willey

11:15 – 11:30 am

Michelle Parchman, MS4

“Adherence to antiretroviral medication in pregnant women with human immunodeficiency virus”

Mentor: Dr. Shirley Hankins

11:30 – 11:45 am

Virginia Planz, MS3

“CT evaluation of common duct diameter in post-cholecystectomy patients with at least two-year follow-up”

Mentor: Dr. Mark Lockhart

Group A

- A-1. Sinifunanya Nwaobi, MSTP (year – graduate 2)**
“Neuroinflammatory role in LRRK2 in Parkinson’s disease”
Mentors: Dr. Andrew West and Dr. David Standaert
- A-2. Stephanie Robert, MS2**
“Mechanisms underlying radio-resistance and chemoresistance of glioma cells”
Mentor: Dr. Harald Sontheimer
- A-3. Faraz Sultan, MSTP (year – graduate 3)**
“The regulator of active DNA methylation, gadd45b, suppresses memory consolidation”
Mentor: Dr. David Sweatt
- A-4. John Rutherford, MSTP (year – graduate 3)**
“Mechanisms of PGC-1 α control of GABAergic genes”
Mentor: Dr. Rita Cowell
- A-5. Mikael Guzman Karlsson, MSTP (year – MS2)**
“The role of epigenetic modifications in reward-related behavior”
Mentor: Dr. David Sweatt
- A-6. Brian Warmus, MSTP (year – graduate 1)**
“Ventral striatum neurodegenerations is linked to behavioral symptoms in frontotemporal dementia”
Mentor: Dr. Erik Robertson
- A-7. Jarrod Meadows, MSTP (year – MS2)**
“Examining the role of microglia in a mouse model of frontotemporal dementia”
Mentor: Dr. Erik Robertson
- A-8. Stephanie Brosius, MSTP (year – MS2)**
“Analysis of 14-3-3 θ binding partners in models of Parkinson’s disease”
Mentor: Dr. Talene Yacoubian
- A-9. Jennifer Hadley, MSTP (year – graduate 2)**
“Organotypic brain slices as a model of glioma invasion”
Mentor: Dr. Harald Sontheimer
- A-10. Nicole Brossier, MSTP (year – graduate 5)**
“Role of ras isoforms in proliferation and migration of malignant peripheral nerve sheath tumors”
Mentor: Dr. Steven Carroll
- A-11. Nicholas Reish, MSTP (year – graduate 4)**
“Monitoring rhodopsin trafficking in transgenic tadpoles”
Mentor: Dr. Alecia Gross

Group B

B-1. Robert Hollis, MS3

“Validation and behavioral characterization of a cholinergic specific conditional knock-out mouse of DYT1 dystonia”

Mentor: Dr. David Standaert

B-2. Vishnu Cuddapah, MSTP (year – graduate 3)

“Chloride channel regulation facilitates glioma cell proliferation”

Mentor: Dr. Harald Sontheimer

B-3. Avinash Honasoge, MSTP (year – graduate 1)

“A potential role for MMP-2 in glioma ion channel regulation”

Mentor: Dr. Harald Sontheimer

B-4. Stacey Watkins, MSTP (year – graduate 2)

“Biophysical and biomechanical aspects of glioma invasion”

Mentor: Dr. Harald Sontheimer

B-5. David Gaston, MSTP (year – graduate 3)

“A conditionally-replicating HSV-1 vector expressing IL-15 for glioma therapy”

Mentor: Dr. Jacqueline Parker

B-6. Carl Odom, MS3

“Natural killer cells activating ligand expression in glioma cell lines following oncolytic HSV-1 infection”

Mentors: Dr. James Markert and Dr. Jacqueline Parker

B-7. Meghan McPheeters, MS2

“Co-expression of CD133 and putative brain tumor stem cell markers CD15, CD73, CD90 and podoplanin”

Mentors: Dr. Gregory Friedman and Dr. Yancey Gillespie

B-8. Jing-Yuan Ma, MS2

“The JAK2 inhibitor AZD1480 attenuates STAT-3 signaling and tumor cell proliferation in glioblastoma models”

Mentor: Dr. Ety Benveniste

B-9. Heather Allen MSTP (year – graduate 1)

“Complement expression in an alpha-synuclein overexpression mouse model of Parkinson’s disease”

Mentor: Dr. David Standaert

Group C

C-1. Carolyn Kezar, MS2

Chronic stress produces bladder dysfunction and hyperalgesics”

Mentor: Dr. Timothy Ness

C-2. John Hammond, MSTP (year – graduate 4)

“Evidence for abnormal forward trafficking of AMPA receptors in frontal cortex in schizophrenia”

Mentor: Dr. Robert McCullumsmith

C-3. Brian Hixon, MS3

“LPS and Pseudomonas aeruginosa filtrate reduce calcium activated chloride channel transport in primary sinonasal epithelial cultures”

Mentor: Dr. Brad Woodworth

C-4. Emad Elsamadicy, MS2

“Expression of NADPH oxidase(s) and voltage gated proton channel cDNAs in MIN6 insulinoma cells”

Mentor: Dr. Louis Philipson (University of Chicago)

C-5. Christopher Azbell, MS3

“Hesperidin stimulates CFTR-mediated Cl⁻ secretion and ciliary beat frequency in sinonasal epithelium”

Mentor: Dr. Brad Woodworth

C-6. Kenneth Smith, MS2

“Adapting the LI-COR on cell western protocol to measure ion channel trafficking in glioma cells”

Mentor: Dr. Catherine Fuller

C-7. Michael Chestnut, MS2

“Transepithelial ion transport is suppressed in hypoxic sinonasal epithelium”

Mentor: Dr. Brad Woodworth

C-8. Don McCormick, III, MS2

“Effects of fluoxetine administration on post-SCI recovery”

Mentor: Dr. Candace Floyd

C-9. Mitchell Alvarez, MS2

“The blocking effect of silma toxin on voltage gated sodium channels specific to glioma cells”

Mentor: Dr. Dale Benos

C-10. Derek Patterson, MS4

“The impact of nicotine on functional recovery and neuropathic pain in spinal cord injuries”

Mentor: Dr. Candace Floyd

Group D

D-1. Michael Alberti, MSTP (year – graduate 3)

“Targeting adenovirus to leukocyte subsets for viral handoff & gene transfer to pulmonary endothelium”

Mentor: Dr. David Curiel

D-2. Ryan Corrick, MSTP (year – graduate 3)

“Hepatic growth hormone resistance following injury is associated with decreased functional receptors”

Mentor: Dr. Joseph Messina

D-3. Eleanor Barr, MS2

“Tandem mass spectrometry of Galactose-1-Phosphate for Galactosemia diagnosis”

Mentor: Dr. Daniel Sharer

D-4. Alana Pearson, MS4

“Influence of ApoE genotype on dose, anticoagulation control and hemorrhagic complications among warfarin users”

Mentor: Dr. Nita Limdi

D-5. Charles Keith, MS2

“Protocol implementation of selective post-operative lumbar spinal drainage after thoracic endograft”

Mentor: Dr. Marc Passman

D-6. Erica Stevens, MS3

“Total sleep deprivation and its effects on blood pressure”

Mentor: Dr. Jennifer Dewolfe

D-7. Drees Griffin, MS2

“First symptoms and timing of presentation in acute idiopathic thrombotic thrombocytopenic purpura”

Mentor: Dr. Marisa Marques

D-8. Natalie Roebuck, MS3

“Outcomes in 200 children with RS: does facial phenotype matter?”

Mentors: Drs. John Grant, Michael Cunningham, and Kelly Evans

D-9. Stephen Johnson, MS4

“Clinical correlates of microalbuminuria in children with sickle cell disease”

Mentor: Dr. Jeffrey Lebensburger

Group E

E-1. Baran Aksut, MS3

"Targeted delivery of endothelial cells by overexpressing Interleukin-8 (IL-8) receptors alleviates left ventricular dysfunction in rats with myocardial infarction"

Mentor: Dr. Suzanne Oparil

E-2. Jonathan Black, MS2

"O-GlcNAc modification of NF κ B p65 subunit in rat aortic smooth muscle cells"

Mentor: Dr. Suzanne Oparil

E-3. James Gladden, MSTP (year – graduate 4)

"Left ventricular and bioenergetic dysfunction in acute VO is mediated by stretch-induced cardiomyocyte XO activation"

Mentor: Dr. Louis Dell'Italia

E-4. Jerry Bradley, Jr, MS2

"The influence of O-GlcNAcylation on circadian proteins within the heart and liver"

Mentor: Dr. Martin Young

E-5. Stephanie Larson, MS2

"Ethnicity effects on mitochondrial and cell function in HUVEC cells"

Mentor: Dr. Namasivayam Ambalavanan

E-6. Caleb Pierce, MS2

"Blockade of the renin-angiotensin system reduces neointima formation in CRPtg mice"

Mentor: Dr. Fadi Hage

E.7. Carolyn Webers, MS2

"Preterm birth is associated with decreased endothelial cell proliferation"

Mentor: Dr. Namasivayam Ambalavanan

E-8. Pallavi Kumbla, MS2

"Evaluation of two novel drug compounds in promoting hypoxia induced vascularization"

Mentor: Dr. Shawn Gilbert

E-9. Tadi Ciszak, MS2

"Systolic and diastolic left ventricular dysfunction in post-myocardial infarction patients with Type II diabetes"

Mentor: Dr. Steven Lloyd

E-10. Nicholas Deep, MS2

"Ankle brachial index (ABI) as a predictor of PAD-specific outcomes in patients without revascularization"

Mentors: Dr. Farrell Mendelsohn and Dr. Robert Bourge

Group F

F-1. Hikel Boohaker, MS4

"An evaluation of 42 failed primary ACL reconstructions and their subsequent revisions"

Mentor: Dr. Brent Ponce

F-2. Joseph Kundukulam, MS2

"Early postoperative mortality following joint arthroplasty"

Mentor: Dr. Jasvinder Singh

F-3. Matthew Owen, MS2

"A novel open-fracture rat model utilizing Acinetobacter baumannii"

Mentor: Dr. Rena Stewart

F-4. Bannon Thorpe, MS2

"Pectoralis major height as an anatomic reference for shoulder fracture hemi-arthroplasty"

Mentor: Dr. Brent Ponce

F-5. David Sarver, MS2

"Association of the presence of bone bars on radiographs and hip fracture"

Mentor: Dr. Robert Lopez-Ben

F-6. Harris Reynolds, MS2

"Facial contact burns at Alabama's major tertiary care center: 2000-2009"

Mentor: Dr. Peter Ray

F-7. Christine Tagayun, MS2

"Imaging and clinical outcomes after arachnoid cyst decompression surgery"

Mentor: Dr. John C. Wellons

F-8. Christopher Kennedy, MS2

"Survival outcomes of liver transplantation with NASH cirrhosis"

Mentor: Dr. Derek DuBay

F-9. Lisa Speake, MS2

"Preoperative Karnofsky performance status (KPS) as a predictor of postoperative complications in gynecologic oncology patients"

Mentor: Dr. Michael Straughn

Group G

G-1. Taoreed Lawal, MS2

"Oxaliplatin-induced hepatoportal sclerosis, portal hypertension, and variceal bleeding successfully"

Mentors: Dr. Hyun Kim

G-2. Sarah Baxley, MSTP (year – graduate 4)

"Wnt5a regulates oxytocin response at parturition"

Mentor: Dr. Rosa Serra

G-3. Jennifer Turnham, MS4

"Loss of membrane E-cadherin and expression of p53 and molecular markers of progression of sun-damage"

Mentor: Dr. Craig Elmets

G-4. Sherry Yang, MSTP (year – graduate 5)

"A TIMP2-armed conditionally-replicating adenovirus for the treatment of ovarian cancer"

Mentor: Dr. Selvarangan Ponnazhagan

G-5. Yevgeniya Byekova, MS3

"Liver kinase B1 (LKB1) in pathogenesis of murine basal cell carcinoma"

Mentor: Dr. Mohammad Athar

G-6. Zachary Dobbin, MSTP (year – Graduate 1)

"Development and characterization of kisspeptins for a novel metastatic breast cancer treatment"

Mentor: Dr. Danny Welch

G-7. Jennifer Stanley, MSTP (year – MS2)

"Kinomic assessment of Her2-amplified breast cancer cells: identifying resistance pathways"

Mentor: Dr. Christopher Willey

G-8. Victor Lin, MSTP (year – graduate 5)

"TRIP6 modulates AKT-mediated downregulation of p27^{KIP1} in cancer"

Mentor: Dr. Fang-Tsyr (Fannie) Lin

G-9. Jason LeGrand, MSTP (year – MS2)

"The effect of KiSS-1 in an immunocompetent metastatic breast cancer model"

Mentor: Dr. Danny Welch

G-10. Jaquelyn Zimmerman, MSTP (year – graduate 2)

"Low levels of amplitude-modulated electromagnetic fields inhibit cell growth and mitotic division in hepatocellular carcinoma cells"

Mentor: Dr. Boris Pasche

Group H

H-1. Evan Thomas, MSTP (year – graduate 2)

“Utilization of flattening filter free mode for improving radiotherapeutic efficiency”

Mentor: Dr. John Fiveash

H-2. Andrew Land, MS4

“Characterization of non-diseased adrenal glands utilizing dual energy spectral MDCT”

Mentor: Dr. Desiree Morgan

H-3. Elliot Bishop, MS2

“Near-infrared labeled EGFR specific antibody molecules: a rapid approach to tumor specific imaging”

Mentor: Dr. Eben Rosenthal

H-4. Lisa Bailey, MS3

“Comparison of conventional multidetector CT (MDCT) and spectral dual-energy MDCT for detecting gallstone”

Mentors: Dr. Lincoln Berland and Dr. Mark Lockhart

H-5. Brian Davis, MS2

“Construction of RPS19 homologous recombination vector for correction of Diamond-Blackfan Anemia”

Mentor: Dr. Tim Townes

H-6. Andrew McDonald, MS3

“Retrospective database study of efficacy and rectal toxicity associated with radiation therapy for prostate cancer”

Mentor: Dr. John Fiveash

H-7. Shaundra Harris, MS2

“Generation of a patient-specific construct to correct the sickle cells anemia mutation in induced pluripotent stem (iPS) cells”

Mentor: Dr. Timothy Townes

H-8. Drew Gunnells, MS2

“New potential combination therapy for pancreatic cancer”

Mentor: Dr. Andrey Frolov

H-9. Rajini Murthy, MS2

“Skin fibroblasts for genetic correction of Epidermolysis Bullosa”

Mentor: Dr. Tim Townes

H-10. Nemil Shah, MS4

“Anti-EMMPRIN therapy in combination with gencitabine for pancreatic adenocarcinoma”

Mentors: Drs. Hyunki Kim and Dr. Kurt Zinn

Group I

- I-1. Swati Bansal, MS3**
"Effects of deep brain stimulation on long and very long latency reflexes"
Mentor: Dr. Erwin Montgomery
- I-2. Thy Huynh, MS2**
"No specific NF1 gene found within a clinical variant Neurofibromatosis Type 1: Familial Spinal Neurofibromatosis"
Mentor: Dr. Bruce Korf
- I-3. Joffre Johnson, MS2**
"Neuroprotective potential of alpha fetoprotein in neural stem cells"
Mentors: Dr. Brian Sims
- I-4. Jonathan Kentros, MS2**
"Modulations in EEG activity in older vs. younger adults during a working memory task"
Mentor: Dr. Kritsina Visscher
- I-5. John Ogorek, MS2**
"Assessing semantic processing in mild cognitive impairment: a MEG analysis of the N400m"
Mentor: Dr. David Clark
- I-6. Amanda Dinsmore, MS2**
"Documentation of stage of retinopathy in patients with diabetes mellitus among primary eye care providers"
Mentor: Dr. Gerald McGwin
- I-7. Farah Khan, MS2**
"Pattern of eye diseases and delay in clinical presentation based on water access in rural north India"
Mentors: Dr. Dale Williams and Dr. Cynthia Owsley
- I-8. David Doo, MS2**
"Long-term follow-up of clinically significant macular edema after focal laser treatment"
Mentor: Dr. James Kimble
- I-9. Walter Parker, MS2**
"Self-reported driving difficulty by persons with hemianopia and quadrantanopia"
Mentor: Dr. Cynthia Owsley
- I-10. Abdurahman Elkhetali, MSTP (year – graduate 1)**
"Examining ongoing activity in retinotopically mapped occipital cortex using fMRI"
Mentor: Dr. Kristina Visscher

Group J

- J-1. Elizabeth Staley, MS2**
"Persistence of host leukocytes following lethal irradiation and bone marrow reconstitution"
Mentor: Dr. Robin Lorenz
- J-2. Jessica Record, MS3**
"High prevalence of inflammatory myositis in patients with pediatric lupus in Alabama"
Mentor: Dr. Randy Cron
- J-3. Catherine Poholek, MSTP (year - graduate 1)**
"Evidence for the role of Th17 cells in the maintenance of intestinal homeostasis"
Mentor: Dr. Charles Elson
- J-4. Kayci Huff, MSTP (year – graduate 4)**
"Extracellular matrix-associated cytokines regulated CD4+ effector T-cell responses in human intestinal mucosa"
Mentor: Dr. Philip Smith
- J-5. Emily Blosser, MSTP (year – graduate 2)**
"The role of Th17 cells and commensal flora in gut mucosal defense"
Mentor: Dr. David Randolph
- J-6. Tarannum Jaleel, MS3**
"Role of Toll Like Receptor 4 in UV induced immunosuppression"
Mentors: Dr. Nabih Yusuf and Dr. Craig Elmets
- J-7. Sarah Whitley, MSTP (year – graduate 5)**
"Regulation of IL17 Transcription in CD4+ T Cells"
Mentor: Dr. Casey Weaver
- J-8. Lindsay Harbin, MS2**
"Does FoxP3 Inhibit or Promote HIV-1 Infection in CD4+ T regulatory Cells?"
Mentor: Dr. Randall Cron
- J-9. Steven Witte, MSTP (year – MS1)**
"Discrete targets of miR-155 during B cell activation"
Mentor: Dr. Stefan Muljo
- J-10. Sara Stone, MSTP (year – MS1)**
"Differential regulation of granule release by a novel neutrophil-specific matrikine"
Mentor: Dr. Amit Gaggar
- J-11. Daniel Sullivan, MS2**
"Longitudinal study examining Ac-PGP as a potential biomarker in COPD"
Mentor: Dr. J. Edwin Blalock

Group K

K-1. Ryan Wells, MSTP (year – graduate 4)

“MmpS4 and MmpS5 are outer membrane proteins of M. tuberculosis involved in siderophore secretion”

Mentor: Dr. Michael Niederweis

K-2. Yu Ting, MS2

“Abnormalities in cerebrospinal fluid indices in neonatal herpes”

Mentor: Dr. David Kimberlin

K-3. Mark Stoddard, MSTP (year – graduate 1)

“Molecular identification of transmitted Hepatitis C viral genomes in acutely infected patients”

Mentor: Dr. George Shaw

K-4. Nicholas Parrish, MSTP (year – graduate 2)

“Envelope content and dendritic cell interaction of transmitted/founder HIV-1”

Mentor: Dr. Beatrice Hahn

K-5. Carson Moseley, MS2

“From fat to flu: prePPARing for a pandemic”

Mentor: Dr. Robert Webster

K-6. Michael Lopker, MSTP (year – graduate 2)

“Delayed viremia in two rhesus macaques following intravaginal inoculation of SIVmac251 “

Mentor: Dr. George Shaw

K-7. Eva Clark, MSTP (year – MS3)

“Long-lasting humoral and cellular responses to Plasmodium falciparum merozoite surface protein-1 in the low transmission Amazon region of Peru correlates with long-term clinical protection”

Mentor: Dr. OraLee Branch

K-8. Juan Calix, MSTP (year – graduate 3)

“Streptococcus pneumoniae serotype 11E is found predominantly in invasive pneumococcal disease”

Mentor: Dr. Moon Nahm

K-9. Olusimidele Akinsiku, MSTP (year – graduate 5)

“In vitro HIV-1 specific CD8 T cell suppression correlates with disease control”

Mentor: Dr. Paul Goepfert

Group L

L-1. Erica Wilson, MS2

"Hyperglycemia and associated risk factors in pregnant women in Tegucigalpa, Honduras"

Mentor: Dr. Edmond Kabagambe

L-2. Stephen Tonks, MS3

"Influence of rurality on the health of patients with diabetes mellitus"

Mentor: Carlos Estrada

L-3. Karen Mai, MS2

"Insulin resistance induced by high fat diet and aging: differential role of adiponectin"

Mentors: Drs. W. Timothy Garvey and Dr. Helliner Hill

L-4. Angela Grochowsky, MS2

"Adult Down Syndrome population shows a reduced prevalence of Type 2 Diabetes Mellitus when compared to the general population"

Mentors: Dr. Edward Lose and Dr. Nathaniel Robin

L-5. Brian Dizon, MSTP (year – graduate 5)

"Modulation of autoimmune diabetes development by B lymphocyte specific for N-acetyl-D-glucosamine"

Mentor: Dr. John Kearney

L-6. Zsu-Zsu Chen, MS2

"Effects of aging and diet-induced obesity on NR4A3 in mouse muscle: correlation with myostatin"

Mentor: Dr. W. Timothy Garvey

L-7. Courtney Blake, MS2

"Actual and perceived cost discounts influence fruit and vegetable consumption"

Mentor: Dr. Jamy Ard

L-8. Christy Foster, MS2

"Cortisol increase hepatic gluconeogenesis by altering the reduced pyridine nucleotide and glucose-6-phosphate dehydrogenase"

Mentor: Dr. Ken McCormick

L-9. David Shelley, MS2

"Skeletal muscle in old vs. young humans is not more susceptible to mechanical injury but appears to be in a pro-inflammatory state even at rest"

Mentor: Dr. Marcos Bamman

Group M

M-1. Megan Brennard, MS4

"Can Pityriasis versicolor be treated with 2% ketoconazole?"

Mentor: Dr. Boni Elewski

M-2. Taylor Hendrixson, MS2

"Data verification and regulatory oversight of an ongoing National Institute of Allergy and Infectious Diseases (NIAID) collaborative antiviral study group (CASG) placebo-controlled investigation of Pleconaril for the treatment of Neonatal Enteroviral Sepsis Syndrome"

Mentor: Dr. David Kimberlin

M-3. Sonia Talathi, MS2

"Seasonal trivalent influenza vaccine given to children in rural India: an ongoing study"

Mentor: Dr. Wayne Sullender

M-4. Sarah Abroms, MS4

"Tuberculosis screening practices in HIV-infected adult patients enrolled at Chawama, Kanyama, and Matero reference ART clinics in Lusaka, Zambia"

Mentor: Dr. German Henostroza

M-5. Sarika Modi, MS2

"Missed opportunities and costs associated with inpatient HIV diagnosis"

Mentor: Dr. Michael Mugavero

M-6. Kathy Jo Carstarphen, MS4

"Factors influencing early HIV treatment in Lima, Peru"

Mentor: Dr. David Freedman

M-7. Sharon Tsay, MS4

"Predictors of condom self-efficacy in an incarcerated juvenile population"

Mentor: Dr. Marsha Sturdevant

M-8. Jesse Tucker, MS2

"Development of a comprehensive tool for tuberculosis contact investigation"

Mentor: Dr. Elizabeth Turnipseed

M-9. Tyler Wahl, MS2

"HIV Peer interventions influencing adherence to medications and clinical care"

Mentor: Dr. Michael Mugavero

M-10. Christina Ho, MS2

"Factors associated with missed visits to mental health care in an urban HIV clinic setting"

Mentor: Dr. James Willig

Group N

N-1. William Clifford, MS4

"Defensive medicine: identifying diagnostic procedures most susceptible to malpractice concern"

Mentor: Dr. John Wheat

N-2. John-Ryan McAnnally, MS3

"Regional disparities in prevailing diseases in the United States, years 1999-2006"

Mentors: Dr. Henry Wang and Dr. Randolph Devereaux

N-3. Jonathan Miller, MS4

"The mini-clerkship: exposing preclinical medical students to emergency medicine"

Mentor: Dr. James Galbraith

N-4. Elizabeth Molony, MS2

"Impact of disparities in health literacy on asthma management"

Mentor: Dr. Kathy Monroe

N-5. Milner Owens, MS2

"Evaluation of informative media educating cystic fibrosis patients about their reproductive options"

Mentor: Dr. Nathaniel Robin

N-6. Cassandra Smola, MS4

"Using high fidelity simulation to prepare caregivers of pediatric ventilator dependent children"

Mentor: Dr. Nancy Tofil

N-7. Samuel Strachan, MS2

"Development and implementation of interactive high-fidelity patient simulation cases for first year medical student curriculum and testing in the large-group setting"

Mentor: Dr. Marjorie Lee White

N-8. Kavita Vankineni, MS4

"High fidelity simulation enhances learning during a third year pediatric clerkship"

Mentor: Dr. Nancy Tofil

N-9. James Oliver, MS2

"OITE correlation with ABOS Part I examination: the predictive power of individual OITE subsections"

Mentor: Dr. Brent Ponce

N-10. Lauren Stephens, MS2

"Frequency and duration of out of bed mobility episodes during hospitalization"

Mentor: Dr. Cynthia Brown

Abroms, Sarah

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	German Henostroza
Co-Authors	German Henostroza
Title:	Tuberculosis screening practices in HIV-infected adult patients enrolled at Chawama, Kanyama, and Matero Reference ART clinics in Lusaka, Zambia

Abstract

Background:

Current WHO guidelines require TB screening in HIV-infected patients with cough greater than 2 weeks duration, while anticipated guidelines will advocate screening in patients presenting with *any* current TB-related symptom. We compared the number of patients requiring screening with existing guidelines with the additional burden posed by new guidelines.

Methods:

A retrospective chart review was performed. All new enrollees to HIV care at three primary care clinics in Lusaka between June and December 2009 were selected. Demographic data, TB symptoms, diagnostic tests (microscopy/chest radiography) and diagnostic outcomes were recorded. A descriptive analysis was performed.

Results:

A total of 1499 patients were included in the chart review. Their median age was 33 years, 60% were female, 47% were WHO stage III or IV, their median body mass index was 19.8, and their median CD4 count was 236. Patients with symptoms at ART enrollment were 1011 (67%). Any cough, weight loss, or fever was documented in 926 (62%) of these patients, and 73 (7%) had documented cough > 2 weeks. Of patients with > 2 weeks of cough, TB screening was initiated in 42 (58%).

Conclusions:

Current TB screening guidelines for new HIV enrollees' are not consistently followed despite the presence of TB symptoms. Implementing anticipated WHO guidelines based on existing screening practices will increase the screening workload by approximately ten-fold. Successful implementation of new intensified case finding guidelines will require significant commitment of additional resources, staff and training.

Akinsiku, Olusimidele

Project Length	Long
Prior Research Experience	Yes
Funding Source	MSTP
Advisor	Paul A. Goepfert
Co-Authors	

Title *In Vitro* HIV-1 specific CD8 T cell Suppression
Correlates with Disease Control

Abstract

Efforts to develop an effective HIV-1 vaccine to date have largely failed. The Step Study was halted when interim analysis failed to show protection in participants receiving vaccine vs. placebo. The vaccine tested in the RV144 Phase III trial slightly impacted HIV-1 acquisition, but had no effect on plasma viral load (pVL) or CD4 T cell count upon seroconversion, suggesting poor induction of virus-specific CD8 T cells. The results emphasize the need for improved methods to evaluate the ability of candidate vaccines to induce protective HIV-1 immune responses. CD8 T cell-mediated virus suppression may be one such benchmark and we have developed a novel *in vitro* suppression assay (*IVSA*) to address this question.

We obtained samples from two patient cohorts—controllers, individuals who maintain pVL < 2,000 copies/mL and progressors (pVL > 2,000 copies/mL). All subjects evaluated were off antiretroviral therapy. Epitope-specific CD8 T cell lines (effectors) were expanded from cryopreserved PBMCs of study participants. Autologous CD4⁺ cells (targets) were infected with HIV-1_{NL4.3}. Effectors (E) and targets (T) were cultured for seven days at multiple E:T ratios and supernatants analyzed for infectious HIV-1 using a reporter cell line.

Using the *IVSA*, we demonstrated that CD8 T cell lines derived from controllers show enhanced virus suppression when compared to progressors (98.8% suppression vs 76.0%, $p=0.001$). This enhanced suppression was detected at low E:T ratios. Furthermore, virus suppression is specific and mediated in an MHC-dependant manner.

All expanded CD8 T cell lines were analyzed for HIV-1-specific effector function (production of CD107a, IFN- γ , IL-2, TNF- α , perforin) using the intracellular cytokine staining assay (ICS). Interestingly, IL-2 production correlated with suppressive capacity ($p=0.006$).

Suppression of HIV-1 replication and IL-2 production appear to be promising markers of an effective CD8 T cell response, hence these results have important implications for developing and evaluating HIV-1 vaccine strategies.

Aksut, Baran

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Suzanne Oparil

Co-Authors Suzanne Oparil, Yiu-Fai Chen, Wei Zhang

Title Targeted Delivery of Endothelial Cells by Overexpressing Interleukin-8 (IL8) Receptors Alleviates Left Ventricular Dysfunction in Rats with Myocardial Infarction

Abstract

Introduction: Interleukin receptors IL8RA and IL8RB on neutrophil membranes bind to IL8 with high affinity and play a critical role in neutrophil recruitment (e.g. adhesion and trans-endothelial migration) to sites of infection and/or inflammation. This study is to test the hypothesis that administration of IL8RA- and IL8RB-transduced endothelial cells (ECs) can accelerate adhesion of ECs to the injured/inflammatory tissue and decrease left ventricular (LV) infarction region in rats with the left anterior descending (LAD) coronary artery ligation-induced myocardial infarction (MI). Method: 12 wk old male Sprague-Dawley rats received LAD ligation and were divided into two groups: Group 1 received i.v. vehicle injection and Group 2 received i.v. transfusion of ECs (0.5×10^6 cells/injection) that have been transduced with Ad-IL8RA and Ad-IL8RB (adenoviral vectors that carry IL8RA and IL8RB genes) at 1, 3, 5 hrs post LAD ligation. MI size was assessed using triphenyltetrazolium chloride (TTC) staining at 28 days post LAD ligation. Rats were euthanized and the LV was cut into six 2 mm slices perpendicular to the apex-base axis. To distinguish between infarcted and non-infarct myocardium, slices were incubated in 1% TTC for 30 min. After TTC staining, the area of infarction appeared pallid, whereas the viable myocardium appeared red. Tissue slices were photographed, and the infarcted, and non-infarcted areas were determined using the computer-based Motic Images system. Results: Comparisons of MI size of rats receiving ECs that overexpress IL8RA and IL8RB or vehicle show that the IL8RA/RB-EC treatment reduced MI size by 25% in this study (results are means \pm SEM, * $p < 0.05$ vs vehicle). Conclusion: These findings indicate that ECs over-expressing IL8RA and IL8RB mimic the behavior of neutrophils that target and adhere to the injured tissues. The targeted delivery of ECs to site of heart with injury provides a novel strategy for the prevention and treatment of cardiovascular disease.

Alberti, Michael

Project Length Long

Prior Research Experience Yes

FundingSource Departmental or Mentor funds

Advisor David T. Curiel

Co-Authors Roth JC, Deshane JS, Pereboeva L, Komarova S, McCauley JM, Tsuruta Y, Chaplin DD, Abraham E, Gerson SL, Curiel DT

Title Targeting Adenovirus to Leukocyte Subsets for Viral Handoff & Gene Transfer to Pulmonary Endothelium

Abstract

Inflammation is a hallmark of many diseases, including a number of debilitating lung diseases such as chronic obstructive pulmonary disease, cystic fibrosis, and acute lung injury. Each is characterized by leukocyte influx associated with release of toxic mediators that leads to extensive tissue damage. Therapeutic interventions that modulate this pathologic response are thus likely to reduce the progressive destruction to lung airways. Adenovirus (Ad) vectors have a long history as therapeutic agents because they robustly transduce a variety of cell types and are easy to genetically manipulate. Despite these advantages, airway delivery has revealed significant roadblocks to efficient Ad gene transfer. However, given that leukocytes naturally circulate, home, and infiltrate tissues in response to inflammatory signals, we hypothesized that we could modulate Ad tropism to myeloid cell subsets in the lung microvasculature for subsequent therapeutic intervention of inflammatory lung disorders. Since leukocytes lack the coxsackie virus and adenovirus receptor (CAR) and are thus resistant to Ad infection, we first identified a myeloid-binding peptide (NBP) by phage panning of murine bone marrow and genetically incorporated the peptide into a recombinant Ad fiber that lacks the native CAR-binding domain, knob. Ad reporter gene expression vectors containing the recombinant fiber were rescued and shown to maintain myeloid-binding specificity. Upon intravenous delivery, this altered tropism realized a lung targeting index five orders of magnitude greater than that obtained with Ad vectors containing the wild type fiber. Lung targeting was specific, with the lowest levels of gene expression detected in liver. Preliminary analyses of the cell types bound and transduced suggest that the NBP virus is first sequestered by pulmonary leukocytes and subsequently “handed off” to lung endothelial cells as leukocytes roll along the endothelium. These studies are an important first-step in validating systemic Ad targeting as an approach for gene therapy of inflammatory disorders.

Albertson, Asher

Project Length	Long Term Project
Prior Research Experience	Yes
Funding Source	Mentor/Departmental Funds
Advisor	Dr. John Hablitz
Co-Authors	Sydney Williams, Dr. John Hablitz
Title	HCN Channels Constrain Network Activity

Abstract

Hyperpolarization activated non-specific cation (HCN) channels are expressed primarily in the distal dendrites of hippocampal and cortical pyramidal neurons where they pass an inward cationic current (I_h) upon membrane hyperpolarization. Within dendrites, HCN channels serve to normalize the time course of synaptic inputs, decrease intrinsic excitability, and depolarize the resting membrane potential. Loss of HCN channels greatly increases neuronal excitability. Specifically HCN channel loss increases spiking and EPSP summation. Interestingly, a variety of epilepsy models are associated with decreased HCN channel expression and reduced I_h . While the role of I_h in regulating small events onto single cells is well characterized, little is known about its potential role in regulating network activity. Given the strong correlation between epilepsy and reduced I_h , we have decided to investigate a potential role for I_h in modulation of network activation. Using voltage sensitive dye imaging, we found that HCN channel inhibition increased the duration of normal and epileptic network activity within the neocortex. We also found that I_h enhancement with the anticonvulsant lamotrigine decreased the spread and amplitude of normal activity. Using whole cell voltage and current clamp recordings we found that I_h inhibition greatly increased the duration of evoked, polysynaptic, epileptic events observed in both cortical pyramidal neurons and interneurons. I_h inhibition increased the duration of events even when cells were held at a membrane potential (-50) which precluded HCN channel opening, suggesting that increased duration of polysynaptic events is due to increased network activation. Together these data suggest that I_h serves in normal circumstances to constrain network activity. Furthermore, our results suggest that loss of I_h may increase network activation and contribute to the initiation and severity of epileptic events.

Allen, Heather

Project Length Short

Prior Research Experience Yes

Funding Source NIH Medical Scientist Training Program Grant

Advisor David Standaert

Co-Authors Shaji Theodore, David Standaert

Title Complement Expression in an Alpha-synuclein Overexpression Mouse Model of Parkinson's Disease

Abstract

Parkinson's disease (PD) is a neurodegenerative disorder caused by a progressive loss of dopamine producing neurons in the substantia nigra pars compacta resulting in tremor, rigidity, bradykinesia and postural instability in 3-5% of people above age 65. Alpha-synuclein is aggregated in Lewy bodies in injured dopaminergic neurons in PD, and alpha-synuclein gene duplications and triplications show an increased severity of PD in a dose-dependent manner, demonstrating this protein's importance in pathogenesis. Recently, research has focused on the immune system as one of the mechanisms contributing to this neurodegeneration: reactive microgliosis is found in PD brains post mortem and more recently, a polymorphism in the HLA region was associated with late-onset PD. Our lab has previously shown that targeted overexpression of alpha-synuclein driven by an adeno-associated virus vector leads to a 30% reduction in the total number of dopaminergic neurons in the substantia nigra six months post-injection. This alpha-synuclein overexpression model recapitulates the reactive microgliosis observed in human PD, and furthermore, knocking out the microglial Fc-gamma-receptor 1 can reduce neuronal degeneration, implicating an inflammation based mechanism of neurodegeneration. The complement cascade is known to play a role in several other neurodegenerative diseases including Alzheimer's, multiple sclerosis, glaucoma and neuropsychiatric manifestations of systemic lupus erythematosus; therefore, we hypothesized that the complement cascade may be contributing to inflammation and cell death in our model. We investigated expression of complement proteins C3, C5, and C9 by immunofluorescence and western blot at 4 weeks and 24 weeks post-injection of adeno-associated virus containing alpha-synuclein or GFP into the substantia nigra of C57BL/6 mice. Previous data shows significantly increased deposition of IgG by immunofluorescence, providing a potential mechanism for fixing complement. Further studies would investigate the pathway-specific proteins of the classical and alternative complement cascade, as well as determine whether complement inhibitors could prevent neurodegeneration in this model.

Alvarez, Mitchell

Project Length	Short
Prior Research Experience	No
Funding Source	CaRES Program
Advisor	Dr. Dale Benos
Co-Authors	Catherine J. Fuller, Mitchell D. Alvarez, Karen Parks
Title	The Blocking Effect of Silma Toxin on Voltage Gated Sodium Channels Specific to Glioma Cells

Abstract

Introduction: PcTx1 is derived from the venom of the West Indies Chevron tarantula, targets ASIC 1 sodium channels, and is an effective inhibitor of glioma cell proliferation and migration. The aim of this project is to explore the ability of using a non-virulent, replication-competent herpes virus (HSV1) to deliver a peptide toxin (PcTx1) in the context of malignant glioma.

Methods: A synthetic gene encoding for PcTx1 and an N-terminal sequence was sub-cloned into an aneurovirulent, replication-competent form of HSV termed MO12. The PcTx1 expressing virus and controls were then grown to high titers in Vero cells, and used to infect the human glioma cell line, D-54 MG, at 3 different MOI. Oocytes from *Xenopus laevis* were also injected with ASIC1 sodium channel RNA and then submerged in an acidic wash to stimulate the ASIC1 channels. Oocytes were then exposed to our PcTx expressing HSV1 and electric potential across the cell membrane was recorded with a two-electrode voltage clamp.

Results: PcTx1 expressing HSV1 and controls were successfully harvested from cultured Vero cells. In initial studies, no inhibition of ASIC1 sodium channels was noted in oocytes infected with PcTx1 expressing HSV1 at any of the MOIs tested.

Conclusion: In this preliminary analysis, use of a PcTx1 expressing HSV1 had no effect on the ASIC1 sodium channels as measured by assessment of electric potential. Ongoing studies are planned to assess quantity of PcTx1 toxin production by this virus.

Azbell, Christopher

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Dr Brad Woodworth

Co-Authors Shaoyan Zhang, PhD, Daniel Skinner, BS, Eric Sorscher, MD, Brad Woodworth, MD

Title Hesperidin Stimulates CFTR-Mediated Cl⁻ Secretion and Ciliary Beat Frequency in Sinonasal Epithelium

Abstract

Objectives: Pharmacologic agents designed to promote mucociliary clearance (MCC) in chronic rhinosinusitis (CRS) represent a novel therapeutic strategy. The objectives of the present study were to investigate whether the natural bioflavonoid hesperidin 1) increases transepithelial chloride (Cl⁻) secretion *in vitro* and *in vivo*, 2) enhances ciliary beat frequency (CBF), and 3) exerts its mechanistic effects through cAMP/PKA dependent pathways.

Study Design: *In vitro* and *in vivo* study

Setting: Laboratory

Subjects and Methods: Transepithelial Cl⁻ transport (Ussing chamber) and CBF were investigated in primary murine nasal septal (MNSE) and human sinonasal epithelial (HSNE) cultures. *In vivo* activity was measured using the murine nasal potential difference (NPD) assay. CFTR R-domain phosphorylation and cAMP levels were investigated to rule out a cAMP/PKA dependent mechanism of activation.

Results: Hesperidin significantly increased CFTR-mediated Cl⁻ transport (change in short-circuit current, Δ ISC) in both MNSE [13.51 \pm 0.77 vs. 4.4 \pm 0.66 (control); p=0.000002] and HSNE [12.28 \pm 1.08 vs. 0.69 \pm 0.32 (control); p=0.000001]. Cl⁻ transport across *in vivo* murine nasal epithelium was also significantly enhanced with hesperidin [-2.3 \pm 1.0 vs. -0.8 \pm 0.8mV (control), p=0.04]. There was no increase in cellular cAMP or phosphorylation of the CFTR R-domain. Hesperidin significantly increased CBF with both basal ((1.32 \pm 0.02 vs. 0.93 \pm 0.02 (control); p=0.003), apical (1.72 \pm 0.09 vs. 1.39 \pm 0.11, control; p=0.046) and basal + apical delivery (2.26 \pm 0.16 vs. 1.60 \pm 0.21, respectively; p=0.043).

Conclusion: Our *in vitro* and *in vivo* investigations provide strong support for future testing of this robust Cl⁻ secretagogue and CBF activator in human clinical trials for CRS.

Bailey, Lisa

Project Length

Prior Research Experience

Funding Source

Advisor

Lincoln L. Berland, M.D., F.A.C.R.
Mark E. Lockhart, M.D., M.P.H.

Co-Authors

Title

Comparison of Conventional Multidetector CT (MDCT)
and Spectral Dual-Energy MDCT for Detecting
Gallstones

Abstract

Background:

Gallstones are widely prevalent in the U.S. and are costly due to ultrasounds required for further evaluation after CT imaging, which has a 20% sensitivity for non-calcified gallstones. Dual-energy spectral multidetector CT (MDCT), a new imaging development, shows promise in characterizing non-calcified gallstones *in vitro*, according to previous studies.

Purpose:

Our aim is to evaluate spectral dual-energy MDCT sensitivity in detecting gallstones and to determine if selected monochromatic energy levels improve visualization.

Methods:

A dual-energy CT scanner imaged 409 consecutive patients for various conditions. A review of the patients' records revealed that 166 also had ultrasounds, which were used as reference standards for gallstone detection. Fifty-four of these 166 patients had intact gallbladders and therefore qualified as subjects in this study. Two experienced radiologists blinded to ultrasound findings reviewed the 54 CTs retrospectively to assess whether calcified gallstones were present and whether non-calcified gallstones could be visualized using simulated images at different monochromatic energies. MDCTs and ultrasounds were compared afterward.

Results:

Of the 54 patients, 16 had gallstones on ultrasound. On CT, 13 of these had calcified gallstones, and three subjects had non-calcified stones. In one case, both readers detected gallstones on both MDCT modalities; in the second case, one reader was uncertain and the other did not visualize stones; neither reader visualized stones in the third case. One reader was uncertain of the presence of non-calcified stones in 9 cases, and no stones were seen on ultrasound in 8 of these patients.

Conclusions:

These findings suggest that only a minute percentage of gallstones are non-calcified, and it may be possible to increase the conspicuity of non-calcified gallstones with dual-energy MDCT. Visualization is mildly improved with lower simulated monochromatic energies. However, the role of dual-energy MDCT appears limited in gallstone detection pending replication of these findings in larger studies.

Bansal, Swati

Project Length

Intermediate (8-10 weeks)

Prior Research Experience

Yes

Source of Funding

the Dr. Sigmund Rosen Scholarship Fund
(Departmental)

Faculty Advisor

Erwin B. Montgomery Jr., MD

Co-Authors

Harrison C. Walker, MD; He Huang; Barton L. Guthrie,
MD; Ray L. Watts, MD

Title

Effects of Deep Brain Stimulation on Long and Very
Long Latency Reflexes

Abstract

Deep Brain Stimulation (DBS) significantly improves motor symptoms in Parkinson's disease (PD). Despite the benefits of DBS, its precise mechanisms of actions are unknown. This study explores the theory that DBS stimulation in the subthalamic nucleus (STN) increases the excitability of the cortex in a frequency-dependent manner. This was accomplished by using long latency reflexes (LLR) as a measure of sensorimotor cortex excitability under different frequencies. LLR, a known normal reflex response that travels through the sensorimotor cortex, has a typical latency of approximately 50ms observed after peripheral nerve stimulation of the corresponding muscle. Therapeutic DBS stimulations should produce an increase in the magnitude of the LLR compared to no or non-therapeutic DBS. Surface electromyographic (EMG) electrodes were used to measure muscle activity from the flexor carpi ulnaris as subjects produced a maximum voluntary wrist flexion force, during which a single stimulation pulse was applied to the ulnar nerve. Using a within-subject design, DBS PD subjects (n=6) were tested under four DBS frequencies (therapeutic high frequency setting (≥ 130 pps), 0, 20, and 70pps). Raw surface EMG signals were converted to the root mean square (RMS) and analyzed by ANOVA with repeated measures design. Under high frequency DBS there was a robust EMG response at approximately 50-80ms following ulnar nerve stimulation, consistent with LLR. In addition, another EMG response was found approximately 120ms following ulnar nerve stimulation, termed the very long latency reflex (VLLR). For both responses, the high frequency DBS was significantly greater than the means at the other frequencies ($p < 0.002$ for LLR, and $p < 0.006$ for VLLR). Our results implicate frequency-dependent activation of sensorimotor cortex as an important component of the therapeutic mechanisms of DBS. Further research must be conducted to explore the significance of the VLLR.

Barr, Eleanor

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Dr. Daniel Sharer

Co-Authors

Title Tandem Mass Spectrometry of Galactose-1-Phosphate for Galactosemia Diagnosis

Abstract

Background: Galactosemia diagnosis usually involves radioactive and fluorescent assays of galactose-1-phosphate uridylyltransferase (GALT) activity in erythrocytes. These assays can lack sufficient analytical sensitivity, and are laborious. Galactose-1-phosphate (Gal-1-P), the primary biomarker of galactosemia, is also useful for diagnosis and management. We hypothesize that a Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) assay can be established for detecting and quantifying Gal-1-P (in the presence of other hexose-monophosphates). This method would be more efficient, sensitive, specific, and directly measure the target compound; however, separation of Gal-1-P from other isomers would be necessary before MS/MS.

Methods: Synthetic α -D-Gal-1-P and α -D-Glucose-1-phosphate (Gluc-1-P) were used as initial separation substrates on a Waters Xbridge Amide 3.5 μ m high performance liquid chromatography column. A multiple reaction monitoring (MRM) MS/MS method was set up for detecting different hexose-monophosphates in negative ion mode at mass transition 259>79. Injection volume, mobile phase, column temperature, flow rate, additives, pH, and sample concentration were varied during method development.

Results: A MRM method for detecting multiple hexose monophosphates from within a complex mixture was first established. After ninety unique protocols, consistent separation of Gal-1-P from Gluc-1-P was not achieved with the Waters Xbridge Amide Column. Two other columns were also unable to separate the compounds. A new protocol was developed to measure Gal-1-P by subtracting endogenous galactose from total galactose (summation of Gal-1-P and galactose) in patient samples. An assay protocol based on the Beutler method of galactosemia diagnosis was designed to convert endogenous Gal-1-P to galactose, using alkaline phosphatase, prior to injection. Unique separation of galactose from glucose and other monosaccharides was achieved by LC/MS-MS using an Aminex HPX 87-C column.

Conclusions: Direct LC-MS/MS separation of Gal-1-P from other hexose-monophosphates has not yet been achieved, but may be possible with other chromatography columns. Indirect Gal-1-P measurement for galactosemia diagnosis by LC-MS/MS is likely achievable.

Baxley, Sarah

Project Length	Long
Prior Research Experience	Yes
FundingSource	Departmental or Mentor funds
Advisor	Rosa Serra
Co-Authors	
Title	Wnt5a regulates oxytocin response at parturition

Abstract

Lactation is the culmination of mammary gland development, an evolutionary adaptation that allows mammals to generate a continuous food supply to feed their young. Milk provides essential nutrients for development as well as immunological protection. The lack of breast feeding in humans has been linked to increases in a range of problems, including dental caries and depression. Therefore, understanding the processes that regulate mammary gland development and lactation are of clinical importance.

Our lab previously demonstrated that Wnt5a, a non-canonical Wnt, plays a role in mammary gland development, potentially through regulation of mammary progenitor cells. Wnt5a is expressed through most stages of mammary development but levels decrease dramatically at parturition, suggesting Wnt5a may regulate milk let down. We hypothesized that exogenously expressed Wnt5a would alter mammary gland development during late pregnancy and lactation, when Wnt5a expression normally decreases.

To determine the Wnt5a's effects on mammary development, we generated mice that overexpress Wnt5a using the mammary gland specific promoter MMTV. Mice overexpressing Wnt5a (MMTV-Wnt5a) were examined during late pregnancy and early lactation. Here, we report that overexpression of Wnt5a within mammary epithelium does not interfere with the normal development, and the production of milk proteins is normal. However, MMTV-Wnt5a dams fail to feed their pups. Milk ejection is initiated by the action of oxytocin on myoepithelial cells within the mammary gland, stimulating their contraction and consequent ejection of milk. We show that MMTV-Wnt5a glands fail to respond to oxytocin. These results suggest that Wnt5a antagonizes the milk ejection response within the mammary gland. We are currently testing several hypotheses of how Wnt5a antagonizes the milk ejection response. In addition, some MMTV-Wnt5a dams fail to deliver their pups. Since parturition also involves contraction in response to oxytocin, we propose that Wnt5a may also antagonizes the uterine response to oxytocin at parturition.

Bishop, Elliot

Project Length Short

Prior Research Experience No

Funding Source CaRES Program

Advisor Eben L. Rosenthal, MD

Co-Authors Joseph A. Knowles, MD, Kurt R. Zinn, DVM, PhD, Zheng Miao, PhD, Stanford, CA; Zhen Cheng, PhD, Stanford, CA; Eben L. Rosenthal, MD,

Title Near-Infrared Labeled EGFR Specific Affibody Molecules: A Rapid Approach to Tumor Specific Imaging

Abstract

Educational Objective: At the conclusion of this presentation, the participants should understand the potential value of antibodies and affibodies to image cancer *in vivo* and to assess surgical margins.

Objectives: To determine the value of an epidermal growth factor receptor (EGFR) targeting affibody and a monoclonal antibody for use in *in vivo* optical imaging.

Study Design: Comparative animal experimental study.

Methods: Affibodies are a class of small scaffold proteins (approximately 6.5 KDa) engineered for high affinity and specificity to various molecular targets. The anti-EGFR affibody and anti-EGFR antibody (cetuximab) were conjugated to a fluorescent agent (Cy5.5). The fluorescently labeled EGFR specific affibody molecule or cetuximab was administered systemically by tail vein injection to immunocompromised mice bearing SCC-1 xenografts. Mice were imaged over 72 hours with a CCD based imaging system utilizing near infrared laser illumination to determine peak fluorescence. Partial tumor resections were performed at various time points to visualize microscopic residual tumor pieces (smaller than 2mm).

Results: Peak tumor fluorescence and signal to background ratios for the affibody group occurred approximately 1.5 hours post-injection while these values peaked approximately 48 hours post injection in the cetuximab group. The affibody group cleared tumor and systemic fluorescence more quickly than the cetuximab group. Residual tumor pieces following post-partial tumor resection were visible.

Conclusions: Fluorescently labeled affibody imaging probes may be used to guide surgical resections of head and neck cancer with a shorter induction time without compromising signal strength compared to fluorescently labeled antibody.

Black, Jonathan

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Suzanne Oparil
Co-Authors	Dongqi Xing, Kaizheng Gong, Yiu-Fai Chen
Title	O-GlcNAc Modification of NFκB p65 Subunit in Rat Aortic Smooth Muscle Cells

Abstract

Our previous in vivo studies have shown that an acute increase in O-linked-N-acetylglucosamine (O-GlcNAc) protein modification with glucosamine (GlcN) or O-(2-acetamido-2-deoxy-D-glucopyranosylidene) amino-N-phenylcarbamate (PUGNAc) treatment attenuates inflammatory responses and neointima formation following endoluminal injury of the rat carotid artery. Other studies have identified the arterial smooth muscle cell (ASMC) as the target cell in the injury response, and have shown that the NFκB signaling pathway is important in both vascular injury and tumor necrosis factor (TNF)-α treated ASMC models of inflammation. In TNF-α treated rat ASMCs, NFκB p65 is phosphorylated and translocated to the nucleus where it binds to DNA and acts as a transcriptional factor to upregulate the production of pro-inflammatory factors. Our study tested the hypothesis that O-GlcNAc modification of NFκB p65 inhibits the phosphorylation of p65, thereby blocking the inflammatory response. Quiescent rat ASMCs were pretreated with GlcN (5 mM), PUGNAc (0.1 mM) or vehicle for 1 hr and then stimulated with TNF-α (10 ng/ml) for an additional 1 or 6 hrs. Both treatments increased global O-GlcNAc modified protein levels [Western blot analysis (WB) with the selective O-GlcNAc antibody CTD110.6] and inhibited TNF-α-induced expression of pro-inflammatory chemokines, adhesion molecules, and NFκB DNA binding activity. Using immunoprecipitation and WB techniques, we demonstrated that GlcN and PUGNAc treatments increased O-GlcNAc modification of NFκB p65 and inhibited TNF-α induced phosphorylation of NFκB p65 in cell lysates and isolated nuclear extracts. These results indicate that pre-treatment with GlcN and PUGNAc enhanced O-GlcNAc modification of NFκB p65 and blocked subsequent TNF-α induced phosphorylation of p65, thus preventing NFκB p65 translocation to the nucleus. In conclusion, increased protein O-GlcNAc modification of NFκB p65 inhibits TNF-α-induced expression of inflammatory mediators in rat ASMCs by blocking phosphorylation of NFκB p65.

Blake, Courtney

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Jamy Ard

Co-Authors Tiffany Cox, Brooks Wingo, Renee Desmond, Jamy Ard

Title Actual and Perceived Cost Discounts Influence Fruit and Vegetable Consumption

Abstract

Background:

Lower socioeconomic status and decreased intake of fruits and vegetables are linked with higher rates of obesity. Several factors contribute to food intake, two of which include cost and convenience. The perception of high cost and low convenience of fruits of vegetables may contribute to decreased intake. This pilot study assumes two components of cost – actual cost and perceived cost. Actual cost can be altered by monetary discounts, while perceived cost is changed by means of shopping and preparation time.

Methods:

Primary household shoppers were randomized into three cohort groups – control, voucher group (50% discount on actual price), and curbside service, prep group (perceived cost discount). The perceived cost discount group purchased fruits and vegetables at full price but in a ready-to-eat form. Data was obtained from surveys and questionnaires, as well as from food journals and receipts. Only fresh produce was targeted for analysis in order to minimize confounding factors associated with canned and frozen forms.

Results:

Preliminary data analysis suggests no significant increase in fruits or vegetables with either the voucher group or the curbside, prep group as compared to control. While not significant, both discount groups show an increase in vegetable purchase compared to baseline (voucher $p=0.19$, curbside prep $p=0.25$). No group showed any change in overall energy density.

Conclusion:

With a larger study population, it is possible that decreasing price and increasing convenience will increase vegetable purchases and lead to increased consumption. Future studies are needed to explore the relationship between food intake and the combination of cost and convenience. A larger study is needed to show that alterations in actual and perceived cost increase fruit and vegetable consumption. Additionally, future studies are needed to explore the influence of produce discounts on overall energy density.

Blosser, Emily

Project Length Intermediate

Prior Research Experience yes

Funding Source MSTP T32

Advisor David Randolph, MD, PhD

Co-Authors

Title The Role of Th17 Cells and Commensal Flora in Gut Mucosal Defense

Abstract

Late-onset bacterial sepsis is a leading cause of morbidity and mortality among premature infants in the United States. Causative organisms in late-onset sepsis vary, but infections with Gram-negative bacteria, such as *Klebsiella pneumoniae*, can be particularly severe. Late-onset sepsis (LOS) is thought to be initiated when pathogenic bacteria translocate across the premature gut epithelium into the bloodstream. Preterm infants are particularly susceptible to LOS due to immaturity of the immune system and delayed colonization with commensal flora.

Th17 cells are a subset of CD4 helper T cells that produce interleukins (IL)- 17 and 22, cytokines known to be important for epithelial barrier function. Individuals deficient in Th17 cells suffer repeated bacterial infections. Little is known about Th17 development in human infants, but in animal models, Th17 development is dependent on colonization with particular species of gut flora.

Commensal flora reinforce the gut barrier in two ways: they compete for space and resources with pathogenic species; and they are believed to interact with the host to induce expression of genes important for epithelial integrity and to promote immune system maturation. The widespread use of antibiotics perinatally helps prevent early infections in preterm infants, but also delays colonization with commensal flora. We hypothesize that the delay in colonization with commensal flora and the resulting delay in Th17 function development are critical to the pathogenesis of LOS.

To better understand the relationships between Th17 development, commensal flora, and pathogens and their roles in LOS, we have established a model for LOS in which we orally challenge neonatal mice with pathogenic *K. pneumoniae*. As in humans, resistance is age dependent with young pups being highly susceptible and adults being resistant. Antibiotic treatment of pregnant dams increases susceptibility of pups. Interestingly, pups who survive oral challenge have comparable numbers of total bacteria in stool regardless of whether or not their mother received antibiotic treatment; however, 1000-fold more *K. pneumoniae* remains in the stool of pups of antibiotic-treated mothers. Further studies are needed to understand the mechanisms of resistance and bacterial clearance.

Boohaker, Hikel

Project Length Intermediate

Prior Research Experience Yes

Funding Source Departmental or Mentor Funds

Faculty Advisor Dr. Brent Ponce

Co-Advisors Brent A. Ponce M.D., E. Lyle Cain Jr. M.D., Ryan Pflugner M.D., Hikel A. Boohaker, Martha P. George M.D., Gerald McGwin Ph.D., Glenn S. Fleisig Ph.D., Jeffrey R. Dugas M.D., Lawrence J. Lemak M.D., William G. Clancy M.D., James R. Andrews M.D.

Title An Evaluation of 42 Failed Primary ACL Reconstructions and Their Subsequent Revisions

Abstract

Background: Anterior Cruciate Ligament (ACL) failure rates have been reported between 3-25%, the majority of studies report failure rates between 10-20%. Surgical technique is cited as the most frequent cause for failure. Other variables associated with revision are poorly understood.

Purpose: The purpose of this study was to evaluate risk factors for revision surgery following primary ACL reconstruction.

Methods: A retrospective analysis of prospectively collected data was performed on 2708 patients with a primary ACL reconstruction at the same institution from 8/01-12/08. Of the 2708 primary reconstructions, 42 required revision surgery. Items assessed included: age, gender, sport, activity level, graft, and concomitant meniscal and chondral injury.

Results: Revision rate for primary ACL reconstruction was 1.55% (42/2708) in this series. Risk factors for revision surgery included graft type, surgeon, patient age, sport, and meniscal injury at time of initial surgery. Allograft usage and age at the time of initial surgery were the most significant risk factors ($p < 0.0001$) for revision ACL reconstruction. Other risk factors included history of meniscal damage at the time of initial surgery ($p = 0.0015$), initial injury from basketball (0.0174), and choice of surgeon ($p = 0.035$), were also associated with revision surgery. Gender, extremity (R vs. L), participation beyond high school level competition, and chondral injury at the time of initial reconstruction were not risks for revision ACL reconstruction.

Conclusion: Failure of primary ACL reconstructions is more likely in younger patients, allograft reconstruction, concomitant meniscal injury, initial injury from basketball, and choice of surgeon.

Bradley, Jerry, Jr

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Martin E. Young, D.Phil
Co-Authors	Betty M. Pat, PhD
Title	The Influence of O-GlcNAcylation on Circadian Proteins within the Heart and Liver

Abstract

BACKGROUND: Cardiovascular disease (CVD) is the leading cause of death in the United States. Like many complex human diseases, CVDs are the product of gene-environment interactions. Circadian clocks are transcriptionally-based molecular mechanisms that modulate cellular function in a time-of-day-dependent manner. For example, the cardiomyocytes circadian clock is sensitive to multiple environmental factors (e.g. diet, adrenergic stimulation), which in turn influences cardiovascular function. Recent studies suggest that glucose metabolism may be an integral component of the mammalian circadian clock, through modulation of protein O-GlcNAcylation. **OBJECTIVE:** This study was designed to investigate whether alterations in protein O-GlcNAcylation influences protein levels of various circadian clock proteins (PER2, BMAL1, CLOCK) in the heart and/or liver. **METHODS:** Tissues were harvested from wild-type mice 6, 12, and 18 hours following treatment with vehicle (saline) or PUGNAc (a reversible O-GlcNAcase inhibitor, resulting in increased protein O-GlcNAcylation levels). Western blotting was performed for determination of PER2, BMAL-1, CLOCK total protein levels as well as PER2 O-GlcNAcylation. Densitometric analysis was performed for semi-quantification; all data were normalized to a loading control. **RESULTS:** Unlike CLOCK and BMAL1, PER2 total protein levels oscillated in both heart and liver in a time-of-day -dependent manner, peaking in the middle of the dark (active) phase. Treatment of mice with PUGNAc, significantly decreased PER2 protein levels in the heart, but not the liver. In contrast, PUGNAc treatment did not significantly effect CLOCK or BMAL1 total protein levels in the investigated tissues. We next investigated whether PER2 was a direct O-GlcNAcylation target (which in turn might influence protein stability). However, immunoprecipitation studies suggest that PER2 is not directly modified by O-GlcNAcylation. **CONCLUSION:** These results suggest that protein O-GlcNAcylation may influence distinct circadian clock components. The mechanism by which this regulation occurs currently remains unknown.

Brennard, Megan

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Dr. Boni Elewski
Co-Authors	Carney, C., Cantrell, W., Elewski, B.
Title	Can pityriasis versicolor be treated with 2% ketoconazole foam?

Abstract

Background: Pityriasis versicolor is a superficial fungal infection of the stratum corneum caused by *Malassezia* species. Its classic appearance of hyperpigmented or hypopigmented, round or oval macules with fine scale allows for clinical diagnosis. Microscopic evidence of short, stubby hyphae and spores confirms the diagnosis. Ketoconazole therapy is primarily used in cream formulas, but foam vehicles have shown increased drug absorption and distribution. This study assessed the safety and efficacy of 2% ketoconazole foam in treating pityriasis versicolor. Methods: This single-center, open-label, one-arm pilot study evaluated 2% ketoconazole foam in eleven adult patients age 19 and older with clinical and microscopic diagnosis of pityriasis versicolor. The subjects were instructed to apply foam to affected areas twice daily for 2 weeks. Mycological and clinical assessment of a target area was done at baseline, week 1, week 2, and week 4, along with static global assessment and body surface area estimation. Patient questionnaires at baseline and week 2 solicited ratings of pruritus and satisfaction with the foam. Results: Following treatment, seven of eleven subjects had microscopically negative skin samples. Three remaining subjects had only yeast forms without hyphae present at final visit. One out of the eleven subjects was lost to follow-up. For all patients, average investigator ratings demonstrated progressive improvement in scale, hyper- or hypopigmentation, erythema, and induration. Though the average pruritus score increased slightly after baseline visit, it then improved steadily over remaining visits. The investigator's global assessment improved for 7 subjects, while others had neither improvement nor progression of disease. One participant noted mild skin burning after application of medicine. Limitations: This was a single-arm, open-label, noncomparative trial. Conclusion: Ketoconazole 2% foam improved overall clinical assessment and microscopic evidence of pityriasis versicolor in all patients. Patient satisfaction with foam vehicle was above average in all categories.

Brosius, Stephanie

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Talene Yacoubian
Co-Authors	
Title	Analysis of 14-3-3 θ binding partners in models of Parkinson's disease

Abstract

Parkinson's disease (PD) is a neurodegenerative disorder of the dopaminergic cells in the substantia nigra that produces symptoms of tremor, bradykinesia, rigidity and poor balance. One of the hallmarks of the disease is the presence of α -synuclein laden Lewy bodies. Though it is accepted that excess α -synuclein promotes neurodegeneration in PD, the mechanism of its toxicity has yet to be elucidated. Recent studies have shown that α -synuclein colocalizes in Lewy bodies with 14-3-3 θ , which is a key regulator in the mitochondrial apoptotic cascade. Our lab has also demonstrated that 14-3-3 θ elicits a neuroprotective effect due to its interaction with the Bcl-2 family protein Bax, which strongly suggests its involvement in the degeneration process. When Bax is no longer bound to 14-3-3, it forms oligomers that disrupt the mitochondrial outer membrane, allowing the release of cytochrome C. Based on this data, we hypothesize that over-expression of α -synuclein, as seen in PD, leads to sequestration of 14-3-3 proteins and a decrease in the interaction between 14-3-3s and Bax, thereby leading to activation of the mitochondrial apoptotic cascade. To test this hypothesis, we transfected HEK 293 cells with α -syn or an empty vector as a control. Cell lysates were collected and then used for immunoprecipitation with Sepharose beads (Protein G) and a Bax monoclonal rabbit antibody as the primary antibody or rabbit IgG as a control. Immunoprecipitants were then immunoblotted with antibodies against 14-3-3 θ and Bax as a control. Preliminary results indicate that there is a decreased interaction between Bax and 14-3-3 θ when α -synuclein is upregulated as compared to controls. This data suggests that an increase in α -synuclein may result in an increase in activated Bax present in cells, triggering apoptosis. Therefore, these experiments substantiate our proposed mechanism for α -synuclein toxicity and suggest that 14-3-3 θ may be a key factor and a potential therapeutic target in preventing or delaying the progression of PD.

Brossier, Nicole

Project Length	Long
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Steven Carroll

Co-Authors

Title	Role of Ras Isoforms in Proliferation and Migration of Malignant Peripheral Nerve Sheath Tumors
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Abstract

We hypothesized that multiple neurofibromin-regulated small G-proteins from the classic Ras (H, N, and K-Ras) and R-Ras (R-Ras, R-Ras2, and M-Ras) subfamilies promote the proliferation and migration of malignant peripheral nerve sheath tumor (MPNST) cells. We found that H-Ras, N-Ras, and R-Ras2 proteins were uniformly expressed in 8 MPNST lines; their expression of K-Ras2b and R-Ras was variable, while M-Ras protein was not detected in these lines. RT-PCR analyses demonstrated that the guanine nucleotide exchange factors necessary to activate these Ras proteins were also present. Using 3H-thymidine incorporation and Transwell migration assays, we assessed the effects dominant negative (DN) H-Ras and R-Ras mutants exerted on MPNST cells. We found that DN H-Ras and DN R-Ras both inhibited MPNST mitogenesis, while only DN R-Ras inhibited migration. Raf-1 RBD affinity assays performed in MPNST cells transiently transfected with Myc-tagged H-Ras, N-Ras, and K-Ras demonstrated that all 3 classic Ras proteins were constitutively activated. However, shRNA-mediated ablation of N-Ras or K-Ras had no effect on proliferation. We conclude that both classic Ras and R-Ras subfamily members contribute to MPNST pathogenesis. Inhibition of multiple Ras isoforms will therefore likely be required to achieve an optimal therapeutic effect. Funded by R01 CA122804 and F30 NS063626.

Byekova, Yevgeniya

Project Length	Intermediate
Prior Research Experience	Yes
FundingSource	Departmental or Mentor funds
Advisor	Mohammad Athar
Co-Authors	Mohammad Athar
Title	Liver Kinase B1 (LKB1) in Pathogenesis of Murine Basal Cell Carcinoma

Abstract

LKB1, a known tumor suppressor, is mutated in Peutz-Jeghers syndrome. It is responsible for the enhanced cancer risk in this population. Its deregulation is also known in various epithelial cancers. Recently, LKB1 expression was shown to be altered by UVB in skin keratinocytes. However, its role in the pathogenesis of skin cancer remains elusive. We investigated the expression of LKB1 in UVB-induced basal cell carcinoma (BCC) developed in Patched^{+/-} mice. BCCs represent the most common human neoplasm. Our data show that LKB1 expression is significantly enhanced in BCC. LKB1-dependent AMP Kinase (AMPK) and acetyl Co-A carboxylase (ACC) are also enhanced in this neoplasm as compared to normal age-matched skin. To further probe the role of increased LKB1 in BCC development, we investigated the Wnt/beta-catenin and mTOR signaling. A high expression of phosphorylated (p) Akt, a kinase known to inactivate GSK3beta through its phosphorylation, was observed. Consistently, we observed an accumulation of p-GSK3beta in BCC. As GSK3beta is a negative regulator of Wnt/beta-catenin signaling, a marked increase in this pathway occurs in BCC. Our data suggest that LKB1 potentiates Wnt signaling in BCC. Then, we examined the expression of mTOR signaling proteins in this neoplasm. mTOR signaling is downstream of LKB1/AMPK axis. Following nutrients deprivation, LKB1/AMPK activation leads to downregulation of mTOR signaling with suppression in protein synthesis. In contrast to this notion, the mTOR signaling is upregulated in murine BCC. Interestingly, we observed a marked decrease in the expression of sestrins, a novel potent negative regulator of mTOR signaling. It is known that the pathogenesis of BCC requires activation of sonic hedgehog signaling, which can also crosstalk with mTOR. Thus our data show that LKB1/AMPK axis is not able to regulate mTOR pathway in UVB-irradiated Patched^{+/-} mice and a complex regulatory mechanism exists for the persistent mTOR activation in BCCs.

Calix, Juan

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Moon Nahm
Co-Authors	Stephen Pelton, Moon Nahm
Title	<i>Streptococcus pneumoniae</i> Serotype 11E is Found Predominantly in Invasive Pneumococcal Disease

Abstract

Background: A novel *Streptococcus pneumoniae* serotype (ST), 11E, was recently discovered among invasive pneumococcal disease (IPD) isolates previously serotyped as the prevalent ST 11A. To date each 11E strain contains a distinct null mutation to the capsule synthesis gene *wcjE*, a putative O-acetyltransferase, indicating that ST 11E strains are unique and have not spread between hosts. One possibility is that 11E strains arise following initial host colonization by a ST 11A strain and only exist in invasive pneumococcal disease. To validate this hypothesis, nasopharyngeal (NP) and IPD isolates previously serotyped as 11A from a pediatric population were screened for the presence of 11E strains.

Methods: 66 clinical NP and 10 IPD isolates previously serotyped as 11A according to the Quellung assay were reexamined using monoclonal antibodies in an inhibition ELISA assay and a newly developed flow-cytometric serotyping assay. To confirm serotyping, *wcjE* was sequenced in some 11A and all 11E isolates.

Results: Two IPD samples were serotyped as 11E. Both of these strains contained unique null mutations in *wcjE* not observed in previous studies. All remaining isolates were confirmed as ST 11A (n=74).

Conclusions: ST 11E was not identified among NP isolates (0/66) and was significantly associated with IPD isolates (2/10, $p=0.015$). The percentage of 11E among IPD isolates previously serotyped as 11A is similar to the occurrence rate stated in a previous study (10-25%). These results support the hypothesis that ST 11E arises by mutation after colonization with 11A is established and is exclusively a disease-causing ST. As ST 11E possibly arises in response to the establishment of an anti-11A immune response, describing the conditions of 11E emergence is important for future polysaccharide-based vaccines against the prevalent ST 11A, and offers insight into how capsule structure influences pathogenesis.

Carstarphen, Kathy Jo

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. David Freedman
Co-Authors	Dr. David Iglesias, Dr. Edward Gotuzzo
Title	Factors Influencing Early HIV Treatment in Lima, Peru

Abstract

Objective: Explore why HIV-positive patients at a large public hospital in Lima, Peru did not receive highly active antiretroviral therapy (HAART) within 3 months of meeting at least one criterion for initiating treatment. **Design:** A case-control study on HIV-positive adults eligible to receive free HAART at Hospital Nacional Cayetano Heredia (HNCH) was conducted from May, 2009 to July, 2009. These patients were diagnosed with HIV by Western blot within the previous six years. **Methods:** Psychosocial variables affecting early treatment (income level, emotional support at time of diagnosis, knowledge of disease, and experience of discrimination) were surveyed by a questionnaire that was administered to patients; medical management variables (hospital bureaucracy and physician recommendations) were surveyed and confirmed by chart review. Outcomes were statistically assessed with the STATA software, using Fisher's exact significance test. **Results:** A total of 177 patients were included in this study: 105 controls, 72 cases. Controls were patients who started HAART within 3 months of meeting a criterion for treatment. The 72 patients not started on HAART largely fall into two groups: patient failure to follow-up, and those for whom treatment was withheld by their physician. There were two variables associated with a delay in starting HAART therapy in eligible patients. In univariate analysis, delay was associated with the patients not communicating an HIV positive diagnosis with another person at time of diagnosis (23% of cases, 10% of controls, $p = 0.022$ by Fisher's exact test). Another strong association (30% of cases, $p=.0001$) for delay in treatment was unexpectedly found in medical management of cases when the managing physician recommended delaying treatment. No discernable differences were discovered in income level, experience of discrimination, knowledge of HIV, or hospital bureaucracy between cases and controls. It was also found that patients (both cases and controls) commonly have a poor understanding of HIV and its transmission, and an extensive wait time for appointments. **Conclusion:** This study displays a psychosocial association of social support at time of diagnosis as an important correlation in triage to therapy, without other psychosocial associations observed. The high rate of postponement in this population prompted investigators to look at medical management factors in addition to the psychosocial and patient motivation assessment. Analysis of this medical management component surprisingly identified that many patients meeting a criterion for treatment were not initiated on HAART therapy by managing physicians until opportunistic infections were diagnosed and treated. Delaying HAART for this reason was previously common, but is contrary to current evidence-based medicine standards of care. In summary, these findings suggest implementation of an HIV education program for both patients and practitioners as: 1) a review and update of current prescribing guidelines of the National Program (NP) of Peru regarding pre-treatment of opportunistic infections before initiation of HAART for physicians treating HIV positive patients, and 2) audiovisual patient education programs implemented during the extensive wait time period for appointments by patients to promote prevention and reduce the psychosocial stigma of HIV.

Chen, Zsu-Zsu

Project Length	Short
Prior Research Experience	Yes
FundingSource	American Federation for Aging Research MSTAR Fellowship
Advisor	W. Timothy Garvey
Co-Authors	R. Grace Walton, Ling Tian, Lusheng Xu, Karen Mai, Helliner Hill, W. Timothy Garvey
Title	Effects of Aging and Diet-Induced Obesity on NR4A3 in Mouse Muscle: Correlation with Myostatin

Abstract

Aging and obesity are states of insulin resistance that predispose individuals to Type 2 Diabetes; however, underlying mechanisms of impaired insulin action are not fully understood. Our lab recently demonstrated that NR4A3, an orphan nuclear receptor, enhances insulin-stimulated glucose transport in muscle cells and that its levels decreased in muscle from elderly individuals. To further explore the role of NR4A3, we studied 3 groups of male C57/BL6 mice: 10 month olds fed a high fat diet (HFO), 10 month olds fed a standard diet (SDO), and 3 month olds fed a standard diet (SDY). These treatment groups assessed the effects of diet-induced obesity (HFO vs SDO) and aging (SDO vs SDY). Since NR4A3 was recently reported to inhibit myostatin transcription in cultured cells, we further hypothesized that myostatin protein and mRNA levels would negatively correlate to NR4A3. Based on fasting insulin levels and insulin tolerance tests, HFO mice demonstrated severe insulin resistance, and SDO an intermediate degree, compared with insulin sensitive SDY. NR4A3 protein and mRNA levels in gastrocnemius were decreased in response to aging and diet-induced obesity. In a combined analysis, NR4A3 protein concentration was negatively correlated with body weight ($r=-.49$; $p=0.02$). Isolated myostatin protein and mRNA levels unexpectedly also decreased with age and diet, causing NR4A3 to be positively correlated with myostatin ($r=+.81$; $p<0.001$).

In conclusion, in mice: 1) insulin resistance increases with age and is exacerbated by a high fat diet. 2) NR4A3 levels in skeletal muscle are reduced as a function of aging and diet-induced obesity and may contribute to skeletal muscle insulin resistance. 3) Contrary to a previous observation in cultured cells, NR4A3 is positively correlated with myostatin expression in vivo. Further research is needed to examine mechanisms by which NR4A3 enhances insulin sensitivity, and what role myostatin plays in this pathway.

Chestnut, Michael

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Brad Woodworth
Co-Authors	Shaoyan Zhang, Daniel Skinner
Title	Transepithelial Ion Transport is Suppressed in Hypoxic Sinonasal Epithelium

Abstract

Objectives/Hypothesis: Sinonasal respiratory epithelial mucociliary clearance (MCC) is dependent on the transepithelial transport of ions such as Cl⁻. The objectives of the present study were to investigate the role of oxygen restriction in 1) Cl⁻ transport across primary sinonasal epithelial monolayers, 2) expression of the apical Cl⁻ channels CFTR and TMEM16A, and 3) the pathogenesis of chronic rhinosinusitis (CRS).

Study Design: *In vitro* investigation.

Methods: Murine nasal septal (MNSE, wild type and transgenic CFTR^{-/-}) and human sinonasal epithelial (HSNE) cultures were incubated under hypoxic conditions (1% Oxygen, 5% CO₂). Cultures were mounted in Ussing chambers for ion transport measurements. CFTR and TMEM16A expression were measured using quantitative RT-PCR.

Results: The change in short-circuit current (DISC (mA/cm²) attributable to both CFTR (forskolin-stimulated) and TMEM16A (UTP-stimulated transport) was significantly decreased by 12 hours in both MNSE [(CFTR, 10.5±0.5 vs. 18.25±0.55 (control); TMEM16A, 38.4±3.4 vs. 54.8±6.1 (control) p<0.05] and HSNE [(CFTR, 19.6±0.56 vs. 26.1±1.0 (control); TMEM16A, 16.75±0.7 vs. 26.1±1.3(control) p<0.05]. Hypoxic suppression of TMEM16A-mediated ISC was confirmed in transgenic CFTR^{-/-} MNSE. Quantitative PCR (reported as relative mRNA levels±S.D.) demonstrated a significant reduction in CFTR (55.2±16.1 vs. 102.8±10.3, p<0.05) and TMEM16A (54.6±12.1 vs. 134.3±26.1; p<0.05) mRNA expression due to physiologic levels of airway epithelial hypoxia.

Conclusions: Sinonasal epithelial CFTR and TMEM16A-mediated Cl⁻ transport and mRNA expression were robustly decreased in an oxygen restricted environment. The findings in the present study indicate persistent hypoxia may lead to acquired defects in Cl⁻ transport and may, in part, explain the persistence of mucociliary dysfunction in CRS.

Ciszak, Tadeusz

Project Length	Short
Prior Research Experience	Yes
FundingSource	Diabetes Research and Training Center
Advisor	Steven G. Lloyd
Co-Authors	Nikhil Jha, Thomas Denney
Title	Systolic and Diastolic Left Ventricular Dysfunction in post-Myocardial Infarction Patients with Type II Diabetes

Abstract

Left ventricular (LV) diastolic filling, typically assessed by Doppler echocardiography blood flow velocity through the mitral valve, has long been established as an accurate predictor of both systolic and diastolic dysfunction. Both Type II diabetes (T2DM) and ischemic heart disease are known to impair diastolic function of the LV. The impact of diabetes on LV filling after myocardial infarction has not been comprehensively studied. Here, we used Cardiac Magnetic Resonance Imaging (CMR) to assess systolic and diastolic function in T2DM and non-diabetic control patients with MI. We hypothesized that T2DM leads to worse diastolic and systolic dysfunction in these patients. We performed quantitative flow analysis via velocity-sensitive, Phase-Contrast (PC) CMR with MI and T2DM (N = 42 patients), and non-diabetic patients with MI (N = 18). CMR was performed within 2 weeks of MI. To assess systolic function, LV volumes and Ejection Fraction (EF) were determined from short axis cine CMR. Early (E) and late (A) diastolic filling peak velocities showed similar diastolic function in both T2DM (59.5% Normal Function, 16.7% Mild Dysfunction, 23.8% Severe Dysfunction) and non-diabetic patients (61.1% Normal, 16.7% Mild, 22.2% Severe). There was no significant difference between T2DM and non-diabetic patients in End systolic volume or EF within each category of diastolic function. In conclusion, we found that T2DM and non-diabetic patients show similar diastolic and systolic function early after first MI. CMR is a promising tool to comprehensively investigate both physiologic function, as well as anatomic extent of myocardial damage after MI.

Clark, Eva

Project Length

Long

Prior Research Experience

Yes

Funding Source

NIH Medical Scientist Training Program Grant

Advisor

OraLee Branch

Co-Authors

Claudia J. Silva, Carlos Padilla, and OraLee H. Branch

Title

Long-Lasting Humoral and Cellular Responses to *Plasmodium falciparum* Merozoite Surface Protein-1 in the Low-Transmission Amazon Region of Peru
Correlate with Long-term Clinical Protection

Abstract

Development of immunity to *Plasmodium falciparum* infections requires years of parasite exposure, a delay attributed to difficulties in developing protective antibody responses. In this study of Peruvian adults and children, the magnitude and longevity of IgG and IgG subclass responses to Merozoite Surface Protein-1 19kD (MSP119) before, during, and after *P. falciparum* infection was determined by ELISA. In this low-transmission region, even one reported prior infection was sufficient to result in a positive anti-MSP119 IgG response for ≥ 4 months in the absence of reinfection. To directly test for immunologic memory, flow cytometry to quantify post-infection B cell subsets as well as antigen-specific memory B cell ELISPOTs were performed. Expansion of the plasmablast (CD19+/CD27+/CD38high) population was observed in the majority of individuals shortly after infection presentation, and MSP1-specific memory B cells were detectable in a subset of individuals. Immunologic memory, particularly sustained IgG1, distinguished asymptomatic from symptomatic individuals.

Clifford, William

Project Length Intermediate

Prior Research Experience No

Funding Source None

Advisor Dr. John Wheat

Co-Authors None

Title Defensive Medicine: Identifying Diagnostic Procedures Most Susceptible to Malpractice Concern

Abstract

Background: The people and government of the United States are embroiled in debate regarding the future of healthcare delivery and payment. Central to the discussion is healthcare cost, which as a significant percentage of gross domestic product, many argue, warrants healthcare reform. Much has been written and much is known about total healthcare expenditures. Yet, a great deal of the health care calculus remains a mystery. One such amorphous topic is the cost of defensive medicine. Though many have studied the topic, few have done so within the firmament of objective evidence. Much of the difficulty encountered by researchers studying the cost of defensive medicine is attributable to the confounding nature of coexisting variables.

Purpose: This study proposes that the absence of threatened individual tort liability in certain healthcare delivery models is associated with a decrease in intensity of diagnostic procedures, a finding that will help quantify the cost of defensive medicine. To that end, the focus of this work is to determine, through review of existing literature, whether diagnostic procedures most susceptible to malpractice concern have been identified.

Methods: The Pubmed (1970 - 2009), CINAHL (1960 - 2009), Westlaw Journals Database, Cochrane Collections, and Google Scholar databases were searched using a recognized search strategy suggested by the Center for Reviews and Dissemination Report No. 4 (2nd Edition).

Results: 1,140 abstracts were identified via database search, but only nine full articles met the inclusion criteria. Of those articles, all highlight a nexus between specific diagnostic procedures and malpractice liability pressures. However, none of the studies firmly establish a strata of diagnostic procedures most susceptible to malpractice concern.

Conclusions: The body of available research does not identify diagnostic procedures most susceptible to malpractice concern. Yet, in the aggregate, it provides robust evidence for procedures that should be considered in any future analysis.

Corrick, Ryan

Project Length	Long
Prior Research Experience	Yes
FundingSource	Departmental or Mentor funds
Advisor	Joseph L. Messina, Ph.D.
Co-Authors	Li Li, M.D., Ph.D. and Ling Zhao
Title	Hepatic Growth Hormone Resistance Following Injury is Associated with Decreased Functional Receptors

Abstract

Acute growth hormone (GH) resistance frequently occurs following trauma, burns, infections and critical illness, contributing to a pronounced catabolic state. Clinical reversal of GH resistance due to injury or critical illness could provide several benefits, including preservation of mobility, strength, and lean body mass, leading to reduced morbidity following intensive care. However, the molecular mechanisms leading to the development of GH resistance are poorly defined, and as a result there are no effective therapies for the reversal of GH resistance. We recently developed a murine model of acute injury that results in impaired activation of hepatic GH-induced JAK/STAT signaling. Surgical trauma alone resulted in a transient, but significant reduction in hepatic JAK/STAT signaling. However, combined trauma and hemorrhage resulted in more severe hepatic GH resistance that was not reversed following resuscitation, similar to GH resistance observed in the ICU. We hypothesized that severe injury or critical illness results in a reduction of functional hepatic growth hormone receptors (GHRs), contributing to impaired activation of hepatic GH-induced JAK/STAT signaling. To test this, we subjected mice to surgical trauma, with or without hemorrhage, for up to 90 min and analyzed liver protein extracts by SDS-PAGE. Hepatic GHR abundance was unchanged following surgical trauma alone. However, surgical trauma followed by a 90 min hemorrhage period resulted in a significant decrease of hepatic GHR and the appearance of a lower molecular weight form of GHR that could not be tyrosine-phosphorylated in response to GH. Time-course studies further revealed that these changes became evident as early as 30 min after the onset of hemorrhage. These results suggest that hepatic GH resistance develops rapidly following injury via multiple mechanisms, including rapid alterations of GHR and at least one additional defect in the JAK/STAT signaling pathway.

Cuddapah, Vishnu

Project Length	Long
Prior Research Experience	Yes
Funding Source	
Advisor	Harald Sontheimer
Co-Author	Christa Whelan Habela
Title	Chloride channel regulation facilitates glioma cell proliferation

Abstract

Glioblastoma multiforme (GBM) is the most common and lethal primary brain cancer in adults, affecting nearly 5 per 100,000 people. This WHO Grade IV tumor is characterized by aggressively infiltrating cells that have enhanced proliferative capabilities, leading to a diffuse tumor mass that rapidly expands. The dispersion and proliferation of glioma cells is facilitated by the activity of several channels fluxing osmotically-active ions, aiding dynamic cell volume changes. Several studies have specifically implicated CIC-3, a voltage-gated chloride channel, in these processes, but the exact relationship between CIC-3 and glioma cell proliferation is not well understood. Using a combination of biophysical, biochemical, and imaging techniques, we demonstrate that CIC-3 activity is enhanced by CaMKII phosphorylation, facilitating glioma cell proliferation. Auto-activated CaMKII delivered to glioma cells via patch pipette led to a 3-fold activation of chloride currents, and this activation was completely inhibited when a specific CaMKII inhibitor was co-delivered. These chloride currents were specifically mediated by CIC-3, as knockdown of CIC-3 inhibited the CaMKII-mediated enhancement of chloride currents. This molecular interaction appears to be functionally significant, because CaMKII enhancement of CIC-3 currents facilitates glioma cell division. Glioma cells in M-phase have 3-fold elevated chloride currents as compared to interphase cells, and complete expression of these chloride currents is CaMKII-dependent. These enhanced chloride currents during M-phase correlate with cytoplasmic volume shrinkage in a process known as pre-mitotic condensation (PMC). During PMC, cells shed cytoplasmic water and salts to reach a preferred volume preceding division. Here we demonstrate that CaMKII inhibition significantly decreases the rate of PMC in glioma cells. Additionally, immunocytochemical staining of dividing glioma cells demonstrates robust colocalization of CIC-3 and CaMKII on the plasma membrane. To understand the clinical significance of this molecular interaction, we probed for CIC-3 expression in human Grade II – Grade IV patient biopsies. We found that Grade IV GBM tumors express 10-fold higher levels CIC-3 as compared to normal human brain and lower-grade gliomas, and this CIC-3 co-immunoprecipitates with CaMKII. Because calcium signaling is intrinsically associated with glioma proliferation and motility, CaMKII may be a link translating $[Ca^{2+}]_i$ elevations to an enhanced chloride conductance. Therefore, inhibition of calcium-sensitive activation of CIC-3 may lead to the development of better therapeutic strategies.

Davis, Brian

Project Length

Short

Prior Research Experience

No

Funding Source

NIH T35 Short Term Training Grant

Advisor

Tim Townes, PhD

Co-Authors

Chia-Wei Chang, PhD

Title

Construction of RPS19 Homologous Recombination Vector for Correction of Diamond-Blackfan Anemia

Abstract

Diamond-Blackfan Anemia (DBA) is an inherited anemia characterized by red blood cell aplasia, decreased erythroid progenitors, and congenital defects. DBA's pathophysiology is based on mutations of the ribosome—25% of DBA patients have mutations in the RPS19 gene, which encodes for a ribosomal subunit. RPS19 mutations follow an autosomal dominant inheritance pattern with variable penetrance. DBA patients often become dependent on blood transfusions within the first decade of life. The goal of this project was to design and construct a RPS19 homologous recombination vector based on the most common mutations in DBA patients. We created a vector with the wild type RPS19 5' arm and 3' arm flanking a pgk-hyg/Neo-kan marker for positive selection and the MCI-TK gene for negative selection. Polymerase chain reaction (PCR) was used to amplify 5' and 3' primers. The PCR product was then amplified in a TOPO vector in *Escherichia coli* cells. DNA sequencing confirmed no mutations in the RPS19 wild type exon sequences. Restriction enzyme assays were used to splice the PCR product from the TOPO vector into the homologous recombination vector and confirm the correct placement of the RPS19 5' and 3' arms in the homologous recombination vector. The RPS19 homologous recombination vector will have applications in DBA therapy. Specifically, the vector will be used to correct patient-specific induced pluripotent stem cells.

Deep, Nicholas

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Dr. Farrell O. Mendelsohn, Dr. Robert Bourge

Co-Authors

Title Ankle Brachial Index (ABI) as a predictor of PAD-specific outcomes in patients without revascularization

Abstract

Critical Limb Ischemia (CLI) is the most severe presentation of peripheral artery disease (PAD) in which there is extreme reduction of arterial circulation to skeletal muscle thereby threatening the viability of the limb. A large subset of CLI patients lack revascularization options despite advancements in percutaneous and surgical revascularization techniques. The advent of novel therapies such as stem-cell-induced angiogenesis call upon the need to establish a suitable marker that reliably predicts clinical outcomes in patients with severe PAD. The ankle-brachial index (ABI) is used to classify PAD severity and has been established as an overall predictor of mortality. The aim of the present study was to determine if ABI independently predicts amputation-free survival in patients without revascularization options.

Four previous trials involving this subset of patients with severe PAD were analyzed in a retrospective cohort fashion. A total of 35 patients (67±16 years, 24-males, 11-females, 11-diabetics) were selected based on specific eligibility criteria (ABI<0.5, Rutherford Category 4-5, non-revascularizable, etc.) The baseline ABI and 3-month follow-up ABI were compared with the primary end-point of amputation-free survival at one-year.

Of the 35 patients at one-year follow up, 6 patients had a major amputation and 29 patients salvaged their limb (83% amputation-free survival rate). Baseline ABI among the salvaged and amputee patients was 0.35±0.16 and 0.22±0.19, respectively (p=0.93). Average 3-month ABI among the salvaged and amputee patients was 0.46±0.24 and 0.17±0.18, respectively (p=0.98). Average change in ABI from baseline among the salvaged and amputee patients was +0.12 and -0.08, respectively (p=0.97).

In conclusion, this study found a numerical difference but not a statistically significant difference between the ABI values for salvaged and amputee patients. The study is limited by lack of statistical power due to the small patient population. Importantly, this study raises the question for the first time of whether ABI predicts amputation-free survival in patients with severe PAD. While ABI is an indirect measurement of blood perfusion through a limb it may or may not be sensitive enough to predict clinical outcomes in patients with the most severe forms of PAD. Statistical analysis on a larger data set is recommended.

Dizon, Brian

Project Length

Long

Prior Research Experience

Yes

Funding Source

NIH Medical Scientist Training Program Grant

Advisor

John Kearney

Co-Authors

Title

Modulation of Autoimmune Diabetes Development by B Lymphocytes Specific for N-acetyl-D-glucosamine

Abstract

Type I diabetes (T1D) is an autoimmune disease in which pancreatic beta cells are targeted for destruction by the immune system. B lymphocytes are found in the beta islet infiltrates of humans and NOD mice inflicted with autoimmune diabetes, and are critical for the development of disease. Exposure to certain bacteria, such as Group A Streptococci (GAS), during childhood is negatively correlated with T1D. Additionally, immune responses to GAS in mice and humans produce N-acetyl-D-glucosamine (GlcNAc) specific antibodies. Since GlcNAc-specific antibodies have potential autoreactivity to cell types expressing high levels of enzymes regulating O-GlcNAcylation, such as beta cells, we hypothesized that GlcNAc-specific B lymphocytes and their secreted antibodies have the capacity to modulate the development of autoimmune diabetes. To determine whether exposure to GAS could influence the development of autoimmune diabetes, NOD mice were immunized with GAS or control bacteria as neonates and monitored for hyperglycemia and glycosuria. NOD female mice immunized with GAS as neonates were protected from the spontaneous development of autoimmune diabetes. Moreover, sera from NOD mice immunized with GAS, as well as monoclonal GlcNAc-specific antibodies, protected WT NOD mice from diabetes, demonstrating a protective role for GlcNAc-specific antibodies. Finally, purified GlcNAc-specific antibodies prevented the activation, proliferation, and production of $TNF\alpha$ and $IFN\gamma$ by a diabetogenic T cell clone in vitro, suggesting that GlcNAc-specific antibodies prevented diabetes by inhibiting the presentation of peptides derived from beta cell antigens to diabetogenic CD4 T cells. These findings suggest that a B lymphocyte clone specific for O-GlcNAc, when activated by microorganism-associated antigens during neonatal development, protects against autoimmune diabetes by a mechanism dependent on secreted antibodies. These data identify a novel contribution and potential therapy in which autoreactive antibodies with the capacity to protect against T1D are generated upon exposure to GlcNAc-expressing microorganisms.

Dinsmore, Amanda

Project Length	Short
Prior Research Experience	No
Funding Source	Diabetes Research and Training Center
Advisor	Dr. Gerald McGwin
Co-Authors	W Rafferty, OD; P Lee, MD, JD; D Lobach, MD, PhD, MS; E Postel, MD; M Hunt; G McGwin, PhD
Title	Documentation of Stage of Retinopathy in Patients with Diabetes Mellitus Among Primary Eye Care Providers

Abstract

Vision loss due to diabetic retinopathy is the leading cause of new cases of blindness among adults in the United States. Though the American Diabetes Association recommends yearly dilated eye exams, it has been suggested that even with universal and routine eye care that diabetes related vision loss would continue. Despite extensive research into the field of diabetic retinopathy, there is little published data that provides insight into how it is being managed in community eye care practices. To address this issue, the current study abstracted and reviewed 741 patient charts (1,482 eyes) from the offices of 87 providers (43 optometrists and 44 general ophthalmologists) from practices across the southeastern United States. The charts were reviewed for both the frequency with which eye care providers documented the stage of diabetic retinopathy and, when stage was present, the concordance between the exam findings and the stage assigned. We found that providers failed to document the stage of retinopathy in 21% of eyes. In addition, among eyes with both stage and findings documented ($n = 945$), 71% had an appropriate match between findings and stage and 87% were close enough as not to significantly change care. In conclusion, there is significant room for improvement in the documentation of the severity of diabetic retinopathy.

Dobbin, Zachary C.

Project Length

Prior Research Experience Yes

FundingSource

Advisor Dr. Danny Welch

Co-Authors Benjamin Beck, Danny Welch

Title Development and characterization of kisspeptins for a novel metastatic breast cancer treatment

Abstract

In the treatment of patients with breast cancer, one of the biggest complications is the formation of metastases. While the 5-year survival rate approaches 100%, the development of metastases reduces the 5-year survival rate to 27%. Unfortunately, there are few curative treatment options for patients with metastases.

A cellular change that can lead to spread and colonization is down regulation of metastasis suppressor genes. When re-expressed in metastatic cancer cell lines, metastasis is suppressed while primary tumor growth is not. When the KISS1 metastasis suppressor is in breast and melanoma cells, they are unable to successfully form metastases.

KISS1 is secreted from cells and processed into smaller polypeptides, known as kisspeptins. The fact that the kisspeptins are generated extracellularly bodes well for KISS1 as an anti-metastatic agent. However, preclinical development requires additional knowledge of KISS1 processing and whether all kisspeptins are biologically active.

We hypothesize that some, but not all kisspeptins will have anti-metastasis activity. To test this, we will systematically mutate predicted processing sites in KISS1. By analyzing which kisspeptins are still made, we will be able to deduce the order in which KISS1 is processed. To complement the mutant analysis, cDNA encoding each possible kisspeptin will be cloned into an expression vector, transduced into tumor cells and assessed for anti-metastatic activity.

Upon completion, the data will provide insight necessary to move the proper kisspeptin toward more exhaustive preclinical testing.

Supported by **RO1-CA134981**, the National Foundation for Cancer Research, METAvivor, and UAB Med-into-Grad Fellowship and Susan G. Komen for the Cure

Donnithorne, Katherine

Project Length

Prior Research Experience	Yes
Funding Source	Cunningham Fellowship (Pediatrics)
Advisor	Timothy Beukelman
Co-Authors	Randy Q. Cron, Timothy Beukelman
Title	Effectiveness of TNF Inhibitors for JIA Categories Other Than Polyarthritis

Abstract

Background. Tumor necrosis factor alpha (TNF- α) inhibitors have been shown to be efficacious in the treatment of children with juvenile idiopathic arthritis (JIA) with polyarticular disease. Data regarding the effectiveness of TNF- α inhibitors for the treatment of other JIA phenotypes are sparse.

Objectives. To characterize the effectiveness of TNF- α inhibitors in all categories of JIA and to determine clinical predictors of quiescent disease one year following initiation of therapy.

Methods. A retrospective chart review was performed on children at one academic center with JIA who initiated TNF- α inhibitor treatment. Demographics and clinical data were obtained. Disease activity measures recorded for each visit included: Childhood Health Assessment Questionnaire (CHAQ) score, joints with active arthritis, erythrocyte sedimentation rate, physician global assessment of disease activity, and inactive disease status. The visit closest to 12 months after initiation of TNF- α inhibitors was assigned as the one-year follow-up visit. Comparisons between JIA phenotypes were made using chi-square tests. Predictors of clinical outcome at one year were determined using logistic regression models. Significant predictors were further analyzed using multiple variable regression.

Results. 125 patients began treatment with TNF- α inhibitors during the study, and 91 patients had one-year follow-up visits available for analysis. Diverse JIA phenotypes were represented: 32% had enthesitis, and 77% did not have active polyarthritis at the initiation of TNF- α inhibitors. Patients with the enthesitis-related arthritis (ERA) category were less likely to achieve inactive disease at one year compared to patients with rheumatoid factor negative polyarthritis. In multiple variable regression analysis, enthesitis and elevated CHAQ score were significant predictors of not achieving inactive disease.

Conclusion. TNF- α inhibitors appear to be less effective in patients with ERA and active enthesitis. Further study is needed for the effectiveness of TNF- α inhibitors with various JIA phenotypes and concerning the optimal treatment of enthesitis.

Doo, David

Project Length

Short

Prior Research Experience

Yes

Funding Source

NIH T35 Short Term Training Grant

Advisor

Clyde Guidry, PhD

Co-Authors

Jeff King

Title

IGFBP-3 is Degraded in Pig Vitreous in the Presence of Serum

Abstract

Insulin-like growth factors (IGF-I and -II) are potent growth factors with a wide distribution and variety of effects. Previous studies from this laboratory have determined that IGF-I and IGF-II drive cell proliferation and tractional force generation in at least two proliferative vitreoretinal disorders. IGFs are regulated through interaction with insulin-like growth factor binding proteins (IGFBPs) and IGFBP-3 is the most abundant IGFBP in human serum. The role of this binding protein in controlling vitreous IGF biological activity is unknown. The purpose of the current study was to examine whether IGFBP-3 is present in its intact form in the vitreous fluid of the eye using western ligand blots. With this method, proteins are separated in a gel based on size, transferred to nitrocellulose paper, and exposed to IGF-II bound to a chemiluminescent marker. If IGFBP-3 is present, it will bind IGF-II and a band will appear at approximately 46 kDa after exposure to film. We found that IGFBP-3 is present in vitreous in a truncated form when compared to serum. Mixing serum and vitreous together results in cleavage of the intact IGFBP-3 to the smaller form. However, purified IGFBP-3 does not degrade in the presence of pig vitreous alone, indicating that IGFBP-3 is actively degraded only when components from the serum and vitreous are present. The lack of intact IGFBP-3 in vitreous likely impacts the pathophysiology of eye diseases that are affected by IGF-I and IGF-II.

Doo, David

Project Length

Short

Prior Research Experience

Yes

Funding Source

Departmental or Mentor funds

Advisor

James Kimble, MD

Co-Authors

Ashley Dahl, MD

Title

Long-Term Follow-Up of Clinically Significant Macular Edema after Focal Laser Treatment

Abstract

Macular edema is a major cause of visual impairment and a common complication of diabetes, affecting an estimated 10% of diabetic patients during their lifetime. In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) Report Number 1 established guidelines for the treatment of Clinically Significant Macular Edema (CSME) with argon focal and grid laser. Since that time, studies employing ETDRS protocol have found stabilization or improvement of the visual acuity of patients with CSME after 1 to 5 years of follow-up, but there have been no studies examining how the ETDRS protocol influences long-term vision loss. The current study is an examination of long-term effects of argon laser treatment in patients with CSME. Thirty-three eyes from 22 unique patients were enrolled retrospectively from a large retina specialty practice where they had been evaluated and treated with focal argon laser according to strict ETDRS criteria by the same clinician at each follow-up visit. Patients were followed for a mean of 15.37 years and their change in Snellen visual acuity was documented over that time period. We found that when following the ETDRS protocol, the most significant predictor of vision loss was time since the initial diagnosis of CSME. Most patients retained reasonable visual acuity until late in the treatment course, with an average of 4 letters of Snellen acuity lost after 9 years and the steepest decline occurring between 9 and 12 years. Interestingly, there was no correlation between vision loss and the number of months with CSME present. These results suggest that focal argon laser treatment is effective at delaying significant vision loss for up to nine years, beyond which visual acuity tends to decline rapidly.

Elkhetali, Abdurahman

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	MSTP
Advisor	Kristina Visscher
Co-Authors	Kristina Visscher
Title	Examining Ongoing Activity in Retinotopically Mapped Occipital Cortex Using fMRI

Abstract

The brain is always active even in the absence of external stimuli; this is referred to as “ongoing activity.” A great deal of energy is used in sustaining ongoing activity even during rest, yet not much is known about its function. We hypothesize that ongoing activity plays a role in the perception and reaction to external stimuli. Specifically we will test the involvement of ongoing activity in sensory cortex during attention to and ignoring of external stimuli. In order to identify what areas within visual cortex show these effects, we will delineate the borders of visual areas using a method called retinotopic mapping.

To measure the relationship of ongoing neural activity to attention subjects will perform an auditory and a visual task while functional magnetic resonance images are acquired. The auditory task requires the discrimination of two successive sounds. The visual task requires the discrimination between two gray and white images. We will examine how the level of ongoing activity changes with task. We will also examine the relationship between the level of ongoing activity and stimulus-driven activity dependent on task.

Within the occipital cortex the visual sensory areas are retinotopically organized. Stimulating the retina will cause activation of the corresponding neurons in the cortex, which can be detected using fMRI. We use rotating wedges and expanding circles at .042 Hz for a total of ten cycles to cause cyclical activation of neurons and record the activation using fMRI. The retinotopic maps will be generated using the phase difference in neuronal activation.

The study is currently in the recruitment and data collecting stage. Retinotopic maps were successfully generated for the data we have collected. Further analysis and conclusions will be made after acquiring data from more participants.

Elsamadicy, Emad

Project Length Short

Prior Research Experience Yes

Funding Source Diabetes Research and Training Center

Advisor Louis H. Philipson (University of Chicago)

Co-Authors Jacqueline Torres, Natalia A. Tamarina, Sindhu Rajan, and Louis H Philipson

Title Expression of NADPH oxidase(s) and Voltage-Gated Proton Channel cDNAs in MIN6 Insulinoma Cells

Abstract

NADPH oxidase (NOX) is a significant source of glucose-stimulated reactive oxygen species (ROS) generation in insulin secreting pancreatic beta cells via protein kinase C activation. The formation of H₂O₂ and O₂⁻ can inhibit insulin secretion and affect beta cell survival. In phagocytic cells, voltage-gated proton channels (Hv1) closely interact with the electrogenic NADPH oxidases in order to provide charge compensation. We previously found that Hv1 channels, when expressed in both MIN6 insulinoma and primary β -cells, were largely localized to insulin granules. Here we investigated whether any of the NADPH oxidase isoforms (Nox1, Nox2, and Nox4) were present in insulin granules. To test this hypothesis, we transfected GFP tagged Nox1, Nox2, and Nox4 constructs in human embryonic kidney cells (HEK) and MIN6 cells and used confocal imaging and immunohistochemistry to determine their subcellular localization. We found that in HEK cells, Nox2 was well-expressed in the plasma membrane, whereas Nox1 was found to be predominantly intracellular. In MIN6 cells, both Nox1-GFP and Nox2-GFP appeared to be intracellular. A similar localization pattern was observed via immunofluorescence when HA tagged Nox1 and Nox2 (HA at the NH₂-terminii) were expressed in MIN6 cells. In contrast, the Nox4-GFP construct expressed in MIN6 cells was found to be colocalized with insulin to insulin- mCherry granules. Additionally, when co-transfected with a plasmid designed to express Hv1-mCherry we found that most of the labeled granules containing Nox4-GFP also expressed Hv1-mCherry channels. This result suggests that Nox4, together with the proton channel Hv1 is present in insulin granule membranes. They may play a role in insulin granule formation, trafficking or exocytosis. Further studies are required to investigate the expression and interactions of Nox4 and Hv1 in insulin granules in pancreatic beta cells, and determine whether they are antigens in type 1 diabetes as are other granule proteins such as ZnT8.

Flowers, Grace Powell

Project Length Short

Prior Research Experience No

Funding Source NIH T35 Short Term Training Grant

Advisor Dr. Vera Bittner

Co-Authors

Title The impact of depression on cardiac rehab outcomes in ischemic heart disease patients.

Abstract

BACKGROUND: Patients reporting depression have been shown to have a significantly increased risk for the development of CVD, as well as poorer treatment outcomes when compared to non-depressed patients. Cardiac rehabilitation (CR) is an important secondary preventive treatment for patients with diagnosed cardiovascular disease (CVD). This study was designed to evaluate the impact of depressive symptoms (measured by Beck Depression Inventory) on treatment outcomes in the CR setting.

METHODS: Using a dataset of patients with ischemic heart disease who completed CR, comparisons were made between “depressed” (BDI \geq 14) and “non-depressed” (BDI $<$ 14) patients for baseline characteristics, changes in selected measures during CR, proportion of patients at secondary prevention treatment goals before and after CR, and the proportion of patients initially enrolled in CR who completed the program. The two groups were compared by ANOVA and chi-square testing as appropriate. Drop-out rates were calculated as the proportion of CR enrollees who completed stratified by BDI score.

RESULTS: The study began with 1200 patients in the database, with an average age of 51. 63.4% of the patients were white, and 69.3% were men. Before calculating and excluding non-completers, there were 322 “depressed” patients, and 878 “non-depressed”. The depressed group had higher drop-out rates, at 60.2%, than the non-depressed group, at 37.7% (p $<$ 0.0001). At baseline, depressed patients had higher body mass indexes, larger waist circumferences, poorer lipid profiles, higher HbA1c (when diabetes was present), shorter 6-min walk distances, poorer diet scores, and higher comorbidity index scores (all p $<$ 0.05). At CR completion, both depressed and non-depressed patients improved among all measures; however, non-depressed showed greater improvements (p $<$.05) than depressed patients in HbA1c levels, as well as in both the mental component and the physical component to the short-form outcomes study questionnaires (all p $<$ 0.001).

CONCLUSIONS: CR patients with higher BDI scores entered CR with greater risk factor and comorbidity burden than non-depressed patients and were more likely to drop-out before CR completion. Among CR completers, both depressed and non-depressed groups exhibited significant improvements, but the degree of improved was less in depressed patients. Depression is an important predictor of CR success.

Foster, Christy

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Ken McCormick, MD

Co-Authors Xudong Wang

Title Cortisol increases hepatic gluconeogenesis by altering the reduced pyridine nucleotide and glucose-6-phosphate dehydrogenase

Abstract

This study explored the possible role of adrenal hexose-6-phosphate dehydrogenase (H6PDH) in providing reducing equivalents to P450 cytochrome enzymes in the endoplasmic reticulum(ER). This enzyme exists in the microsome, and co-localize with the bidirectional enzyme 11 β -HSD1 which converts cortisone to cortisol. Given this spatial interaction with 11 β -HSD1, H6PDH provides 11 β -HSD1 with NADPH to activate glucocorticoids in hepatic and adipose tissue. Within cells, two sources provide NADPH, cytosolic glucose-6-phosphate dehydrogenase and microsomal H6PDH. Because pyridine nucleotides cannot transverse ER membrane, other NADPH-requiring enzymes therein may rely on H6PDH. Our study examined whether H6PDH generates pyridine nucleotides for other ER enzymes (e.g.-P450 enzymes).

The first unresolved issue was whether purified glucose-6-phosphate dehydrogenase reacts with diverse phosphoester hexoses as substrate. Using a radioisotopic assay, the amount of NADPH generated is stoichiometrically equivalent to the reacted substrate. There was significant NADPH produced when glucose-6-phosphate (G6P) was provided but not with other phosphoester hexoses, fructose-6-phosphate (F6P) and glucosamine-6-phosphate (Gln-6-P). This data indicated glucose-6-phosphate dehydrogenase reacts solely with G6P.

Another aspect of the project involved 21-hydroxylase, a pivotal P450 enzyme within the ER. Rat adrenal microsomes were tested with radiolabeled 17OH-progesterone as substrate, and 11-deoxycortisol, the product, was quantified to indicate NADPH production. 11-deoxycortisol increased when G6P, F6P and Gln-6-P were added to the microsomes-only possible with H6PDH, not glucose-6-phosphate dehydrogenase. DHEA, an inhibitor of glucose-6-phosphate dehydrogenase, had no effect on the G6P produced- further suggesting that H6PDH provides NADPH.

Finally, adrenal 17-hydroxylase, another P450 cytochrome enzyme in the ER, was assayed using the same three substrates. The product, 17-hydroxyprogesterone, was increased with each substrate. This strengthens evidence that H6PDH is the source of NADPH.

In conclusion, microsomal P450 enzymes exploit NADPH generated from H6PDH and not cytosolic glucose-6-phosphate dehydrogenase, buttressing the kinetic importance of this enzyme. Further studies will address the hormonal regulation of H6PDH.

Gaston, David

Project Length	Long term (>1 year)
Prior Research Experience	Yes
Source of Funding	Non-UAB Funding (External Funding Source)
Faculty Advisor	Jacqueline Nuss Parker, PhD
Co-Authors	Carl Odom
Title	A Conditionally-Replicating HSV-1 Vector Expressing IL-15 for Glioma Therapy

Abstract

Conditionally replication-competent oncolytic herpes simplex type-1 viral vectors (oHSV) are promising therapeutic agents for malignant glioma. oHSV vectors lyse infected glioma cells through their replicative cycle, and can be engineered to promote anti-tumor immune responses through the expression of immunostimulatory cytokines. Microarray data from a recent Phase Ib clinical trial of the oHSV G207 found increased transcript levels of interleukin (IL)-15 and all receptors necessary for optimal IL-15 signalling in patients surviving 6 months following G207 therapy. Transcripts indicating presence and cytotoxic activity of natural killer (NK) cells, which are potentially activated by IL-15, were also higher in these patients. These results suggest IL-15 activated NK cells may have contributed to patient survival, and led to the hypothesis that IL-15 expressed from an oHSV vector may promote glioma size reduction or clearance by increasing recruitment and activation of NK cells in gliomas. To investigate this hypothesis a murine (m)IL-15 expressing oHSV vector, Jm150, was constructed. Jm150 was found to replicate equally well as a parental non-IL-15 encoding vector *in vitro*, and determined to produce physiologically relevant levels of mIL-15 in multiple cell lines, including the human glioma line D54-MG. Following establishment of flank D54-MG tumors in athymic nude mice, tumors treated with Jm150 demonstrated a trend of growth reduction as compared to tumors treated with a parental oHSV vector. Viral recovery from Jm150 infected tumors was similar to recovery from tumors infected with parental oHSV. Importantly, increased infiltration of CD45⁺ CD49b⁺ NK cells was associated with this growth reduction in Jm150 treated tumors. These results suggest virally produced mIL-15 lead to increased infiltration of NK cells, which may have contributed to growth restriction of the tumors. Although preliminary, these results warrant further studies investigating the role of NK cells activated by oHSV produced IL-15 in anti-glioma immune responses.

Gladden, James

Project Length Long term (>1 year)

Prior Research Experience Yes

Source of Funding MSTP

Faculty Advisor Louis Dell'Italia

Co-Authors

Title Left Ventricular and Bioenergetic Dysfunction in Acute VO is Mediated by Stretch-Induced Cardiomyocyte XO Activation

Abstract

Background: There is no effective medical therapy to prevent progressive cardiac remodeling and failure in chronic volume overload states. We previously demonstrated upregulation of xanthine oxidase (XO) in the myocardium of volume overloaded mitral regurgitation patients accompanied by increased oxidative stress; however a causative association between these findings and disease progression has not been established. In the current investigation we hypothesized myocardial stretch induces XO activity and inhibition of XO would prevent progressive remodeling and preserve cardiac function in chronic volume overload in the rat.

Methods: Age-Weight matched Sprague-Dawley rats were randomized to either Sham or aortocaval fistula (ACF) ± allopurinol, (n=7 per group). Allopurinol (100 mg/kg/day) was delivered in standard chow. Echocardiography was performed at 8-weeks post induction of ACF. Additionally, cardiomyocytes were isolated and subjected to bioenergetics studies using the Seahorse cell flux analyzer. Cardiomyocytes were also stretched on a silicone membrane at 5% strain for 3 hours and treated with either allopurinol or Mito Q.

Results: Left ventricular (LV) end-diastolic dimensions were significantly increased in both ACF groups as compared to Sham. LV end-systolic dimension, a critical marker of adverse remodeling was increased in untreated ACF vs. Sham, however this increase was attenuated in ACF+allopurinol group. LV ejection fraction, fractional shortening, and velocity of circumferential shortening were all significantly depressed in the untreated ACF as compared to Sham, however these indexes of LV function did not differ significantly from Sham in the ACF+allopurinol group. Stretched cardiomyocytes demonstrate increased XO activity associated with myofibrillar degeneration and mitochondrial swelling both of which are prevented by either allopurinol or mitochondrially targeted Mito Q.

Conclusions: Stretch induces XO activity in volume overload by a mitochondrial oxidant dependent pathway. XO inhibition with allopurinol attenuates adverse LV remodeling and preserves LV function in the chronic volume overload of ACF in rats. Inhibition of XO may provide a novel strategy for treatment of chronic volume overload states such as MR in humans.

Griffin, Drees Jr

Project Length Short

Prior Research Experience Yes

Funding Source Non-UAB Funding (External Funding Source)

Advisor Marisa B. Marques, MD

Co-Authors Zayd L. Al-Nouri, Darrshini Muthurajah, John R. Ross, Riley B. Ballard, Deirdra Terrell, Sara K. Vesely, James N. George, Marisa B. Marques

Title First symptoms and timing of presentation in acute idiopathic thrombotic thrombocytopenic purpura

Abstract

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Although TTP is a heterogeneous syndrome, we focused on idiopathic TTP patients. ADAMTS13 metalloprotease deficiency, present in approximately half of patients with idiopathic TTP, allows unusually large multimers of von Willebrand factor to enter circulation and to cause thrombosis. Therapeutic plasma exchange (TPE) cures TTP patients by replacing the deficient enzyme and improves survival from 10% to 80%. A systematic review of the literature failed to identify a study that explored the clinical symptoms that occur in the month preceding an acute episode of idiopathic TTP. The Oklahoma TTP-Hemolytic Uremic Syndrome (HUS) Registry provided the model for this research. Objective: In this study, we used patient histories from a cohort of patients seen at UAB and at Oklahoma to determine the first symptom experienced by each patient and the time that it occurred in relation to diagnosis (defined by the first TPE). Methods: We conducted a retrospective chart review of patients seen at the two centers from January 1, 2007 to June 30, 2010. We excluded patients who had apparent etiologies or associated conditions. Results: 49 patients reported 27 different first symptoms. Of those, many were nonspecific complaints such as altered mental status or malaise. 40.8% of first symptoms were neurological in nature and 26.5% were gastrointestinal. The median time to treatment from the onset of symptoms was 5 days. The median ADAMTS13 activity was 4. Significance & Conclusions: Our data confirms the heterogeneity of presentation and nonspecific nature of symptoms for TTP. Physician education and vigilance is necessary because TTP presents in a variety of ways. TPE must begin promptly as patients may not present immediately upon the onset of symptoms.

Griffith, Zachary

Project Length Short

Prior Research Experience yes

Funding Source CaRES

Advisor Andrey Frolov

Co-Authors Drew Gunnells, Lilian C Azih, J. Pablo Arnoletti and

Title A Novel Humanized Monoclonal Anti-ErbB3 Receptor Antibody (MM-121) Slows Tumor Growth and Reduces Ligand-Activated Intracellular Signaling in Murine Model of Pancreatic Cancer.

Abstract

Overexpression and aberrant activation of the ErbB tyrosine kinase receptor family promotes tumorigenesis and confers resistance to small molecular inhibitors such as gefitinib and erlotinib in several adenocarcinomas. We have previously demonstrated that ErbB3 influences pancreatic cancer cell response to EGFR inhibition with erlotinib. Activation of the ErbB3 receptor by its ligand, neuregulin 1 (NRG1), causes receptor phosphorylation and subsequent activation of the AKT pathway leading to proliferation of cancer cells. MM121 is a fully human monoclonal antibody that targets the ErbB3 receptor and blocks its phosphorylation, and thus reduces activation of downstream cytoplasmic proteins important to tumor growth. In this study, we assessed MM-121's efficacy as an in vivo inhibitor of tumor growth in murine pancreatic adenocarcinoma xenografts. Tumor measurements showed that MM121 administered as a sole agent does significantly inhibit tumor growth in the animal model. We subsequently interrogated cellular signaling pathways of the tumor tissue in an attempt to explain the molecular mechanisms inhibiting tumor growth. Western blotting analysis of tumor tissue revealed that pancreatic adenocarcinoma xenografts treated with MM-121 had lowered basal levels of phospho-EGFR, phospho-ERK 1/2 and phospho-AKT. In addition, our early results found that treatment with MM-121 may also reduce the expression of the ErbB3 receptor. Thus, these results suggest that MM-121 could be an effective addition to the future chemotherapeutic regimen for pancreatic adenocarcinoma.

Grochowsky, Angela

Project Length Short

Prior Research Experience Yes

Funding Source Diabetes Research and Training Center

Advisor Dr. Edward Lose and Dr. Nathaniel Robin

Co-Authors Dr. Edward Lose and Dr. Nathaniel Robin

Title Adult Down syndrome population shows a reduced prevalence of Type 2 Diabetes Mellitus when compared to the general population

Abstract

It is well known that there is a correlation between excess body weight and Type 2 diabetes. Approximately 90% of Type 2 diabetes is accredited to excess body weight (Hossain et al, 2007, *NEJM*). It is also known that the Down syndrome (DS) population is prone to the development of obesity with 58% of DS males and 83% of DS females being categorized as overweight and obese (Bell et al, 1992, *J. Intellect. Disabil. Res.*) To date no study has examined the prevalence of Type 2 diabetes in the DS population. Interestingly, clinical observation has suggested there is a decreased prevalence of Type 2 diabetes among the DS population. We hypothesize that DS is associated with a decreased risk for Type 2 diabetes. 129 patients from the Adult Down Syndrome Clinic at UAB (ADSC) were selected for review. 17 patients were excluded due to being under the age of 20. From the remaining 112 charts, the following data was collected: race, sex, dates of evaluation and lab work, height, weight, serum glucose value, and whether the glucose value was non-fasting or fasting. Of the 112 charts, 48 have complete data. Based on recent data from the American Diabetes Association, the predicted number of Type 2 diabetics from the evaluated patients would be 12, however only 3 DS individuals in our population are diagnosed as Type 2 diabetics and 9 suggest possible glucose intolerance based upon a single glucose measurement. Our preliminary findings support our hypothesis and indicate a reduced prevalence of Type 2 diabetes in DS patients. Although the protective factor(s) associated with DS are unknown, potential candidates range from genetic to environmental factors. We are planning on expanding our study to additional DS centers and to compare our DS patients to patients in the CARDIA study.

Gunnells, Drew

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Andrey Frolov
Co-Authors	Zach Griffeth
Title	New Potential Combination Therapy for Pancreatic Cancer

Abstract:

ErbB3, a member of the epidermal growth factor receptor family, has recently been found to critically affect tumor progression for pancreatic adenocarcinoma, specifically in epidermal growth factor receptor (EGFR) signaling. Initially ErbB3 was discounted due to its lack of tyrosine kinase activity. However, it has been demonstrated that ErbB3 preferentially heterodimerizes with EGFR. Moreover, a high expression of ErbB3 and an overexpression of an ErbB3 ligand, neuregulin (NRG1- β), directly correlates with a worse pancreatic cancer clinical prognosis. The expression of ErbB3 also influences the sensitivity of anti-EGFR therapy. Erlotinib, an EGFR targeted tyrosine kinase inhibitor (TKI), is currently the only approved anti-EGFR approved therapy. MM-121 is an experimental fully human IgG2 monoclonal antibody (mAB) that binds to ErbB3 and blocks NRG1- β from binding to ErbB3. We have shown that MM-121 in combination with Erlotinib inhibits both ErbB3 and EGFR signaling *in vitro*. In this study we examined the efficacy of MM-121 and Erlotinib in tumor bearing mice. The goal was to determine the effectiveness of combination therapy vs. monotherapy *in vivo*. In completing the first part of this study, we performed a murine clinical trial testing monotherapy with different dosages of each drug. The animals were treated for 28 days then sacrificed and the tumors excised. To demonstrate the molecular effects of the drugs Western blots were performed for total EGFR, ErbB3, and Erk/Akt vs. phospho (p)-EGFR, p-ErbB3, and p-Erk/Akt. MM-121 and Erlotinib as single therapies slowed tumor growth across all dosages compared to the control. The suboptimal dosing for MM-121 was found to be between 75-150 $\mu\text{g}/100\mu\text{L}$ and between 25-50 $\mu\text{g}/100\mu\text{L}$ for Erlotinib. These dosages will be used in the next phase of our study that will test combination therapy.

Guzman Karlsson, Mikael

Project Length Long Term

Prior Research Experience Yes

Funding Source MSTP

Advisor J. David Sweatt

Co-Authors Mercy Kibe, Jeremy Day, J. David Sweatt

Title The Role of Epigenetic Modifications in Reward-Related Behavior

Abstract

The ability to create associations between environmental stimuli and rewards is the foundation for adaptive behavior. However, such stimuli-reward associations can sometimes exceed their adaptive benefit and instead result in pathological states such as drug abuse and addiction. Previous research suggests that the encoding of stimuli-reward associations is dependent upon dopaminergic signaling within the nucleus accumbens (NAc). Activation of dopamine receptors in the NAc initiates a series of intracellular signaling cascades that culminate in an array of epigenetic modifications such as DNA methylation and histone acetylation. Although such epigenetic modifications have long been associated with cell differentiation and development, recent studies have also implicated epigenetic mechanisms in various forms of learning and long-term behavioral change. However, the role of epigenetic modifications in stimuli-reward learning has yet to be investigated. Additionally, it is unclear how learning-related modifications differ from those induced by drug administration. Our central hypothesis is that both drug administration and reward-related learning induce distinct and behaviorally relevant epigenetic modifications in the NAc. To examine the role of epigenetic modifications in reward-related learning, food-deprived rats were behaviorally conditioned to associate the presentation of a tone with the delivery of a food reward. NAc tissue samples were collected following the 1st, 3rd, or 5th day of training, allowing for a complete investigation of epigenetic modifications associated with different stages of learning. In a second experiment, histone modifications induced by cocaine administration (20mg/kg, IP) were examined at different time points following drug injection. Preliminary data indicates that exposure to the conditioning paradigm itself resulted in a robust decrease in DNA methylation of an immediate early gene (*Arc*, activity-regulated cytoskeleton-associated protein) that is associated with synaptic plasticity and learning. Furthermore, cocaine administration also induced a similar decrease in *Arc* methylation. In contrast, cocaine delivery (but not the learning experience) resulted in time-dependent alterations in two histone modifications that are associated with transcriptional activation. These findings indicate that drugs of abuse and reward experiences trigger epigenetic modifications in the NAc.

Hadley, Jennifer

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Harald Sontheimer
Co-Authors	Chris Chapleau, Susan Campbell
Title	Organotypic Brain Slices as a Model of Glioma Invasion

Abstract

Gliomas are the most common primary brain tumors, and have a uniformly poor prognosis. While they rarely metastasize, they are highly invasive and can spread diffusely throughout the brain, making them impossible to completely resect. Previous work has suggested that the biophysical and biochemical changes that permit glioma cells to invade surrounding brain may also be responsible for the generation of seizures, a common side effect of gliomas. To better understand the effects of invasion on healthy brain tissue, we cultured glioma cells with organotypic brain slice cultures.

Brains were removed from 3- to 7-day old rats and coronal slices were prepared using a microslicer. The slices were then grown in culture for 4 days, at which time slice viability was verified through visual inspection using DIC microscopy and by recording evoked field potential responses from the hippocampal and cortical regions. GFP-labeled glioma (D54) cells were seeded onto the slices and the co-culture was incubated for 7 days. Slices were then fixed in paraformaldehyde and stained immunohistochemically with a fluorescent antibody to GFAP, so that the invasion of glioma cells into the cultured slice could be evaluated. Further studies will reveal the electrophysiological changes induced in the organotypic slices by the invading glioma cells.

Hammond, John

Project Length	Long
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Robert McCullumsmith, MD PhD
Co-Authors	Robert McCullumsmith, Adam Funk, Vahram Haroutunian, James Meador-Woodruff
Title	Evidence for Abnormal Forward Trafficking of AMPA Receptors in Frontal Cortex in Schizophrenia

Abstract

Endosomal trafficking of AMPA receptors may facilitate changes in synaptic strength, surface expression, and localization of receptors to the synapse. There is a growing body of evidence that alterations in trafficking of AMPA receptors may underlie the pathophysiology of schizophrenia.

Receptors expressed on the cell surface may be endocytosed, a process which involves formation of a clathrin-coated pit, enveloping of the plasma membrane, and closing of the involved membrane upon itself to form of an endosomal vesicle. These endosomes and the receptors located within may be recycled to the plasma membrane or targeted for degradation. Turnover of receptors in the plasma membrane is a critical event for regulation of neuronal transmission at the synapse in limbic circuits implicated in schizophrenia. We hypothesize that alterations in endosome content may underlie neuropathological alterations in schizophrenia. In particular, we hypothesize that there is an increase in AMPA receptors contained in early endosomes in schizophrenia, suggesting increased turnover of AMPA receptors in this illness. The aim of this study is to isolate the early endosomes from postmortem human brain tissue, and to use a modified subcellular fractionation technique to probe for alterations in endosome content and AMPA receptor subunit expression. Tissue from human frontal cortex was homogenized and stored at -80 C until used. The tissue was pre-cleared of non-specific binding via incubation with magnetic beads. Using this pre-cleared tissue homogenate, we then targeted endosomes for immunoprecipitation using a magnetic bead-antibody complex (specific binding) or using magnetic beads only (negative control). Captured material was removed from the beads and analyzed by Western blot analysis. Markers for early endosomes (Early Endosome Antigen 1) were detected by Western blot in the pre-clear pellet (non-specific binding) and in the immunoprecipitation (specific binding) lanes, but not in the negative control lane. As confirmation of endosomal isolation, electron microscopy (EM) imaging was used. Enrichment of endosomes in the immunoprecipitation (specific binding) sample over the pre-clear (non-specific) and negative control samples was confirmed with double-blinded evaluation of EM imaged beads. In the negative control, no endosomes were observed (n=56 beads), confirming that our preclear step eliminated non-specific binding. In beads from the pre-clear (non-specific) pellet, there were 0.045 endosomes per bead (n=890 beads). In the immunoprecipitation (specific binding) pellet, there were 0.28 endosomes per bead (n=560 beads), a 6.15 fold enrichment of endosomes in the immunoprecipitation (specific binding) sample compared to the pre-clear (non-specific) pellet sample. We have further examined the contents of these early endosomes by Western blot. We found no significant difference in total EEA1 expression between schizophrenia and control samples. Relative to EEA1 expression in the same lane, we found a significant increase in GluR1, but not GluR2 or GluR3, in the isolated early endosome fraction in subjects with schizophrenia. Further analyses revealed that patients off medication for greater than 6 weeks prior to death had significantly more GluR1 expression relative to EEA1 expression than the comparison group and patients on medication. In summary, we have developed a modified immunoprecipitation protocol to isolate early endosomes from postmortem tissue. Using this technique we found changes in the level of GluR1 expression in early endosomes of subjects with schizophrenia. Understanding the importance of endosomes in the trafficking of AMPA receptor from the synapse may identify novel deficits involved in the pathophysiology of schizophrenia.

Harbin, Lindsay

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental and Mentor Funds
Advisor	Randall Q. Cron
Co-Authors	Mingce Zhang, M.D. and Randall Q. Cron
Title	Does FoxP3 Inhibit or Promote HIV-1 Infection in CD4+ T regulatory Cells?

Abstract

Recently, it has been described that FoxP3, a transcriptional factor found in human CD4+ T-Regulatory Cells, may inhibit infection of primary Human CD4+ T-regulatory cells by inhibition of HIV-LTR promoter activity [1]. In addition, it was found that FoxP3 positive cells have the potential to inhibit infection of FoxP3 negative cells[1]. However, the opposite result has also been shown: that FoxP3 may be a transcription factor responsible for increased infection of CD4+ T regulatory cells[1]. While the original goal of my research was to determine the mechanism by which FoxP3 positive cells inhibit infection of FoxP3 negative cells, my early results seem to support the fact that FoxP3 may increase HIV-LTR activity. Early experiments include generating several truncated expression vectors using FoxP3 and the FoxP3 mutants: Δ FKH, Znf/Zip, and FKH as well as lentiviral expression vectors. In addition, we co-transfected the 293 T Cell line with the truncated expression vectors and the HIV-1 LTR and the lentiviral vectors and the HIV-LTR. Preliminary results via flow cytometry showed an increased infection of the 293 T cells by HIV. While the preliminary results do not seem to support the original hypothesis, we believe that it cannot be ruled out because there may be some discrepancies between the 293 T Cell line and the Human CD4+ T regulatory cells that we plan to use in later experiments. We believe that the human CD4+ T regulatory cells will be more representative and may still show decreased infection of CD4+ T regulatory cells by HIV in the presence of FoxP3, pending future experiments.

Harris, Shaundra

Project Length Short
Prior Research Experience Yes
Funding Source NIH T-35 Training Grant
Advisor Dr. Timothy Townes

Co-Authors

Title: Generation of a Patient-Specific Construct to Correct the Sickle Cell Anemia Mutation in Induced Pluripotent Stem (iPS) Cells

The results of sickle cell disease can be devastating--strokes, renal failure, and splenic infarction are just a few of the consequences of a point mutation in the human β -globin gene. The disease is autosomal recessive and is most common in the African American population. The A to T point mutation in the 6th codon of the beta-gene causes a sickle-fiber accumulation in human red blood cells.

Recently, iPS cells have been shown to effectively cure sickle cell anemia in humanized mice. The iPS cells derived from human skin fibroblasts form teratomas when injected into immunodeficient NOD/scid/ mice. In the case of sickle cell anemia, the mutation in the β -globin gene will be corrected and in vitro differentiated into hematopoietic stem cells (HSC) for transplant to cure the disease. Previously the correction construct was done using human genome DNA from a bacterial artificial chromosome (BAC). This corrected the sickle mutation in ips cells derived from sickle patients, but with relatively low efficiency.

We hypothesized that a patient specific correction construct would increase the homologous recombination efficiency in the ips cells dramatically. DNA purified from a sickle cell patient donor was used for this project. To create the targeting construct, the sickle mutation had to be corrected by mega primer Polymerase Chain Reaction (PCR). This was done by amplifying the 5' homology sequence without the mutation by mega primer PCR. The 3' homologous sequence was generated with regular PCR. The construct contains pGK/Neo and pGK/TK cassettes inserted into intron 1 of the β -globin gene as positive and negative controls, respectively. Unfortunately, the construct was not completed before the end of the summer.

Hatch, Neal

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. Bradford Woodworth
Co-Authors	Dr. Bradford Woodworth
Title	Resveratrol inhibits LPS-induced IL-8 secretion <i>in vitro</i> : implications for chronic rhinosinusitis

Abstract

Objective/Hypothesis: Conventional interventions for the inflammation associated with chronic rhinosinusitis (CRS) have been limited by the deleterious side effects of steroids. Safer, alternative compounds with similar anti-inflammatory activity could provide significant therapeutic advantages in this regard. The objectives of the present study were to investigate whether the natural polyphenol resveratrol inhibits LPS-induced IL-8 secretion and examine its effects when compared to topical nasal steroids *in vitro*.

Methods: Lipopolysaccharide (100 ng/ml) was administered to the apical surface of well characterized murine nasal septal (MNSE) and human sinonasal epithelial (HSNE) cultures. Resveratrol (100, 200, 500 μ M), fluticasone propionate, budesonide, triamcinolone acetonide, and ciclesonide were co-incubated with LPS. The basal media of the cultures were collected and analyzed using the mouse CXCL1/KC (functional homolog of human IL-8) and human CXCL8/IL-8 immunoassays.

Results: Resveratrol significantly decreased LPS-induced KC (functional homolog of human IL-8) secretion in a dose-dependent fashion (pg/ml) in MNSE [500 μ M: 16 \pm 22 pg/ml, 200 μ M: 94 \pm 16pg/ml, 100 μ M: 181 \pm 39pg/ml, 10 μ M: 1183 \pm 67pg/ml vs. 1196 \pm 355pg/ml (LPS control); $p < 0.05$]. Anti-inflammatory effects with 500 μ M resveratrol were consistent in HSNE [161 \pm 80pg/ml vs. 1017 \pm 316pg/ml (control); $p < 0.05$]. Resveratrol robustly abrogated KC/IL-8 secretion when compared to fluticasone propionate [65 \pm 47pg/ml], budesonide [742 \pm 428pg/ml], triamcinolone acetonide [561 \pm 124pg/ml], and ciclesonide [765 \pm 139pg/ml]; $p < 0.05$. Resveratrol did not induce cell death at the doses tested according to live-dead assays.

Conclusion: These *in vitro* findings indicate resveratrol is a robust topical anti-inflammatory with stronger effects on LPS induced KC secretion than most topical steroids. Given resveratrol's excellent safety track record, further exploration of this compound as a topical anti-inflammatory for CRS and other inflammatory diseases of the airway are warranted.

Hendrixson, Taylor

Project Length Short

Prior Research Experience No

Funding Source T-35 Short Term Training Grant

Advisor David Kimberlin

Co-Authors Penelope Jester, David Kimberlin, Zhiying You

Title Data Verification and Regulatory Oversight of an ongoing National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) Placebo-Controlled Investigation of Pleconaril for the Treatment of Neonatal Enteroviral Sepsis Syndrome

Abstract:

Background. A double-blind, placebo-controlled efficacy trial of pleconaril in the treatment of neonatal enteroviral sepsis syndrome has been conducted by CASG from 1999 to the present. The primary endpoints of the study seek to test the virological and clinical efficacy, safety, and pharmacokinetics of pleconaril in infants with neonatal enteroviral sepsis syndrome. Subjects are eligible for enrollment in the study if they present at ≤ 15 days of age with suspected enteroviral sepsis accompanied by evidence of liver involvement, disseminated intravascular coagulopathy, and/or myocarditis. A total of 59 subjects have been enrolled by August 2010. Although efficacy analysis cannot be initiated, data verification and general safety reviews have begun. Case record forms (CRF) were designed and provided to each participating study center for recording required data. CRFs underwent double data entry by CASG data personnel into the study database.

Methods. Two independent reviewers verified printouts from the database by comparing them to the original CRFs. Inconsistencies between CRFs and the database were flagged by reviewers and queried by the data manager. Additionally, a review of all SAE data was undertaken, and a summary of the SAE implemented. An event was determined to be an SAE by the existing criteria from the Division of AIDS (DAIDS) toxicity table for the grading of adverse events in pediatric patients. Reported SAEs were then classified by organ system according to standard categories provided by NIAID

Results. 59 CRFs were reviewed and verified against the database. Discrepancies were flagged and queried. SAEs were summarized and classified according to the study institution at which they occurred, the body system affected, and the severity. Of the 59 subjects enrolled in the study, 37 subjects experienced a total of 67 SAEs of which 16 resulted in death of the subject.

Conclusions. Large-scale multi-institution studies require strict regulation and oversight to maintain quality and safety of the study. Stringent data verification procedures ensure the quality of the results and maintain the integrity of current medical knowledge. Safety monitoring is a complex process involving different grading/staging systems of events that guarantee the safety of subjects.

Hixon, Brian

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Dr. Brad Woodworth

Co-Authors Dr. Eric Sorscher, Shaoyan Zhang, Daniel Skinner

Title LPS and *Pseudomonas Aeruginosa* Filtrate Reduce Calcium Activated Chloride Channel Transport in Primary Sinonasal Epithelial Cultures

Abstract

Background: The cystic fibrosis transmembrane conductance regulator (CFTR) represents the predominant Cl⁻ transport conduit within respiratory epithelial cells. Activation of secondary Cl⁻ transport pathways through calcium-activated chloride channels (CaCCs) provides a potential mechanism to circumvent CF-related airway defects in mucus clearance. The Cl⁻ channel TMEM16A has recently been identified as a major pulmonary CaCC. In these experiments, primary murine nasal septal epithelial (MNSE) cultures (wild type (wt) and transgenic CFTR^{-/-}) were exposed to lipopolysaccharide (LPS) or an ultrafiltrate of PAO1 *Pseudomonas aeruginosa*. Basal media was collected from airway cell monolayers and analyzed for murine CXCL1/KC (human IL-8 analogue) by ELISA to confirm activation of NF κ B mediated inflammatory signaling. Cultures were mounted in Ussing chambers for ion transport measurements. The presence of TMEM16A mRNA and protein in primary cell culture was determined using RT-PCR and immunofluorescence, respectively.

Results: MNSE cultures incubated with PAO1 filtrate or LPS for 24 hours produced significantly elevated CXCL1/KC (PAO1, 1267.4 \pm 54.3 pg/ml; LPS, 1774 \pm 159.4 pg/ml) when compared to controls (660 \pm 139.5 pg/ml) (p<0.05). CaCC-mediated Cl⁻ transport [change in short-circuit current, DISC (mA/cm²)] measured using the purinergic agonist UTP was significantly decreased in wt MNSE compared to controls (PAO1, 8.6 \pm 0.72-----; LPS, 10.6 \pm 0.91; control, 14.1 \pm 0.87, p<0.05). Results were confirmed in the absence of CFTR, which also demonstrated significant inhibition of Δ ISC (PAO1, 12.3 \pm 0.34; LPS, 13.2 \pm 0.96; control, 19.2 \pm 2.1, p<0.05). Expression of TMEM16A mRNA and protein were qualitatively verified in MNSE cultures.

Conclusions: Exposure to LPS or PAO1 extract in primary airway epithelial cells led to decreased CaCC-mediated Cl⁻ transport. Because we have verified TMEM16A expression and cell surface localization, quantitative studies of mRNA and protein are in progress to establish the mechanisms underlying CaCC repression described here. The findings have implications for rescue strategies aimed at restoring Cl⁻ transport via TMEM16A in CF airway disease.

Ho, Christina

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor James Willig

Co-Authors Jonathan Peters, James Willig

Title Factors associated with missed visits to mental health care in an urban HIV clinic setting

Abstract

Introduction: Linkage to care is an important first step for longitudinal adherence to care, which impacts HIV outcomes. Co-morbid mental health disorders are very common in HIV-infected populations and may lead to poor clinical outcomes. Though studies of linkage to care have been performed for primary HIV care, little is known about linkage to mental health services in this at-risk population.

Methodology: A retrospective cohort study of HIV-infected patients at the UAB 1917 HIV/AIDS Clinic who were referred to mental health care (MHC; psychology or psychiatry) between 4/1/2008-6/1/2010. The primary outcome was “no show” or failure to attend an MHC visit within 6-months of referral. Descriptive statistics were used to characterize study groups and multivariable logistic regression models were fit to evaluate factors predicting “no show” to psychiatric or psychology visits.

Results: Among patients referred to psychiatry care, 370 patients met the inclusion criteria. The mean age was 42 ± 10 , and most were white male (51%), publicly insured (49%), and lived locally (66%). In multivariable analysis, minority race-sex [non-white females (OR=3.92; CI=1.82-8.44) and non-white males (3.57; 1.79-7.09) with the referent group being white men] increased odds of no-showing. The further the appointment date from the referral date, the higher the no-show odds (1.12:1.06-1.17 per 7-days). Factors associated with lower no-show odds included age (0.70; 0.52-0.94 per 10-years) and a diagnosis of schizophrenia (0.15; 0.03-0.73).

348 patients met the inclusion criteria for psychology care. Among these, the mean age was 42 ± 10 , and most were white male (38%), publicly insured (46%), and lived locally (69%). In separate univariate models, being publicly insured (3.58; 1.01-12.67 with the referent group being privately insured) and having a diagnosis of schizophrenia (4.57; 1.38-15.18) increased odds of no-showing. Increased CD4 count decreased odds of no-showing to a psychology visit (0.81; 0.67-0.99 per 100-units).

Discussion: Both patient (age, gender/race, psychiatric diagnosis, etc.) and clinic logistics (time to appointment) affected linkage to MHC. Due to the high incidence of mental health co-morbidities and their impact on HIV treatment outcomes, it is imperative to understand barriers to linkage to care in order to promote increased care adherence.

Hollis, Robert

Project Length

Intermediate

Prior Research Experience

Yes

Funding Source

Bachmann-Strauss Dystonia & Parkinson Foundation

Advisor:

David Standaert, M.D., Ph.D

Title:

Validation and behavioral characterization of a cholinergic specific conditional knock-out mouse model of DYT1 dystonia.

Abstract

DYT1 dystonia is the most common and severe form of primary dystonia and is characterized by abnormal involuntary contraction of muscles. DYT1 dystonia is caused by a 3-bp deletion in the DYT1 gene that encodes for the protein torsinA. How this mutation leads to the pathogenesis in DYT1 dystonia is largely unknown. Due to the efficacy of anticholinergic drugs in alleviating symptoms in patients and because of the known role of the striatum in the regulation of movement, striatal cholinergic interneurons have been implicated in DYT1 dystonia. Studies have shown an altered response of striatal cholinergic neurons to D2 receptor agonist in a mouse model of DYT1 dystonia as well as alterations in plasticity that are alleviated by reducing cholinergic transmission. To investigate what pathological role torsinA plays in cholinergic neurons, a mouse model was created in which the *dyt1* gene, the mouse homolog of the human DYT1 gene, is selectively deleted in cholinergic neurons. To validate that torsinA expression is decreased in cholinergic knock-out (ChKO) mice, we used laser capture microdissection and real-time PCR to measure torsinA mRNA in striatal cholinergic neurons. In addition, human carriers of DYT1 show impairments in motor learning, and a similar motor learning defect has been observed in a mouse model of DYT1 dystonia. We hypothesized that ChKO mice would also show motor learning impairments but not other cognitive defects. To test this hypothesis we examined ChKO mice using the accelerating rotarod, open field, elevated plus maze, and Barnes's maze behavioral paradigms. Results from the validation and behavioral characterization of ChKO mouse in addition to further electrophysiological differences found in these mice will reveal any cell-autonomous effect of torsinA in cholinergic neurons contributing to DYT1 dystonia.

Honasoge, Avinash

Project Length	Short
Prior Research Experience	Yes
FundingSource	NIH Medical Scientist Training Program Grant
Advisor	Harald Sontheimer
Co-Authors	
Title	A Potential Role for MMP-2 in Glioma Ion Channel Regulation

Abstract

Gliomas are the most common and deadly type of primary brain tumor. Highly invasive, they offer few treatment options and poor prognosis. Their invasiveness stems from a combination of tissue destruction (via metalloproteinases and glutamate excitotoxicity) and migration throughout the intracranial cavity (via cell shrinkage). One protein, matrix metalloproteinase-2 (MMP-2), is potentially at the crossroads of these two mechanisms. MMP-2 is part of a family of matrix metalloproteinases (MMPs) with a diverse array of both intracellular and extracellular actions. Initially discovered as extracellular proteases, MMPs have been implicated in everything from cell proliferation and survival to ion channel regulation. In gliomas, MMP-2 has already been shown to modulate cell migration both by cleaving the extracellular matrix protein type IV collagen and by inhibiting cellular adhesion; now MMPs are also being implicated in ion channel regulation. For instance, inhibition of MMP-2 activity with phenanthroline activates chloride currents in human airway epithelial cells. Additionally, MMP-23 has a domain that shares structural similarity with a potassium-channel blocker and has been demonstrated to block certain potassium channels.

BK channels are large-conductance, voltage- and calcium-activated potassium channels that are highly expressed in human glioma cells. They colocalize on glioma invadopodia (leading edge cell surface) with a chloride channel (ClC-3); together, these channels may facilitate expulsion of free water from the cytoplasm of an invading glioma cell, allowing it to navigate the tight and tortuous brain cavity. Here we show potassium and chloride currents in human glioma cells that can be blocked by paxilline and 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB), respectively. We also show the inherent gelatinolytic properties of recombinant human MMP-2 (rhMMP-2) using a fluorescent zymographic assay, and that this activity is actually greater without the known MMP-2 activator aminophenylmercuric acetate (APMA). Finally, preliminary results show an increase in outwardly rectifying, voltage-activating current consistent with that from BK channels upon addition of rhMMP-2 to glioma cells under whole-cell, voltage-clamped conditions. It is yet to be determined if this MMP-2 sensitive current can be blocked with the paxilline; but induction of a paxilline-sensitive current by MMP-2 would provide evidence toward a novel role for MMP-2 in glioma pathogenesis via ion channel regulation.

Huff, Kayci

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Phillip D. Smith
Co-Authors	Lisa Nowoslawski Akhtar, Anna L. Fox, Jamie A. Cannon, Phillip D. Smith, and Lesley E. Smythies
Title	Extracellular Matrix-associated Cytokines Regulate CD4+ Effector T-cell Responses in Human Intestinal Mucosa

Abstract

The extracellular matrix (stroma) conditions mucosal macrophage responses to immunostimulatory antigens in the intestinal lamina propria, but little is known about stromal conditioning of mucosal T-cell responses. Using a model that recapitulates the in vivo exposure of newly recruited blood T-cells to the intestinal lamina propria, we uncovered a role for lamina propria stromal products in the regulation of effector T-cells. T-cells cultured in stroma-conditioned media (S-CM) derived from normal human intestinal mucosa (TGF- β hi/IL-6lo/IL-1 β lo) were significantly down-regulated for proliferation and IFN-g production compared to T-cells cultured in S-CM derived from inflamed Crohn's mucosa (TGF- β hi/IL-6hi/IL-1bhi). Antibody neutralization experiments showed that the TGF- β in normal S-CM inhibited T-cell proliferation and cytokine (IFN- γ) production, whereas the IL-6 plus IL-1b in Crohn's S-CM promoted T-cell proliferation, and IL-1b alone promoted IFN-g and IL-17 production. Importantly, normal S-CM inhibited T-bet expression, whereas Crohn's S-CM activated STAT3, suggesting that the discordant T-cell responses in the respective mucosae are regulated at the transcription factor and signaling levels. These findings indicate a role for stromal TGF- β in the down-regulation of T-cell responses in normal intestinal mucosa but stromal IL-6 and IL-1b in the promotion of Th1 and Th17 responses in inflamed Crohn's mucosa, underscoring an innate regulatory function for the intestinal extracellular matrix.

Hull, Travis

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	James George, PhD
Co-Authors	James George, PhD
Title	Heme Oxygenase-1 Expression Affects Dendritic Cell Development and Localization

Abstract

Background: Heme oxygenase-1 (HO-1) is an enzyme that catalyzes the oxidative breakdown of heme into carbon monoxide (CO), biliverdin (BV), and iron. Additionally, cytoprotective and immunoregulatory functions of HO-1 have recently been described. For example, overexpression of HO-1 protects against allograft rejection and expression of this protein in dendritic cells (DC) is required for T regulatory cell-mediated immunosuppression in vitro. This suggests that HO-1 is important in dendritic cell function, and therefore, may be a putative immunotherapeutic target.

Hypothesis: In this work, we characterized the effect of HO-1 expression on the development and peripheral localization of subpopulations of DCs found in central and peripheral lymphoid organs to clarify the role of HO-1 in DC biology. We hypothesized that HO-1 directly regulates the maturation of DCs from precursor cells, and further, this protein influences the localization of specific DC populations in the host.

Methods/Results: A large proportion of splenic CD8⁺ DCs strongly express HO-1, and flow cytometry showed a significant depletion of this subpopulation in HO-1^{-/-} mice. No such reduction was observed in the thymus or peripheral lymph nodes of HO-1 deficient mice. To further examine the role of HO-1 in the development of CD8⁺ DCs in the spleen, we analyzed DC subsets by flow cytometry in HO-1^{-/-} mice in which HO-1 expression was restored using human HO-1 from a bacterial artificial chromosome (BAC). We found that peripheral DC subpopulations in these mice exhibited a normal distribution, indicating that the appearance of these cells in the spleen was truly HO-1 dependent. Additional analysis showed a unique subpopulation of DC in HO-1^{-/-} mice that could represent a subset of DC precursors that fail to develop or localize to the periphery in the absence of HO-1 expression.

Conclusion: HO-1 has an important role in the development and/or localization of peripheral DC.

Huynh, Thy

Project Length

Short

Prior Research Experience

Yes

Funding Source

T-35 Training Grant

Advisor

Bruce Korf

Co-Authors

Ludwine Messiaen

Title

No specific NF1 gene found within a Clinical Variant of Neurofibromatosis Type 1: Familial Spinal Neurofibromatosis

Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant multi-system disorder caused by genetic alteration of NF1 gene, a tumor suppressor gene on chromosome 17q11.2 encoding the protein neurofibromin. National Institute of Health (NIH) diagnostic criteria for NF1 include 6 < café au lait macules; 2 < neurofibromas; groin/axilla freckling; optic glioma; bone abnormality; 2 < Lisch nodules; or first-degree relative with NF1. Spinal tumors occur in 40% of NF1 patients and cause clinical symptoms in 5% of NF1 patients. Familial spinal neurofibromatosis (FSNF), which is characterized by multiple spinal nerve neurofibromas, but few other clinical features of NF1, may be an alternate form of neurofibromatosis caused by a specific type of NF1 mutation. We intend to expand molecular analysis of spinal NF patients to investigate the gene defect causing spinal neurofibromas without pervasive skin manifestations. Clinical evaluation based on NIH criteria and molecular analysis on 75 patients, of which included 12 different sets of families and 34 unrelated patients, were conducted. Genomic sequencing revealed predominantly missense mutations in 5 families; splicing mutations in 3 families; deep intronic splicing mutations in 2 families; and, in-frame duplication or deletion in 2 families. Molecular analysis of 34 unrelated patients with spinal tumors indicated 13 individuals had missense mutations; 12, splicing; 7, deep intronic splicing; 1, in-frame deletion; and, 1 without a mutation. We conclude that a specific NF1 gene was not responsible for manifesting spinal neurofibromas without cutaneous involvements in FSNF patients. Further genetic analysis will elucidate the gene responsible.

Jaleel, Tarannum

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	SDRC
Advisor	Dr. Nabiha Yusuf Dr. Elmets
Co-Authors	Dr. Nabiha Yusuf
Title	Role of Toll Like Receptor 4 in UV induced immunosuppression

Abstract

Introduction: Ultraviolet radiation primarily within the UVB range (290-320 nm) is immunosuppressive. In humans, UV-induced suppression is genetically determined and those individuals in whom UV radiation does suppress cell-mediated immunity have an increased risk of developing skin cancers.

Stimulation of TLR4[Toll-like receptor 4] leads to signaling pathways that activate innate and adaptive immunity. TLR4 has been shown to play an important role in cancer, which apparently depends on the stage of tumor development, the tumor type and the initiating agent. Our preliminary experiments have suggested a role of this signaling molecule in UV-induced immunosuppression.

Purpose: To evaluate the role of TLR4 and its downstream targets such as Myd88 and TRIF in UVB induced immunosuppression

Methods: Control, TLR4 K/O, TRIF K/O, and MYD88 K/O mice were divided into 3 groups. Group one was irradiated with sub-carcinogenic doses of UVB for 4 days prior to DNFB sensitization on the back and subsequent DNFB application to the ears before measuring ears for inflammation. Group 2 received no UVB but the rest of the steps were followed as is. Group 3 only received DNFB application to the ears. T regulatory cells were isolated from these groups to evaluate the role of them during TLR4 mediated immunosuppression.

Results: Our results clearly indicate that TLR4 and Myd88 play a definite crucial role in UVB induced immunosuppression as the K/O mice show lack of immunosuppression despite UV. TRIF plays a variable role.

Jarboe, John

Project Length	Intermediate
Prior Research Experience	Yes
FundingSource	Departmental or Mentor funds
Advisor	Chris Willey
Co-Authors	John S. Jarboe, Sherard Chiu, Joshua A. Anderson
Title	MARCKS Can Regulate Glioma Cell Migration, Proliferation, and Radiation Sensitivity.

Abstract

Activation of the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway is associated with increased cell growth and survival. Phosphatidyl inositol bisphosphate (PIP2) is converted to the triphosphate (PIP3) by PI3K which leads to Akt activation. Since levels of PIP3 are controlled both by the production (from PIP2) and conversion (back to PIP2), the balance between these two processes can influence cell growth and survival. Myristoylated Alanine Rich C-Kinase Substrate (MARCKS) is capable of sequestering PIP2 at the membrane and therefore is a potential regulator for the availability of PIP2 to the PI3K/Akt pathway. We have thus evaluated the effects of the manipulation of MARCKS levels on cell proliferation, migration, and radiation sensitivity of the U251 glioma cell line. MARCKS knockdown was achieved with a set of lentiviral human shRNA and assessed by western blot. Phospho-Akt (pAkt) was also assessed by western blotting. Tumor cell migration was determined by *in vitro* migration chamber assay and the number of cells migrated were quantified by the program ImageJ. Cell proliferation assay was performed using Quickcell Proliferation Assay. Clonogenic assays were used to measure changes in radiation sensitivity. Knockdown of MARCKS resulted in a 27% reduction of the migration of U251 glioma cells. There was an inverse correlation, however, between MARCKS levels and proliferation. The MARCKS knockdown resulted in a 43% increase in the proliferation rate of U251 which was associated with an increase in pAkt. Importantly, clonogenic survival of U251 cells was significantly increased with MARCKS knockdown. We have demonstrated that MARCKS can regulate migration, proliferation and radiation sensitivity in glioma cells and that this is associated with changes in activation of the PI3K/Akt pathway. We suspect that these changes in Akt are related to MARCKS-induced changes in PIP2 availability. Therefore, MARCKS might be an important biologic target for improving response to therapy.

Johnson, Joffre

Project Length

Prior Research Experience

No

Funding Source

NIH T35 Short Term Training Grant

Advisor

Brian Sims, MD, PhD

Co-Authors

Melinda Clarke

Title

Neuroprotective potential of Alpha Fetoprotein in Neural Stem Cells

Abstract

Background: Neonatal brain injury is a devastating condition that can be caused in utero or during the perinatal period. Studies have shown that hypoxic-induced brain injury causes insults such as cerebral palsy and mental retardation. Alpha-fetoprotein (AFP) is present in normal fetus serum as early as four weeks of gestation, reaching peak levels at 25-30 weeks. The biological function of AFP is largely unknown. However, AFP has been labeled feto-specific because after the 30th week, AFP levels decrease drastically due to the rapid expansion of fetal blood volume, reaching normal adult levels at six months. Some isoforms of AFP can also serve as dual regulators of growth, capable of enhancement or inhibition of growth, in cancer and fetal cells, although the mechanism through which AFP functions is largely unknown.

Hypothesis: We hypothesize that AFP may protect neural precursor stem cells (NSC) from oxidative stress *in vitro*.

Methods: Mouse NSC were studied *in vitro*. Cells were plated in prepared and differential (no growth factors) neurobasal medium, and incubated at 37°C under separate normoxic and hypoxic conditions for 48 hours. Standard Western blotting procedures were used along with immunocytochemistry to assess AFP protein levels under normoxic and hypoxic conditions. Western blot data were quantified by densitometry.

Results: Neural stem cells cultured under hypoxic conditions showed a two-fold increase in AFP protein levels in comparison to those under normoxic conditions. However there was no significant change in AFP levels in normoxic and hypoxic NSC cells under differential growth.

Conclusions: Based on these data, we conclude that NSC cells may increase levels of AFP in response to oxidative stress. Additional studies need to be performed to quantify and assess the transcription of AFP within NSC cell lines in order to further understand the mechanism by which AFP protects NSC cells from oxidative stress.

Johnson, Stephen

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Jeffrey Lebensburger, D.O.

Co-Authors Lebensburger, Jeffrey and Rozario, Nigel

Title Clinical Correlates of Microalbuminuria in Children with Sickle Cell Disease

Abstract

Background: Sickle cell anemia (SCA) is a chronic hemolytic anemia that progresses to multi-organ complications, including chronic kidney disease in twenty percent of adult patients. In diabetes and related chronic illnesses, detection of microalbuminuria (MA) during childhood is predictive of adult kidney disease and requires preventative intervention. At present, no interventions or diagnostic guidelines exist for patients with pediatric SCA at risk for MA. We therefore conducted a retrospective chart review to identify laboratory markers associated with MA.

Methods: Urinary microalbumin levels were obtained in 142 patients with HbSS or HbSB⁰ thalassemia during a recent routine office visit. Laboratory and clinical data associated with these levels were recorded. Patients with urinary microalbumin/creatinine >30 were classified as having MA. A subset analysis was conducted to review results for patients receiving no therapy, hydroxyurea (HU) therapy, or chronic transfusion therapy.

Results: Of 142 patients, 33 (23%) were found to have MA. In subset analysis, the incidence of MA was 27% (20/82) in patients receiving no therapy, 13% (4/30) in patients on HU and 36% (8/30) in patients receiving transfusion therapy. In patients receiving no therapy, patients with MA had lower Hb (7.41 vs 8.53, $p < 0.001$), lower hemoglobin F (HbF) (4.32 vs 8.22, $p = 0.01$), and higher LDH (1962 vs 1287, $p = 0.002$) than patients without MA.

Discussion: These data suggest a direct relationship between MA and severe hemolytic anemia (low hemoglobin and high LDH) and an inverse relationship with HbF. HU increases both Hb and HbF and reduces markers of hemolysis (bilirubin and LDH). In this study, patients on HU had the lowest incidence of MA. The results of this study suggest, but do not confirm, the amelioration of MA by hydroxyurea. Based on these results, patients with MA will be enrolled in a prospective therapeutic trial of hydroxyurea for MA progression.

Keith, Charles

Project Length Short

Prior Research Experience No

Funding Source NIH T-35 Training Grant

Faculty Mentor Marc Passman, MD

Co-Authors Passman, Nagre, Taylor, Patterson, Jordan

Title Protocol Implementation of Selective Post-Operative Lumbar Spinal Drainage after Thoracic Aortic Endograft

Abstract

BACKGROUND: Spinal cord ischemia (SCI) remains a concern in patients undergoing endovascular repair of the thoracic aorta (TEVAR). This study analyzes the efficacy of a protocol using selective lumbar drain for patients experiencing SCI following TEVAR.

METHODS: A computerized registry was reviewed to identify all patients who underwent TEVAR from January 2000 through June 2010. Pre-operative factors, intra-operative details, and outcomes were determined. Patients developing SCI post-operatively were compared to those without neurologic symptoms. SCI patients who received drainage were grouped by resolution of neurologic function (full, partial, and no resolution). Risk factors and outcomes were analyzed via chi-square, t test and logistic regression.

RESULTS: 278 TEVAR procedures were performed on 251 patients. Five patients accounting for five procedures experienced SCI pre-operatively and were excluded. Of the remaining 273 procedures in 246 patients, 17 (6.2%) developed SCI within the 30-day post-operative period. Significant risk factors for SCI included length of aortic coverage ($p=0.029$) and existence of infra-renal aortic pathology ($p=0.03$). History of stroke ($p=0.051$) and hospital length of stay ($p=0.057$) reached marginal significance. In SCI patients, increased all cause mortality was observed at one year (52.3% vs 21.5%; $p=0.006$). 11 of the 17 SCI patients received lumbar drains and were categorized into groups of full resolution ($n=4$; 36.4%), partial resolution ($n=4$; 36.4%), and no resolution ($n=3$; 27.3%). No factors reached significance in comparison of symptom resolution across drained and non-drained patients. Six of 7 patients without complete resolution died within one year while all complete responders survived ($p= 0.06$).

CONCLUSION: A protocol utilizing selective post-operative lumbar spinal drainage demonstrates an acceptably low rate of permanent neurologic deficit in patients developing SCI after TEVAR, although overall outcome of patients experiencing SCI is diminished relative to non-SCI patients.

Kennedy, Christopher

Project Length	short
Prior Research Experience	yes
Funding Source	NIH T-35 Training Grant
Advisor	Derek DuBay, MD
Co-Authors	Devin Eckhoff, MD & Stacey Kelpky, PhD
Title	Survival Outcomes of Liver Transplantation with NASH Cirrhosis

Abstract

Non-alcoholic fatty liver disease (NAFLD) is characterized by a fatty accumulation in the liver that can progress to necroinflammation—at this progressive stage, the condition is referred to as non-alcoholic steatohepatitis (NASH). Type II diabetes mellitus, obesity, hyperlipidemia, and hypertension are conditions associated with NASH, suggesting that NASH is the hepatic manifestation of metabolic syndrome. The immunosuppressive regimen given to patients post-transplantation may have an especially deleterious effect on NASH patients because immunosuppressants exacerbate the effects of metabolic syndrome. In this study we analyzed 924 liver recipients from October 1999 through February 2010 at UAB Hospital to compare NASH recipients with all others. Patients transplanted with NASH were compared with those transplanted for hepatitis C, Laennec's (alcoholic) cirrhosis, cryptogenic cirrhosis, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). Patients under age 18 were excluded from the study. Due to NASH not being included as a diagnosis before 2006 at UAB, patients diagnosed with cryptogenic cirrhosis that had metabolic syndrome were included in the NASH category.

Survival rates of patients with NASH (135 patients) were compared with patients diagnosed of conditions specified above. Due to the likelihood of having comorbidities associated with peri-operative death (diabetes mellitus, hypertension, etc.), NASH patients had the lowest 1-year survival rate (88.1%). However at 5 years NASH patients had similar mortality rates to alcoholic cirrhosis and PSC, worse mortality rates than cryptogenic cirrhosis and PBC, and a better mortality rate than those with hepatitis C. Since NASH patients were originally coded as cryptogenic cirrhosis before this decade, it is important to note that the 5-year survival rate for NASH is 83.3% and cryptogenic cirrhosis is 94.8%. In conclusion, it is important to distinguish NASH from cryptogenic cirrhosis so that these liver transplant recipients can be strictly monitored within the first year.

Kentros, Jonathan, II

Project Length Short

Prior Research Experience No

Funding Source NIH T35 Short Term Training Grant

Advisor Kristina Visscher

Co-Authors

Title Modulations in EEG activity in older vs. younger adults during a working memory task

Abstract

The way in which the brain processes any given input depends on the person's task state. For example, you are more likely to remember stimuli to which you attended. Behaviorally, it has been shown that people who are better at ignoring irrelevant, distracting information tend to have better working memory abilities, and that this distinction is especially apt for older adults. The experiments described in this poster attempt to characterize EEG activity associated with preparation to attend or ignore upcoming stimuli with memory performance for older and younger adults.

These experiments explored how ongoing neural activity characterizing the state of the nervous system is altered based on instructions (to attend or ignore a to-be-presented stimulus). Electroencephalography (EEG) was used to determine whether brain activity *before* each trial of a task correlates with subsequent behavioral performance. The main frequency band that was investigated was the alpha band (8-12 Hz), which is typically associated with decreased attention to a task. The major goal being pursued was to quantify differences between older (65 - 90 y.o.) and younger (19 - 30 y.o.) adults in the levels of modulation of oscillatory neural activity in anticipation of a stimulus as well as to correlate this level of modulation with individuals' performance on a neuropsychological measure of working memory.

Subjects performed different tasks requiring either ignoring of or attention to various images followed by an image recall test. Reaction times and percentages correct for performance on each task were measured. In order to assess how ongoing neural activity impacts encoding of distracting stimuli, we focused on oscillatory EEG activity during the 400 ms prior to presentation of a to-be-ignored stimulus.

For all tasks, older adults showed delayed responses and lower proportion correct than did younger adults. No significant correlation was found between an individual's pre-stimulus alpha activity and working memory score. Across subjects, it was shown that the younger group of adults had higher prestimulus alpha levels than the older group, however this difference was not statistically significant ($p > 0.05$). Younger subjects showed much sharper and more well defined peaks in the alpha band than older subjects, whose peaks were typically flatter. This pattern was quantified and determined to be significantly different across age groups ($p < 0.05$). This quantifiable pattern may allow a means for more precise investigation into the relationship between aging, memory, and EEG activity.

Kezar, Carolyn

Project Length	Short
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. Timothy J. Ness
Co-Authors	Cary DeWitte, Chelsea Ball, Corrine Harris, Britney Jones, Dr. Meredith Robbins
Title	Chronic stress produces bladder dysfunction and hyperalgesia

Abstract

Background: Studies have shown that chronic stress induces bladder hyperalgesia to distention. The goal of this study was to investigate the effect of chronic stress on bladder motor function as measured using cystometrograms in anesthetized rats. CRF receptor activation is known to play a role in bladder nociception. α -adrenoceptors affect motor function. Hence, spinal CRF1/CRF2 receptors and α -adrenoceptors were examined.

Methods: Female Sprague-Dawley rats were studied. Stressed animals experienced 15 minute footshock (FS) treatments on seven consecutive days. Non-footshock (NFS) animals received handling but no shocks seven times. Immediately after their last FS or NFS treatment, while under isoflurane/urethane anesthesia, abdominal incisions were made for bladder dome catheter placement for pressure measures and saline infusion. After 10 minutes of baseline pressure recording during saline infusion, an injection of drug (CRF1 (antalarmin) and CRF2 (aSVG30) antagonists intrathecally; phentolamine intraperitoneally) or appropriate vehicle was made and urodynamics were recorded for an additional hour.

Results: Unlike bladder nociception, bladder motor function was inhibited by FS as indicated by increased Inter-Contraction Intervals (ICI) for repeated bladder contractions compared to NFS rats. This inhibition was unaffected by CRF1 or CRF2 antagonists, but phentolamine shortened the ICI, particularly in FS treated rats.

Conclusions: These results suggest that chronic stress leads to bladder motor dysfunction, with increased pain sensitivity to this dysfunction. Mechanisms of the dysfunction differ from those of the hyperalgesia but are responsive to alpha blockade. These findings are clinically relevant in that they suggest stress as a potential etiology of some painful bladder disorders.

Khan, Farah

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. O. Dale Williams and Dr. Cynthia Owsley
Co-Authors	
Title	Pattern of Eye Diseases & Delay in Clinical Presentation Based on Water Access in Rural North India

Abstract

Background: Dr. Shroff's Charity Eye Hospital (SCEH), a tertiary level eye hospital in New Delhi, has established secondary care facilities outside of Delhi to enhance the availability of eye care in rural settings. Studies suggest that these SCEH initiatives could overcome barriers to obtaining eye care. Presently, no studies have examined environmental barriers, specifically water access, in the context of eye-care. Rural areas in India vary from very fertile (Rampur, U.P) to very barren (Alwar, Rajasthan). Objective: To evaluate the relationship between access to water for use in the home and pattern of eye diseases and delay in presentation in a rural setting via patient interviews at secondary eye-care facilities. Methods: An English version 1 questionnaire was established at SCEH and then transliterated into Hindi for consistency of administration in the field. A pre-test of the questionnaire was done with 6 patients at SCEH. Following the pre-test, a version 2 questionnaire was used for a pilot study with 11 patients at a secondary care facility in Alwar. Following additional changes, the version 3 questionnaire was used to interview 26 patients in Rampur. Only patients from rural villages were selected. Diagnosis and treatment information was obtained via chart reviews and on-site hospital staff interviews. Questionnaire results are awaiting final analysis. Results: Preliminary results show that Rampur and Alwar are similar in socioeconomic status, however the majority of Alwar participants (63.6%) were in rural class 4 while the majority of Rampur participants (46.2%) were in rural class 3. A key finding was that 54.5% of study participants in Alwar had a duration of complaint >12 months, a finding not seen in Rampur. Conclusions: Preliminary results suggest there are correlations between water access and pattern of eye diseases and delay in presentation. This study is pending finalization until on-site volunteers gather more data.

Kirkman, Jennifer

Project Length Short

Prior Research Experience Yes

Funding Source NIH T35 Short Term Training Grant

Advisor Wellons, J

Co-Authors Shannon C, Anderson T, Tubbs R, Rozzelle C, Wellons J

Title When can we not screen infants for tethered spinal cord? An analysis of presenting factors in 1141 infants

Abstract

Introduction: Certain cutaneous stigmata and congenital anomalies are accepted as sufficient reason to perform lumbar imaging to rule out tethered spinal cord. A low risk midline skin stigmata group was recently identified in which the need for lumbar imaging was questioned. The purpose of this study was to correlate presenting skin or congenital findings with lumbar imaging results.

Methods: 1273 infants underwent LUS screening for tethered cord at a major pediatric tertiary referral center over a 5 year period. 1141 had adequate documentation for retrospective chart review. Referral sources included urban academic, urban private practice, and surrounding rural private practice pediatricians. Presence of cutaneous stigmata and/or congenital anomalies and LUS results on all patients were recorded. When available, MRI and surgical findings were recorded.

Results: Sacral dimple (638, 66%) and hair patch (96, 10%) were the most common cutaneous reasons for LUS referral. 37 patients (4%) were referred for deviated gluteal folds and none were associated with an abnormality on imaging. The relative risk for any combination of lesions was 0.93 (CL 0.23, 3.67). Imperforate anus (44, 29%) and TEF/esophageal atresia (31, 21%) were the most common congenital reasons for referral and 8 (18%) and 2 (6%) were associated with abnormal findings on imaging.

Conclusions: Deviated gluteal folds alone do not appear to be associated with abnormal LUS findings and clinicians may consider excluding these from screening. Other cutaneous and congenital anomalies as discussed appear to warrant lumbar imaging. Combinations of cutaneous lesions do not appear to increase the risk of abnormal imaging.

Kumbla, Pallavi

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Shawn Gilbert, M.D.
Co-Authors	
Title	Evaluation of Two Novel Drug Compounds in Promoting Hypoxia Induced Vascularization

Abstract

A key component of the vascularization process during healing is the transcription factor known as hypoxia inducible factor (HIF). Under normal conditions, HIF is subject to prolyl hydroxylation, allowing it to be degraded by a proteasome. However, in cases of hypoxia, prolyl hydroxylation, which requires oxygen, is inhibited. As a result, HIF binds to hypoxia response element (HRE) promoters, upregulating downstream genes such as vascular endothelial growth factor (VEGF), stimulating vascularization. One way of activating the HIF pathway is through small molecule inhibitors of prolyl hydroxylase (PHD), such as Desferrioxamine (DFO), which hinders cofactors used by the PHDs (Shen *et. al*, 2009, *J Orthop Res.*). However, current HIF activators suffer from potential unwanted mechanisms (Shen *et. al*, 2009, *J Orthop Res.*). This study sought to explore more efficient HRE and VEGF activation by evaluating two new compounds identified to activate HIF from a screening program involving 300,000 new drug compounds. Mesenchymal stromal cells (MSC) and U2OS-HRE (human osteosarcoma) cells were cultured for enzyme-linked immunoabsorbent assay (ELISA) and luciferase assay, respectively, to evaluate the effects of four doses (2.5 μ M, 5.0 μ M, 10 μ M, and 50 μ M) of the two lead compounds and DFO (control) on HRE and VEGF activation. Results of the luciferase assay demonstrated that for both drug compounds, luminescence of HRE was higher at all doses except 50 μ M for drug compound one compared to DFO. 50 μ M of drug compound one proved toxic to cells. ELISA showed that for all four doses, the two drug compounds increased VEGF concentrations as compared to DFO. Thus, preliminary results of this study suggest that these new drug compounds are more effective at activating HRE and VEGF compared to DFO. Future studies include exploring Western Blotting and Fetal Metatarsal Angiogenesis Assays to evaluate dosing of these drug compounds compared to DFO.

Kumbla, Rekha

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor funds
Advisor	Desiree Morgan, MD
Co-Authors	DE Morgan, NS Fineberg, LL Berland
Title	Quantifying hepatic steatosis utilizing Spectral MDCT and material density analysis

Abstract

PURPOSE: To evaluate MDCT Spectral Imaging (SI) quantitative assessment of fat within the liver parenchyma compared to conventional MDCT evaluation of hepatic steatosis.

METHOD AND MATERIALS: IRB-approved HIPAA-compliant study of 122 adult subjects (76M, 47F, mean age 58), being evaluated for hepatic disease with abdominal Spectral MDCT using a standardized multiphasic protocol consisting of dual energy hepatic arterial phase, and conventional MDCT unenhanced and venous phases. A Gemstone Spectral Imaging (GSI) Viewer®, using Iodine-water and Iodine-fat material-density basis pairs provided values of fat and water in mg/cc on virtual unenhanced images. These were compared to Hounsfield Units (HU) attenuation on the conventional unenhanced images in the same patients. Identical regions of interest within each of 4 hepatic segments were measured. SI fat and water values in mg/cc were correlated with average HU using linear regression.

RESULTS: With conventional noncontrast MDCT, 31 subjects had HU<40 (moderate to severe steatosis) corresponding to mean mg/ccH₂O=1024.59 and mean mg/ccFat=1016.14; 71 had HU between 40 and 55 (mild steatosis) corresponding to mean mg/ccH₂O=1030.13 (range 1023.98 - 1047.37) and mean mg/ccFat= 1025.05 (range 1016.17-1036.55); 20 had HU>55 (normal) corresponding to mean mg/ccH₂O=1041.30 and mean mg/ccFat=1032.99. For spectral water material density measurement versus HU correlation factor, R² value=0.86 excluding 2 outliers with SI ROI values <1000. SI units (mg/cc) converted to HU_{water}: HU = -1074.9 + 1.084x, (x = SI_{water}). For spectral fat material density measurement versus HU, R² value=0.87 excluding 1 outlier with SI ROI value < 990. SI units (mg/cc) converted to HU_{fat}: HU= -1074.3 + 1.093x, (x = SI_{fat}).

CONCLUSION: There is good correlation between conventional MDCT HU density and water and fat material density values in mg/cc for the population studied. However, the conversion of values for an individual patient are uncertain because of large 95% confidence intervals.

CLINICAL RELEVANCE/APPLICATION: The goal of this study is to quantify fatty infiltration of the liver utilizing the Gemstone Spectral Imaging CT. Quantifying fatty infiltration at a lower threshold and providing clinicians with an actual correlative number regarding mild, moderate, and severe steatosis may aid in prevention and plans of treatment as well as predict patients more at risk for hepatic pathology such as cirrhosis and NASH.

Kundukulam, Joseph

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Jasvinder Singh
Co-Authors	Dr. Daniel L. Riddle, Dr. Vibeke Strand, and Dr. Peter Tugwell
Title	Early Postoperative Mortality Following Joint Arthroplasty

Abstract

Background: Joint arthroplasties, such as knee and hip joint replacements, are generally successful procedures. Though infrequent, mortality can occur. Due to the elective nature of most joint replacements, estimation and correlates of mortality, despite its rarity, are nonetheless important to both patients and surgeons.

Objective: To perform a systematic review of published studies in order to examine 30- and 90-day mortality rates in patients undergoing hip or knee arthroplasties.

Hypothesis: We hypothesized that factors such as patient age, co-morbidities, gender, and type of procedure would impact mortality rates.

Methods: A search of six databases yielded 650 abstracts, which were reviewed independently by two investigators (JK and JS) to determine whether the full text article should be reviewed. Of 650 abstracts reviewed, 145 studies underwent a full text review, of which 80 were assessed to have usable data. Data abstracted from the full text included study characteristics (study type, type of joint replacement, length of study), setting (country, community hospital vs. referral/tertiary hospital), patient characteristics (age, gender, race/ethnicity, body mass index, co-morbidity) and system characteristics (hospital volume, surgeon volume).

Results: Overall 30-day mortality rates published across all types of arthroplasties were 0.3% while 90-day mortality rates were 0.7%. For those reports with specific rates, 30-day mortality was significantly higher in men than women (1.8% vs. 0.4%) and bilateral vs. unilateral procedures (0.5% vs. 0.3%), but no differences were noted by the underlying diagnosis of osteoarthritis vs. rheumatoid arthritis (0.4% vs. 0.3%). 90-day mortality showed non-significant trends favoring women, osteoarthritis as the underlying diagnosis, and unilateral procedures.

Conclusions: Several demographic and surgical factors were associated with higher 30-day mortality rates following knee and hip arthroplasties. More studies are needed to examine the effect of BMI, co-morbidities, and other modifiable factors to identify interventions designed to lower mortality rates following arthroplasty procedures.

Land, Andrew

Project Length Intermediate

Prior Research Experience Yes

Funding Source Departmental or Mentor funds

Advisor Desiree Morgan, MD

Co-Authors

Title Characterization of Non-Diseased Adrenal Glands
Utilizing Dual Energy Spectral MDCT

Abstract

Purpose: Adrenal pathology is often characterized using unenhanced computed tomography (CT). We compared conventional unenhanced (CU) CT measurements of non-diseased adrenal glands with IV contrast enhanced spectral multi-detector CT (SMDCT) measurements from 140 keV images and virtual unenhanced (VU) material density images to assess whether either could replace unenhanced image acquisition.

Methods: 386 patients with both SMDCT and CU scans were identified with 825 total non-diseased adrenal glands measured at multiple slice thicknesses. Density and standard deviations (SD) were measured using CU and SMDCT scanning at an energy of 140 keV, to effectively discount the contribution of iodine. The average difference between the mean CU density and the 140 keV SMDCT density was calculated and repeated for each SD. A Gemstone Spectral Imager® generated water concentrations (mg/cc) from water-iodine (VU) images, which were compared to CU density using linear regression analysis.

Results: SMDCT measurements were made on 5mm (n=288), 2.5mm (n=114), 1.25mm (n=53), and 0.625mm slices (n=309). The average CU and 140 keV SMDCT density difference was -1.46 Hounsfield units (HU) for 5mm slices, -5.84HU for 2.5mm, -9.84HU for 1.25mm, and -13.52HU for 0.625mm. The average CU and 140 keV SMDCT SD difference was 0.07 for 5mm, -8.85 for 2.5mm, -11.58 for 1.25mm, and -25.58 for 0.625mm. The average water concentration from spectral MDCT scans was 996.98mg/cc for 5mm slices, 1005.73mg/cc for 2.5mm, 1002.74mg/cc for 1.25mm, and 1012.98mg/cc for 0.625mm, respectively. Linear regression analysis of CU density vs. spectral MDCT water concentration yielded R2 values of 0.0027 for 5mm, 0.0015 for 2.5mm, 0.0146 for 1.25mm, and 0.012 for 0.625mm slices.

Conclusions: Non-diseased adrenal gland measurements from SMDCT scans at 140 keV using 5mm slices are most comparable to CU adrenal density & SD measurements, and might serve as a useful replacement for CU acquisitions, thereby decreasing radiation dose to patients.

Larson, Stephanie

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Advisor	Dr. Namasivayam Ambalavanan
Co-Authors	Scott Ballinger, David Krzywanski, Carolyn Webers
Title	Ethnicity effects on mitochondrial and cell function in HUVEC cells

Abstract

Susceptibility to obesity and cardiovascular disease differs by ethnic background, with African-Americans at higher risk compared to Caucasians. The Ballinger laboratory has investigated the concept that these differences in susceptibility are possibly influenced by the efficiency of mitochondria and their oxidant production. Ancestors of Caucasians acquired mutations that allowed their mitochondria to be less energy efficient and generate more heat, perhaps as an adaptation during migration to colder temperate regions from warmer tropical regions. These alterations in mitochondrial bioenergetics are associated with decreased oxidant stress. Oxidant stress on endothelial cells can cause low-density lipoprotein (LDL) to become oxidized and contribute to the pathogenesis of atherosclerosis. We hypothesized that endothelial cells from African-Americans will show differences in their mitochondrial bioenergetics and thus not multiply as rapidly and will exhibit more apoptosis as compared to cells from Caucasians. We isolated human umbilical vein endothelial cells (HUVEC) from 12 Caucasian, 7 Hispanics, and 12 African American newborn infants using collagenase treatment. Cells were grown in complete endothelial basal medium (EBM) on Petri dishes. Subculturing for 2 passages was done using 0.25% trypsin. We then evaluated cell proliferation using a 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell proliferation kit and apoptosis using Annexin – V staining. Mitochondrial bioenergetics testing was done using a Seahorse Bioscience XF analyzer. Seahorse testing indicated that African-American and Hispanic HUVEC have more efficient mitochondria than Caucasian HUVEC at maximal capacity ($p=0.012$) and at baseline ($p=0.140$), though at baseline it was not significant. There were no significant differences between African-Americans and Caucasians regarding cell proliferation ($p = 0.18$) or apoptosis ($p = 0.72$). Thus, we confirmed ethnic differences in mitochondrial efficiency, although no differences were evident in apoptosis and cell proliferation. Further characterization of the mitochondrial differences under conditions of increased oxidant stress is required, with a larger sample size.

Lawal, Taoreed

Project Length Short

Prior Research Experience Yes

FundingSource CaRES Program

Advisor Dr. Hyun S. Kim, M.D.

Co-Authors Alton B Farris, III, M.D.; Bassel F El-Rayes, M.D.; Ram M Subramanian, M.D.; Hyun S Kim, M.D.

Title Oxaliplatin-Induced Hepatoportal Sclerosis, Portal Hypertension, and Variceal Bleeding Successfully

Abstract

Herein, the authors describe a case of symptomatic portal hypertension, hepatoportal sclerosis, and variceal bleeding secondary to use of oxaliplatin, a conventional chemotherapeutic drug for metastatic colorectal cancer. Liver biopsy revealed no signs of cirrhosis but did demonstrate evidence of hepatoportal sclerosis and vascular injury. The patient was successfully treated with a transjugular intrahepatic portosystemic shunt (TIPS) and remained in good health with no recurrence of symptoms for 3.5 years. Although oxaliplatin has been associated with hepatic injury, to the authors' knowledge, symptomatic portal hypertension is a rare manifestation; furthermore, subsequent successful long-term treatment with TIPS has not been reported.

LeGrand, Jason

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Danny Welch
Co-Authors	Dr. Benjamin Beck
Title	The effect of KiSS-1 in an immunocompetent metastatic breast cancer model

Abstract

The metastasis suppressor gene KiSS-1 has been shown to dramatically suppress the incidence of breast cancer metastases to the lung in prior xenograft mouse models using athymic mice. Although its mechanism of action has not yet been fully elucidated, it has been shown that the product of the KiSS-1 gene must be secreted and cleaved into smaller active forms called kisspeptins in order to affect metastasis. Because cellular immunity plays an important role in the metastatic process, we decided to investigate KiSS-1's metastasis suppression ability in a mouse model which was fully immunocompetent. KiSS-1 expression vectors and controls were stably transfected into a luciferase expressing metastatic mouse breast cancer cell line and expression was measured by RT-PCR and sandwich ELISA using antibodies against selected kisspeptins. RT-PCR results showed ectopic expression of KiSS-1 mRNA; however, we could not detect kisspeptins by ELISA. We proceeded to tail vein inject the KiSS-1 cell line into immunocompetent syngeneic mice along with appropriate controls. After allowing two weeks for metastasis development, the mice were injected with luciferin and imaged using an in vivo imaging system (IVIS) bioluminescence camera to detect overt metastasis. The results showed large metastatic burden in all mice, and no discernable difference in metastasis suppression between the experimental and control groups. We hypothesize that the lack of metastasis suppression is most likely related to the absence of kisspeptin formation. Our work suggests that expression of the KiSS-1 gene is either being blocked at a post-transcriptional level, or the kisspeptins are being processed in a manner undetectable by our current methods.

Lewis, Travis

Project Length Long
Prior Research Experience Yes
Funding Source Non-UAB Funding (External Funding Source)

Advisor David G. Standaert, David T. Curiel

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

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

Abstract

Background: Gene-based therapy is a new paradigm for treatment of Parkinson disease (PD), offering considerable promise for precise targeting and flexibility to impact multiple pathobiological processes for which small molecule agents are unavailable. Some success has been achieved utilizing adeno-associated virus for this approach, but it is likely that the characteristics of this vector system will ultimately create barriers to progress in clinical therapy. Adenovirus (Ad) vector overcomes limitations in payload size and targeting. The cellular tropism of Ad serotype 5 (Ad5)-based vectors is regulated by the Ad attachment protein binding to its primary cellular receptor, the coxsackie and adenovirus receptor (CAR). Many clinically relevant tissues are refractory to Ad5 infection due to negligible CAR levels, but can be targeted by tropism-modified, CAR-independent forms of Ad. Our objective was to evaluate the role of CAR protein in transduction of dopamine (DA) neurons in vivo. Methodology/Principal Findings: Ad5 was delivered to the substantia nigra (SN) in wild type (wt) and CAR transgenic animals. Cellular tropism was assessed by immunohistochemistry (IHC) in the SN and striatal terminals. CAR expression was assessed by western blot and IHC. We found in wt animals, Ad5 results in robust transgene expression in astrocytes and other non-neuronal cells, but poor infection of DA neurons. In contrast, in transgenic animals Ad5 infects SNc neurons resulting in expression of transduced protein in their striatal terminals. Western blot showed low CAR expression in the ventral midbrain of wt animals compared to transgenic animals. Interestingly, hCAR protein localizes with markers of post-synaptic structures, suggesting synapses are the point of entry into dopaminergic neurons in transgenic animals. Conclusions/Significance: These findings demonstrate that CAR deficiency limits infection of wild type DA neurons by Ad5, and provide a rationale for the development of tropism-modified, CAR-independent Ad-vectors for use in gene therapy of human PD.

Lin, Victor

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Fang-Tsyr (Fannie) Lin
Co-Authors	Yun-Ju Lai
Title	TRIP6 modulates AKT-mediated downregulation of p27 ^{KIP1} in cancer.

Abstract

p27^{KIP1} is a CDK inhibitor that suppresses cell proliferation by regulating the G1/S cell cycle checkpoint. It is an important tumor suppressor protein that has been heavily implicated in the prognostic outcome of a wide variety of malignancies. In general, low nuclear expression of p27^{KIP1} correlates with a poor outcome, as does high expression of cytosolically mislocalized protein, which acts paradoxically to promote cell motility and tumorigenicity. Despite its strong ties to cancer prognosis, p27^{KIP1} mutations have rarely, if ever, been shown to be the root cause of human cancers, suggesting that its dysregulation through other mechanisms is to blame. Recently, our laboratory found that knockdown of thyroid-hormone receptor interacting protein 6 (TRIP6), a putative adaptor protein that is highly expressed in a variety of cancer types, including glioblastoma and ovarian cancer, and has been tied to a number of oncogenic signaling pathways, results in cell cycle delay through the G1/S checkpoint, and this was in part explained by the upregulation of p27^{KIP1}. We hypothesized that TRIP6 overexpression in cancer cells inhibits p27^{KIP1} by reducing its expression and by changing its subcellular localization.

Our findings indicate that TRIP6 is capable of binding to p27^{KIP1} under physiological conditions *in vivo* and binds directly *in vitro*, suggesting that any regulation might be triggered by direct interaction. p27^{KIP1} function is known to be controlled in a threefold manner: through its transcription, subcellular localization, and proteosomal turnover. Our data show that TRIP6 knockdown in U373-MG cells does not affect p27^{KIP1} transcription, but does promote its nuclear localization and stability. Furthermore, we found that phosphorylation of p27^{KIP1} at T157, an AKT-mediated event that promotes cytosolic localization of p27^{KIP1}, was specifically inhibited by TRIP6 knockdown. Finally, we demonstrate that membrane recruitment and subsequent activation of AKT are also impaired by TRIP6 knockdown. Because of its high expression in certain cancers and its effects on p27^{KIP1}, AKT, and other previously reported targets, TRIP6 represents a novel therapeutic target in cancer.

Lopker, Michael

Project Length Long

Prior Research Experience Yes

Funding Source NIH Medical Scientist Training Program Grant

Advisor George Shaw

Co-Authors Keele BF, Li H, Wang S, Hahn BH, Klasse PJ, Moore JP, Veazey RS, Barouch DH, Shaw GM

Title: Delayed Viremia in Two Rhesus Macaques Following Intravaginal Inoculation of SIVmac251

Abstract:

Background: The eclipse phase in SIV and HIV infection is the period of undetectable viremia following inoculation and preceding viremia and seroconversion. In SIV infection of Indian rhesus macaques, the eclipse phase generally lasts no longer than 10 days. Here we report delayed viremia (>28 days) following a single intravaginal SIV inoculation in two rhesus macaques and a detailed molecular analysis of the “breakthrough” viral genomes.

Methods: 6 progesterone-treated rhesus macaques were given a partially protective dose of T-1249 gel and then challenged intravaginally once with high-dose SIVmac251. One week after inoculation, 4 animals exhibited detectable viremia while 2 others remained vRNA negative for greater than 4 weeks. By week 6, both animals were viremic.

Results: We performed single genome amplification (SGA) followed by direct amplicon sequencing on plasma from both animals with delayed viremia and showed that each monkey was productively infected by a single virus. In one animal, “breakthrough” virus showed evidence of strong positive selection (dN/dS) in Tat (SL8), a known immunodominant epitope in Mamu A*01 positive monkeys. In the other animal, “breakthrough” virus demonstrated striking positive selection in stem loop 1 of the leader RNA, a presumed untranslated region. The pattern and concentration of amino acid substitutions within a potential 9mer peptide in virus from both animals suggested cytotoxic T lymphocyte (CTL) selection. Confirmatory CTL ELISPOT analyses are underway.

Conclusions: Delayed viremia in rhesus macaques has been reported but is uncommon and underlying mechanisms are unknown. Here, we show evidence for early CTL containment and escape in an immunodominant epitope in one animal and in a putative cryptic epitope in another. If confirmed, this would be the first example of cryptic CTL epitope expression from an untranslated region of the genome and would expand the number of cryptic epitopes potentially contributing to SIV and HIV containment.

Ma, Jing-Yuan

Project Length	Long
Prior Research Experience	Yes
Funding Source	Dept of Cell Biology and CaRES Program
Advisor	Etty Benveniste
Co-Authors	Braden McFarland
Title	The JAK2 inhibitor AZD1480 attenuates STAT-3 signaling and tumor cell proliferation in glioblastoma models

Abstract

Glioblastoma [GBM] is the most common and aggressive human brain neoplasm. The JAK/STAT signaling pathway has been shown to be important in GBM progression with STAT-3 being persistently active and elevated. The elevated STAT-3 correlates with the increased target gene expression that drives GBM progression. We hypothesize that pharmacologic inhibition of JAK2/STAT-3 signaling can have therapeutic values in GBM. AZD1480, a pharmacological competitive JAK2 inhibitor, has been shown to attenuate growth of other tumor types, but its efficacy on GBM has not been previously demonstrated. First, the efficacy of AZD1480 was tested *in vitro* with U251-MG and U87-MG (human) and 4C8 (murine) GBM cell culture lines. In these cell lines, AZD1480 successfully attenuated the constitutive and stimulus-induced JAK2 and STAT-3 phosphorylation and down-regulated expression of downstream GBM promoting genes. AZD1480 treatment also inhibited proliferation of U251-MG and 4C8 cells. We also tested AZD1480 in combination with the current GBM chemotherapeutic agent temozolomide. Preliminary results suggest that the combination treatment may have synergistic potential in inhibiting GBM proliferation. Next, *in vivo* models of GBM were analyzed by implanting human xenograft tumors into the flanks of nude mice. AZD1480 treatment (intraperitoneal injection) significantly attenuated the growth of these GBM tumors. Future studies include validating these *in vivo* results with oral administration of AZD1480 and examining the efficacy of the drug with intracranial tumors. Our current findings suggest that the inhibition of JAK2/STAT-3 pathway by AZD1480 has therapeutic potential to attenuate GBM progression in a clinical setting.

Mai, Karen

Project Length

Prior Research Experience

Funding Source

UAB DRTC

Advisor

W. Timothy Garvey, MD
Helliner S. Hill, MD, PhD

Co-Authors

Title

Insulin Resistance Induced by High Fat Diet and
Aging: Differential Role of Adiponectin

Abstract

Aging and high fat diet (HFD) are known as risk factors for the development of insulin resistance and type 2 diabetes (T2DM). Insulin resistance associated with obesity is characterized by a chronic systemic low-grade inflammatory state, and involves infiltration of adipose tissue by macrophages associated with alterations in tissue production of cytokines such as the pro-inflammatory interleukin-6 (IL-6) and the anti-inflammatory interleukin-10 (IL-10), as well as the adipokine adiponectin. High molecular weight adiponectin (HMW) is considered the active form of adiponectin and a better marker of insulin sensitivity than total adiponectin. To better understand the role of inflammation in IR due to either aging or HFD, we assessed the levels of IL-6, IL-10, and adiponectin multimers in serum from 3 mouse treatment groups: (1) 10 month-old mice fed a high fat diet (10 Mo-HFD) over month 7 to 10; (2) 10 month-old mice fed a normal chow diet (10 mo-NCD); (3) 3 month-old mice fed normal chow (3 Mo-NCD). Thus, we were able to individually assess effects of diet (10 mo-HFD vs 10 mo-NCD) and aging (10 mo-NCD vs 3 mo-NCD). Insulin resistance was greatest in 10 mo-HFD, and intermediate in 10 mo-NCD, when compared to insulin-sensitive 3 Mo-NCD, as demonstrated by higher fasting insulin concentrations (34 ± 8 ; 3.3 ± 0.6 ; 0.45 ± 0.1 $\mu\text{g/mL}$, respectively; $p < 0.05$) and diminished glucose decline during insulin tolerance tests (ITT). We assessed effects of the HFD and aging on serum adiponectin multimers HMW, medium molecular weight (MMW), and low molecular weight (LMW) by western blot. We found that the high fat diet (10 mo-HFD) reduced the HMW (536890 ± 60256 ; 743226 ± 37501 , $p < 0.05$) and MMW (180604 ± 18432 ; 318019 ± 42659 , $p < 0.05$) multimers, with no effect on LMW (1583000 ± 188604 ; 1677000 ± 71730) when compared to 10 mo-NCD. Aging on the other hand led to an increase in these adiponectin isoforms; both HMW (743226 ± 37501 ; 361610 ± 29144 , $p < 0.05$) and MMW weight fractions (318019 ± 42659 ; 122504 ± 27363 , $p < 0.05$) were increased in 10 mo-NCD when compared with 3 mo-NCD, with no differences in LMW. To examine inflammation in adipose tissue, we observed that IL-6 secretion was not altered in 10 mo-HFD in ex vivo cultured adipose tissue when compared to a 10 mo-NCD (4169 ± 335 ; 3981 ± 481 ng/mL), whereas IL-10 was decreased by 43% (144 ± 26 ; 254 ± 49 ng/mL, $p < 0.05$), measured by ELISA.

In conclusion: (i) high fat feeding and aging both induced a state of relative insulin resistance in mice; (ii) HMW and LMW adiponectin were reduced by high fat feeding, while these isoforms were increased in older versus young mice. Therefore, these two forms of insulin resistance involved different mechanisms with regard to the role of adiponectin (iii) in cultured adipose tissue, high fat feeding led to a reduction in IL-10 without a change in IL-6 secretion. This highlights the fact that a decrease in the anti-inflammatory cytokine IL-10 can predominate in the adipose tissue inflammation associated with IR. The observed increase in HMW and MMW adiponectin isoforms in aging despite worsening insulin resistance is a novel observation that requires further study.

McCormick, Don, III

Project Length

Prior Research Experience

No

FundingSource

NIH T35 Short Term Training Grant

Advisor

Dr. Candace Floyd

Co-Authors

Tracy D'Alessandro

Title

Effects of Fluoxetine Administration on Post-SCI Recovery

Abstract

Background

Traumatic spinal cord injury (SCI) is a debilitating condition that can significantly affect a person's quality of life physically, socially, and psychologically with depression and anxiety being prevalent in these patients. Although the underlying neurobiology of post-SCI depression is poorly understood, it is generally agreed upon in the clinical community that these complications are associated with poor outcomes in recovery. One of the most commonly prescribed antidepressants is fluoxetine (Prozac®) which belongs to the class of antidepressants known as selective serotonin reuptake inhibitors (SSRI). . No previous studies have evaluated the effects of SSRIs in persons with SCI even though serotonin (5-HT) is a critical regulator of plasticity and functional recovery after SCI.

Hypothesis

We hypothesize that SSRIs will alter spinal cord circuitry, plasticity, and functional recovery after SCI.

Methods

We induced SCI in male rats and administered fluoxetine at a fixed dose of 2mg/day beginning on post-SCI day 14 and continued until post-SCI day 46 since recovery seems to plateau at this point. We evaluated locomotor and sensory function weekly after SCI. Also, we evaluated anxiety and depression-like behaviors before initiation of drug administration and again at the end of the study. Finally, we extract tissue and evaluate lesion architecture.

Results

We have shown that fluoxetine administration in mid-thoracic SCI male rat model when compared to the vehicle SCI group may;

- impair recovery of hind-limb locomotion and may induce greater hyperalgesia and allodynia.
- exacerbate injury-induced motor neuron loss and white matter damage at the lesion epicenter.
- Inhibit functional recovery.

Conclusion

Since the effects of an SSRI had not previously been examined in a SCI model, showing that it may have a negative impact on recovery from an SCI injury is significant due to the prevalence of this therapy in the SCI patient population.

McDonald, Andrew

Project Length Intermediate

Prior Research Experience No

Funding Source

Advisor Dr. John B. Fiveash

Co-Authors Michael C. Dobelbower, Robert Y. Kim, Rojymon Jacob, Justin Bishop, John B. Fiveash

Title Retrospective Database Study of Efficacy and Rectal Toxicity Associated with Radiation Therapy for Prostate Cancer

Abstract

Purpose: To assess the biochemical control rates and long-term rectal side effect profile of hypofractionated external beam radiation therapy for prostate cancer. We hypothesize that daily CT-based image guidance will allow a higher dose per fraction to be safely administered, shortening the overall treatment time from 8 weeks to 4 – 5.5 weeks.

Methods: 162 patients were treated with external beam radiation with or without adjuvant hormonal ablation between 2005 and 2009 for patients \leq T3a Nx/N0 Mx/M0. Patients were classified into risk groups with 51 patients defined as low risk, 67 as intermediate risk, and 44 as high risk. All patients were treated with 60/67.6/70/70.2 Gy divided into 20/26/28/27 fractions. Daily CT or fiducial-based image guidance was performed prior to each fraction. The median follow up was 34 months; mean age was 70.2 years.

Results: Average biochemical no evidence of disease at most recent follow-up is 96.3%. 10.5% of patients had grade 2 rectal toxicity at 6 months or later after the induction of radiation treatment.

Conclusion: We conclude that, even though >5% of patients experienced grade 2 or greater late rectal toxicity, hypofractionated radiation therapy with daily image guidance has a modest amount of rectal toxicity with excellent efficacy.

McAnnally, John-Ryan

Project Length Intermediate

Prior Research Experience No

Funding Source

Advisor Henry E. Wang, MD, MS
Randolph S. Devereaux, PhD, MSPH

Title Regional Disparities in Prevailing Diseases in the
United States, years 1999-2006

Abstract

Background: Despite recent advances in medical care and policies directed at relieving health inequalities, wide disparity exists with regard to health outcomes in the United States (US). Regional clusters of disease populate the US with high or “excess” mortality. We sought to characterize the geographic mortality variation for several prevailing disease groups.

Methods: We identified US mortality rates for groups of disease using the Centers for Disease Control and Prevention Compressed Mortality File (CMF), a national registry of all US deaths. We combined data from 1999-2006, calculating age-adjusted mortality incidence at the county level. We determined groups of disease based on biologic or pathophysiologic plausibility, including cardiovascular disease, cerebrovascular disease, hepatorenal disease, infection, cancer, and trauma/burns. We calculated a matrix of pairwise correlation coefficients to determine associations between diseases, defining significant associations as $|r| > 0.5$. We next stratified the analysis by region to assess the impact of geographic context.

Results: We observed wide geographic variation in the disease groups included in the study: cardiovascular disease median 164 per 100000 (IQR 137-193), cerebrovascular disease 45(39-53), COPD 64(54-74), hepatorenal disease 25(21-31), infection 37(30-46), cancer 227(206-246), and trauma/burns 77(62-94). We also evaluated associations between groups, which revealed significant associations between infection:cerebrovascular ($r=0.52$), infection:hepatorenal (0.61), cancer:cerebrovascular (0.51), cancer:pulmonary (0.54), cancer:infection (0.55), trauma:hepatorenal (0.54). On regional analysis, the South region had only one significant association, infection:hepatorenal (0.52). The Northeast region revealed an inverse relationship between infection:pulmonary (-0.31) and trauma:infection (-0.02). The Midwest region had a stronger association between pulmonary:neoplasm (0.65). The West region revealed inverse relationships for cerebro:trauma (-0.16) and cerebro:hepatorenal (-0.066).

Conclusions: Death rates in the US demonstrate wide geographic variation. Underlying associations between diseases may explain variations in US mortality. Regional context appears to influence the magnitude and direction of association between death rates for select diseases.

McPheeters, Meghan

Project Length Short

Prior Research Experience No

Funding Source CaRES Program

Advisor Gregory Friedman, M.D. and G. Yancey Gillespie, PhD.

Co-Authors Marilyn Haas, Gregory Friedman, M.D. and G. Yancey Gillespie, PhD.

Title Co-expression of CD133 and putative brain tumor stem cell markers CD15, CD73, CD90 and podoplanin

Abstract

Background: A subpopulation of brain tumor cells has been identified as having stem cell properties including multipotency, self-renewal, and the ability to proliferate and exclusively maintain the neoplastic clone. These brain tumor stem cells (BTSC) have been distinguished by expression of the cell surface marker CD133. However, new data suggests that CD133 is an imperfect BTSC marker; CD133- cells can initiate tumors, and CD133 has been shown to be a marker of bioenergetic stress.

Objective: We sought to determine if other surface proteins in concert with CD133 may provide a better marker of BTSC.

Methods: Human glioma xenografts (D456MG, GBM6, GBM12) with previously determined CD133+ percentages (21-65%) were disaggregated from murine flank tumors and maintained for 7 days in vitro under physiologic hypoxia or normoxia using medium designed to support neural stem cell growth. Flow cytometric analysis was performed to evaluate co-expression of CD133 and putative BTSC markers CD15, podoplanin, CD73, and CD90.

Results: High levels (>97%) of expression of podoplanin, CD73 and CD90 were seen in each xenograft irrespective of oxygen tension. CD15 expression was variable in normoxia (1.9±1.0% in GBM12; 6.7±0.5% in GBM6; 44.4±5.2% in D456MG). In normoxia 1.5±1.1% of GBM12 cells, 5.2±0.3% of GBM6 cells and 6.5±0.2% of D456MG cells coexpressed CD133 and CD15 versus 1.6±0.4%; 3.9±1.8%; and 13.5±1.9%, respectively, under hypoxia. Importantly, CD133 expression increased and CD15 expression decreased significantly under physiologic hypoxia. Currently neural colony forming assays are being performed to examine the ability of CD133(+/-)/CD15(+/-) cells to self-renew and proliferate.

Conclusions: CD73, CD90 and podoplanin were non-specific cell markers. We suspect that CD15 in conjunction with CD133 will prove to be a more specific BTSC marker; however, further studies are needed to confirm this and to determine the mechanism by which oxygen tension alters expression of CD133 and C15.

Meadows, Jarrod

Project Length

Prior Research Experience

Funding Source

Advisor Erik Roberson

Co-Authors

Title: Examining the Role of Microglia in a Mouse Model of Frontotemporal Dementia

Abstract

Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by atrophy of the frontal and temporal brain lobes and a progressive decline in behavioral and executive function. Patients develop various neuropsychiatric disturbances such as marked apathy, loss of inhibition, and obsessive-compulsive behaviors. Unfortunately, there are currently no treatments. It has been well documented that development of FTD is closely associated with dysfunction in the microtubule-associated protein tau, with brain inclusions made of insoluble aggregates of tau. However, the mechanism through which tau dysfunction leads to neuronal death is unclear. Recently, studies have shifted focus to the role of microglia in the development of FTD. Microglia are resident macrophages in the central nervous system, and once activated, release cytotoxic substances with the potential to cause devastating collateral damage to surrounding tissue. Autopsy data in humans with FTD have revealed that patterns of neuronal loss and microglial activation are identical, and some mouse models of FTD have shown microglial activation occurs before the appearance of tau inclusions and neuronal loss. In this study, we examined a transgenic mouse model of FTD expressing the V337M mutant human tau found in a familial form of FTD. This model displays typical FTD characteristics such as compulsive behavior and disinhibition compared with transgenic mice expressing normal human tau. We hypothesize that these behavioral changes are precipitated by neuronal dysfunction and death due to activated microglia. Using immunohistochemistry we analyzed microglial number and morphology in several brain regions implicated in FTD, testing the prediction that these regions will show microgliosis, as indicated by increased numbers and amoeboid-type morphology of microglia, before the onset of behavioral abnormalities.

Merino, Aimee Marie

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Richard Kaslow
Co-Authors	James Tang, Richard Kaslow
Title	Killer Immunoglobulin-like Receptor Genes and Heterosexual HIV-1 Transmission

Abstract

Background: Killer immunoglobulin-like receptor (KIR) genes regulate natural killer (NK) cell function. KIR gene content and allelic variations have been reported to influence HIV-1 acquisition. We investigated the impact of KIR genes on heterosexual transmission in an African cohort.

Methods: Between 1995 and 2006, 566 HIV-1 serodiscordant couples in Lusaka, Zambia, were enrolled and followed for quarterly counseling and serologic testing for a minimum of nine months. KIR genes and HLA alleles were detected with standard typing methods. In univariate and multivariable analyses, we tested the association of KIR genes as well as a KIR gene/HLA ligand combination with HIV-1 transmission and with index partner viral load (VL) in copies/mL as a continuous (mean log₁₀) and as a categorical (<10⁴, 10⁴ - 10⁵, and >10⁵) variable. All analyses of VL by linear regression were statistically adjusted for sex, and time from enrollment to first VL measurement. Covariates in proportional hazards models of HIV-1 transmission included VL in all index partners and genital ulcers in all partners.

Results: In the index partners KIR2DS4*001, the only known KIR2DS4 allele to encode a full length receptor, was associated with higher rates of HIV-1 transmission (OR=2.40, 95% CI=1.31-4.39, p=0.003) by logistic regression. Survival analysis for KIR2DS4*001 demonstrated accelerated transmission of HIV-1 (RH=1.72, p=0.005). Carriage of this allele in the seronegative partners was not associated with acquisition. The KIR2DS4*001 allele was also associated with a high VL (0.17 ± 0.08 log₁₀, p<0.05). No association was observed with a presumptive ligand, HLA-Cw*04, or with the HLA-Cw*04/KIR2DS4*001 combination

Conclusions: We observed a novel association of KIR2DS4*001 carriage by a seropositive partner with an increased hazard of HIV-1 transmission and with relatively high VL. Whatever the significance of this KIR allele association in Zambian serodiscordant couples, it did not depend on epistatic interaction with HLA-Cw*04, a putative ligand.

Miller, Jonathan

Project Length	Intermediate
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	James Galbraith, MD
Co-Authors	John Ryan McAnnally
Title	The Mini Clerkship: Exposing preclinical medical students to Emergency Medicine

Abstract

Studies indicate there is inadequate exposure to Emergency Medicine (EM) within US medical schools. In fact, the most recent survey reported only 36% of medical schools require students to participate in an EM rotation. Other schools only offer EM as a senior elective; many times after residency applications have been submitted.

We present an easily reproducible EM experience for pre-clinical medical students designed to increase both exposure to the scope of EM and familiarity with common EM procedures such as suturing, ultrasound, intubation, and central line placement. We hypothesized that the experience would not only increase a student's self-assessed level of familiarity to EM, but also increase the likelihood of the student considering EM as an elective and/or career.

Analysis of post-experience surveys revealed a significant increase in the number of students understanding the scope of EM, the number considering EM as a career, and the number perceiving competency in taught procedures, but not a significant increase in the number planning to take an EM elective.

It is clear that programs like this have a notable role in affecting medical specialty understanding and preferences in pre-clinical medical students. This model can be duplicated by other specialties that desire to increase awareness of their field.

Modi, Sarika

Project Length Long

Prior Research Experience Yes

Funding Source

Advisor Michael Mugavero

Co-Authors S Modi, J Willig, Tamhane, C Nevin, J Raper, M Saag, M Mugavero

Title Missed Opportunities and Costs associated with Inpatient HIV Diagnosis

Abstract

Background: Limited data on the impact of implementation of the revised 2006 HIV testing recommendations are available. We evaluated factors associated with diagnosis site (Hospital vs. Outpatient), quantified prior hospital contacts (missed opportunities) and potentially avoidable costs had earlier diagnosis been performed.

Methods: Newly diagnosed patients entering care at the 1917 Clinic 9/06 – 12/09 were categorized as Hospital [emergency room (ER) or inpatient] or Outpatient diagnoses. Bivariate comparisons of patient characteristics by diagnosis category and multivariate (MV) logistic regression analysis of factors associated with hospital diagnosis were performed. Hospital visits (missed opportunities) in the two years prior to diagnosis, mean costs and lengths of stay were calculated for those diagnosed at UAB.

Results: Among 300 newly diagnosed patients, 84 (28%) Hospital and 216 (72%) Outpatient diagnoses were identified. Significant differences ($p < 0.05$) in race (Black/Other 83% vs. 60%), insurance (Public 32% vs. 11% Private), initial CD4 levels (≤ 200 60% vs. 23%), opportunistic infection < 90 days from diagnosis (29% vs. 6%), were found between the Hospital vs. Outpatient diagnosis groups. In MV analysis, public insurance (OR=8.72; 95%CI=3.26-23.36), Black/Other race (5.00; 1.96-12.75), CD4 ≤ 200 (6.13; 2.53-14.90), early OI (6.63; 2.18-20.18), and no prior HIV test (2.23; 1.06-4.70) increased likelihood of hospital diagnosis.

Overall, 35% ($n=29$) of the Hospital group were diagnosed as inpatients at UAB. Median length of stay and cost were 6 days (3; 9) and \$23,230 (11,686; 43,162) respectively. Among these patients, 52% ($n=15$) had prior UAB visits (missed opportunities) in the previous two years (10 admissions; 47 ER visits).

Conclusion: Sociodemographic disparities in hospital diagnosis of HIV were observed. Over half of hospital diagnosed patients had prior missed opportunities for HIV screening. Earlier diagnosis would potentially have avoided expensive inpatient hospitalization during which HIV was diagnosed. These data lend support to the call for routine HIV testing in the hospital setting.

Molony, Elizabeth

Project Length	Short
Prior Research Experience	yes
Funding Source	Cunningham Fellowship
Faculty Advisor:	Kathy Monroe, MD; Kelly Clayton, MD
Co-Authors:	Kelly Clayton, MD; Cecily Collins; Rebecca Smith
Title:	Impact of disparities in health literacy on asthma management

Abstract:

Thirteen percent of American children under the age of 18 have been diagnosed with asthma. A disproportionate amount of these children are African-American and from families of lower socioeconomic status, two groups that are four to five times more likely to be seen in the emergency department (ED) for asthma-related visits. Recent studies have shown that this disparity in asthma prevention and ED admissions is not the result of access to health care and could be a result of caregiver health illiteracy, a factor associated with low socioeconomic status and minority groups. Based upon these studies, we hypothesized that parents coming to the ED will have lower health literacy scores and will be more likely to have inappropriately treated their children's asthma at home. To test this hypothesis we assessed the health literacy of English-speaking parents of children four to fourteen years of age who had been previously diagnosed with asthma and came to the Children's Hospital of Alabama ED with a chief complaint of asthma. Participants were given a questionnaire in order to determine the parent's health literacy score and appropriateness of the management of their child's asthma medications. Although this is an ongoing study with the goal of enrolling 100 participants, the preliminary results based on 54 participants show 31% with non-adequate health literacy scores and 69% with adequate health literacy scores. The results showed a trend for association between non-adequate health literacy scores and inappropriate asthma management ($p = 0.098$). We hope to show the impact of health literacy on asthma management at home, with the idea that this modifiable factor can be improved with educational programs that could possibly lower asthma-related morbidity and mortality.

Moseley, Carson

Project Length	Short
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. Robert G. Webster
Co-Authors	Robert G. Webster and Jerry R. Aldridge Jr.
Title	From fat to flu: prePPARing for a pandemic

Abstract

In 2009, a novel influenza A (H1N1) virus was isolated from humans in North America and developed into the first pandemic of the 21st century. Reports of a worldwide shortage of antiviral drugs, the evolution of drug-resistant influenza virus variants, and a six-month delay in vaccine availability underline the need to develop new therapeutics that may be widely distributed during future pandemics. Historically, an epidemiological comparison of influenza pandemics to the seasonal influenza epidemics has resulted in a paradox. While seasonal influenza epidemics often result in a heavy burden of disease among infants and the elderly, influenza pandemics often cause severe disease in young, immuno-competent individuals. Recently, our group has shown that the pathology following infection with highly pathogenic (HP) influenza viruses is associated with the enhanced recruitment of a subset of inflammatory monocyte-derived cells (iM), capable of damaging the lung when recruited in large numbers. In an effort to discover alternatives to conventional therapeutic strategies, we performed an in vivo screen of several classes of immunomodulatory agents to test their potential to suppress iM trafficking to the lung and thus mitigate the effects of influenza virus-induced immunopathology. Here, we provide preliminary evidence that two classes of drugs which are commonly used to treat Type II Diabetes—peroxisome proliferator activated receptor-gamma (PPAR γ) agonists and AMP-activated protein kinase (AMPK) agonists—provide protection in mice infected with highly pathogenic and pandemic (H1N1) strains of influenza virus. The extensive production in the developed world, combined with the significant degree of protection described here, establishes these drugs as a potential therapeutic option that may be broadly implemented to combat serious disease caused by future influenza pandemics.

Murthy, Rajini Krishna

Project length	Short-term
Prior Research Experience	Yes
Funding Source	NIH T35 Short Term Training Grant
Faculty Advisor	Tim M. Townes
Title	Skin Fibroblasts for Genetic Correction of Epidermolysis Bullosa

Abstract

Epidermolysis Bullosa (EB) refers to a group of inherited skin disorders characterized by extreme mechanical fragility of the skin. In normal individuals, the basement membrane zone (BMZ) tightly anchors the epidermis and dermis. In individuals with EB, this tight connection is lost due to a genetic mutation of one of the components of the BMZ, resulting in severe skin blistering.

This project focused on recessive dystrophic EB (RDEB), which results from mutations in both alleles of collagen type VII (*COL7A1*) gene, a major component of anchoring fibrils that connect the lower BMZ to the dermis.

The aim of this project was to adapt the method developed by Dr. Tim Townes at UAB and Dr. Rudolf Jaenisch at MIT in curing a humanized sickle cell mouse model by replacing the sickle mutation in β -globin (β^S) gene with a normal β -globin (β^A) gene in induced pluripotent stem (iPS) cells by homologous recombination. The corrected iPS cells were differentiated *in vitro* into hematopoietic stem cells (HSC) for transplant to cure the sickle animals. The objective of this study was to correct the *COL7A1* mutation in iPS cells derived from skin fibroblasts of RDEB patients.

Skin biopsy from EB patients is pending IRB approval in reprogramming human keratinocytes into iPS cells. An alternative project was started to generate a sickle correction targeting construct containing 5'- and a 3'-homology sequences, and a positive and a negative selection cassette located in intron 1 of the β -globin gene. The correction construct will be transferred into sickle iPS cells by electroporation. The correct targeted iPS cells will be isolated by the positive and the negative selections and differentiated into HSC for transplant. Once the patient-specific correction constructs are generated, they will be used for gene therapy to repair the *COL7A1* genetic mutations in iPS cells from EB patients.

Nwaobi, Sinifunanya

Project Length	Long Term
Prior Research Experience	Yes
Advisor	Dr. Andrew West and Dr. David Standaert
Title	Neuroinflammatory Role of LRRK2 in Parkinson's Disease

Abstract

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common known genetic cause of late-onset Parkinson disease (PD). Approximately 5-6% of familial cases of PD have been associated with LRRK2 mutations in Western populations. Mutations in LRRK2 result in a form of PD that is phenotypically similar to that of the more prevalent idiopathic late-onset PD. Thus, understanding the function of LRRK2 in the development of genetic PD may also provide insight into the more predominant idiopathic causes of PD.

Current research focuses on uncovering the function of LRRK2 within neurons that leads to cell dysfunction, an approach which emphasizes cell-autonomous effects of LRRK2. However, LRRK2 (and other familial PD genes such as α -synuclein) are also expressed within non-neuronal cells in the brain leading to the possibility that neuronal damage may be a result of non-autonomous mechanisms. Recent work has demonstrated that immune cells important in neuroinflammation express high levels of LRRK2. Here, we begin to examine a potential neuroinflammatory function of LRRK2.

We utilized two endogenously expressing LRRK2 cell types, a human acute monocytic leukemia cell line (THP-1) and primary rat microglia to study non-neuronal function of LRRK2. We hypothesized that LRRK2 is a mediator of inflammation in monocyte-macrophage lineage cells whereby a reduction of LRRK2 activity attenuates a lipopolysaccharide (LPS)-induced immunogenic response in THP-1 cells and microglia. mRNA was isolated and changes in cytokine expression were measured using quantitative polymerase chain reaction (Q-PCR). Lentiviral knockdown of LRRK2 allowed for comparisons of cytokine expression with and without LRRK2 following LPS stimulation. Our data show that with significant knockdown of LRRK2, there is a striking reduction in the expression of IL-1 β , an inflammatory cytokine. This study implicates LRRK2 in the inflammatory pathway and opens the door for greater exploration into the role of LRRK2 in PD.

Odom, Carl

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Departmental or Mentor Funds
Advisor	Dr. James Markert and Dr. Jacqueline Parker
Co-Authors	David Gaston

Title	Natural Killer Cell Activating Ligand Expression in Glioma Cell Lines Following Oncolytic HSV-1 Infection
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Abstract

Despite advances in radiosurgery and chemotherapy, outcomes for patients with malignant glioma (MG) remain poor. Experimental therapeutic strategies include oncolytic herpes simplex type-1 virus (oHSV) vectors containing deletions of the neurovirulence gene, γ 134.5. Following a Phase I trial of the oHSV vector G207, a microarray analysis demonstrated increased expression of molecules associated with natural killer (NK) cell activation in patients responding to G207 therapy: 1) the activating receptors NKG2D and DAP10, and 2) the activating ligand MICB. These data led to the hypothesis that NK cells recognizing oHSV infected glioma cells through increased activating ligand expression may positively impact oHSV efficacy. To begin addressing this hypothesis, mRNA levels of the NK cell activating ligands MICA, MICB and ULBP1-6 change following oHSV infection of human D54-MG and xenograft 456 cells were determined using RT-PCR. Expression of activating ligands was established in these cell lines and expression levels of most transcripts were shown to be impacted by oHSV infection. Whether an individual transcript level was found to increase or decrease following oHSV infection was both transcript and cell line dependent. These data suggest oHSV is capable of changing activating ligand expression of infected glioma cells, which may result in differing susceptibility to NK cell mediated lysis. These data also provide a foundation upon which to continue investigation into the functional effects of activating ligand transcriptional changes following oHSV infection.

Ogorek, John

Project Length	Short
Prior Research Experience	No
Funding Source	Departmental or Mentor funds
Advisor	David Clark, M.D.
Co-Authors	
Title	Assessing Semantic Processing in Mild Cognitive Impairment: a MEG Analysis of the N400m

Abstract

Background: Mild Cognitive Impairment (MCI) is largely considered to be a transitional state between normal aging and Alzheimer's Disease (AD). Patients with MCI have a memory impairment that is out of proportion to that expected for their age, yet they do not meet commonly accepted criteria for dementia or AD. Related to this concept, semantic memory is impaired in individuals with AD but appears to start declining before a diagnostic progression from Mild Cognitive Impairment to AD. However, detecting this subtle change can be difficult to diagnose, especially in very high functioning individuals. As such, detecting the neuroanatomic or electrophysiologic correlates that accompany early declines in semantic memory performance may serve as valuable diagnostic tools.

Cognitive event related potentials (ERPs) are measured brain responses comprised of the summation of excitatory and inhibitory postsynaptic potentials. The N400 is a component of the ERP that is related to semantic memory or semantic integration processes during sentence processing. In the healthy adult brain, the N400 is proportional to semantic processing load and inversely proportional to semantic expectancy. In contrast, individuals with AD tend to display a severely diminished N400, if any at all.

Objective: This investigation focused on the neuromagnetic homologue of the N400, which will term the N400m. This is an event related magnetic field that is triggered by the same sorts of stimuli as the N400 and has the same latency, but is measured with magnetoencephalography (MEG). This was an attempt to demonstrate a diminished N400m magnitude in individuals with MCI compared to age matched controls.

Method: Subjects (N=5) underwent MEG recordings while participating in a self-paced reading task in which half the sentences ended with an unpredictable word, designed to elicit an N400m response. We then computed N400m magnitude as the total area between averaged curves elicited by predictable and unpredictable words in channels selected for visually obvious N400m effects. Results and their implications will be discussed herein as they pertain to the goals of future analyses, working towards the goal of demonstrating MEG's usefulness in evaluating and staging MCI and early AD.

Oliver, James

Project Length

Intermediate

Prior Research Experience

No

Funding Source

Departmental/ Mentor Funds

Advisor

Dr. Brent Ponce

Co-Authors

Dr. Brent Ponce, Dr. Steven Theiss, Dr. Jay Savage, Thomas Seales

Title

OITE Correlation with ABOS Part I Examination: The Predictive Power of Individual OITE Subsections

Abstract

The Orthopaedic In-Training Exam (OITE) and ABOS examinations are benchmarks used by the American Academy of Orthopaedic Surgery and the American Board of Orthopaedic Surgery. Analysis of the twelve subsections on the OITE with correlation of the ABOS part I performance has not been reported. The purpose of this study was to evaluate OITE subsection results with ABOS Part 1 performance. OITE and ABOS scores of graduating residents from 1999-2009 were analyzed using general linear modeling. Annual OITE scores, including the subsections of the exam, were averaged across the years. The subsection totals as well as total questions answered correctly and national percentile rank were analyzed to find a correlation (R coefficient) with passage of the ABOS examination. Overall total number of questions answered correctly each year as well as yearly national percentile rank highly correlated with ABOS passage ($R=0.21643$, $p=0.0045$ and $R=0.41584$, $p<0.0001$). Analyzing the OITE subsections individually, the Musculoskeletal Trauma subsection had the strongest association with ABOS rank ($R=0.28534$, $p<0.0002$). Of the remaining 11 subsections, Hip and Knees, Spine, Orthopedic Science, and Orthopedic Disease all were significant but did not have as strong correlation as the Musculoskeletal Trauma. The Musculoskeletal Trauma subsection showed the strongest correlation to ABOS rank compared to the rest of the OITE subsections. Despite trauma being a small percentage of the OITE, the knowledge required mirrors the knowledge required for successful ABOS Part I performance. Therefore, residents and residency directors should look closer at the Musculoskeletal Trauma subsection when trying to predict a resident's performance on the ABOS Part 1 Exam.

Owen, Matthew

Project Length Short

Prior Research Experience No

Funding Source Departmental or Mentor funds

Advisor Rena L. Stewart M.D.

Co-Authors

Title A Novel Open-Fracture Rat Model Utilizing
Acinetobacter baumannii

Abstract

Introduction: The purpose of this study is to develop a reproducible model of a contaminated, open fracture in rats using a clinically relevant bacterium, *Acinetobacter baumannii*.

Methods: An open, comminuted fracture and soft tissue injury was created in the femurs of 26 Brown Norway rats. Groups of 4-5 rats were inoculated with increasing concentrations of *A. baumannii* from 1×10^5 to 1×10^9 CFU. All other aspects of the surgery were consistent for each rat. Post-operative radiographs were taken weekly until sacrifice on day 28. At 28 days, femurs were explanted, examined for gross biomechanical strength, and sent for microbiological analysis.

Results: 3 rats died due to intra-operative complications. Nonunion of the gap was found in all specimens. Radiographic analysis at 4 weeks showed osteomyelitis in 3/14 rats given less than 10^8 CFU (lower concentration group) versus 4/9 rats given inoculums of greater than 10^8 CFU (higher concentration group). Hardware failure and loss of gap height was seen in 61% of total specimens. Microbiologic analysis showed the presence of bacteria in 78% of bone cultures overall. The lower inoculum group showed 2/14 infected with *A. baumannii*, 7/14 with other opportunistic pathogens and 0 with both *A. baumannii* and another pathogen. In the higher inoculum group, 5/9 showed *A. baumannii*, 2/9 showed other pathogens and 1/9 showed both *A. baumannii* and another pathogen.

Conclusions: Our clinically isolated strain of *A. baumannii* shows decreased virulence in rats. To increase virulence, we have produced new inoculum cultured from specimens that showed radiographic osteomyelitis. We are presently increasing inoculum concentration up to 1×10^{10} CFU. Several specimens showed positive bone cultures but no radiographic signs of osteomyelitis, representing quiescent infection instead of the florid osteomyelitis necessary for this model. A different strain with more rodent virulence may need to be selected.

Owens, Milner

Project Length

Intermediate

Prior Research Experience

Yes

Funding Source

NIH T35 Short Term Training Grant

Advisor

Nathaniel Robin

Co-Authors

Nathaniel Robin, Kevin Leon

Title

Evaluation of informative media educating cystic fibrosis patients about their reproductive options

Abstract

Cystic fibrosis (CF) is an autosomal dominant disorder affecting over 30,000 Americans. In a previous preliminary study, it was shown that the majority of patients with cystic fibrosis surveyed knew about their potential as regards their ability to have a child, but only a portion knew about the specific options for assisted reproduction or their risk to have a child with CF. It has also been determined that cystic fibrosis patients that have a relationship show more satisfaction and higher ratings of their quality of life and furthermore, that men with CF especially felt that their infertility status affected their ability to have a romantic relationship. In order to address these issues, this study created an educational brochure for use in CF clinics that addresses the fertility status, genetic status and possible reproduction options of CF patients. The ability of the brochure to effectively communicate important information to patients with CF with various backgrounds and levels of education was tested via the administration of two surveys. The first survey, given before the patient has access to the brochure, measured the baseline knowledge that CF patients have about reproductive and genetic issues. The second survey, given out with the brochure and taken while the patient could reference the brochure, ultimately measured the amount of information that the brochure effectively communicated to patients. Preliminary results have shown that the brochure does indeed effectively expand the patient's current knowledge about their disease, their ability and options to reproduce and the genetics involved with having a child. The percentage of correct answers has increased noticeably. In addition, via patient feedback, it has been made clear several times that these issues are important to patients and many have not had a talk with a clinician about having a child. It is hoped that when the study is finished in January 2011, that the brochure can be revised, according to patient input, and disseminated as a learning tool for patients that have cystic fibrosis and as a conversation starter for clinicians that take care of these patients.

Parchman, Michelle

Project Length Intermediate

Prior Research Experience No

Funding Source Departmental

Advisor Shirley Robinson Hankins

Co-Authors Kanyare, L., Johnson, D., Sturdevant, M., Kempf, M. C., Hankins, S.

Title: Adherence to Antiretroviral Medication in Pregnant Women with Human Immunodeficiency Virus

Abstract

With the advent of antiretroviral therapy (ART), Human Immunodeficiency Virus (HIV) can now be considered a chronic but manageable disease. Unfortunately, these drugs require strict adherence to be maximally effective. Optimal adherence to ART in pregnant women living with HIV is not only critical for the health of the women, but also for the prevention of HIV transmission to their unborn children. Several factors such as depression, age, and clinical factors such as CD4 count and viral load have been identified as predictors of ART adherence among this particular subset of women. In this pilot study, we conducted a retrospective review of medical records from 54 pregnant women living with HIV who received care in a university sponsored HIV clinic (2004 to 2008). Descriptive and correlation analyses were performed using women's self-reported number of missed doses in the past month and selected lab values, depression scores, and demographic variables. When available, data were collected from one year prior to women's estimated dates of conception through one year after delivery. Preliminary analyses revealed a significant positive correlation between number of missed ART doses and HIV viral load during pregnancy ($n=27$, $r=.46$, $p=0.015$). During the year following delivery, a negative trend was observed between number of missed doses and maternal age at conception ($n=24$, $r=-.37$, $p=0.070$). Maternal depression was also negatively correlated with age at conception during pregnancy ($n=9$, $r=-.75$, $p=0.021$) and after delivery ($n=27$, $r=-.53$, $p=0.004$). While the sample size of this study was small and not all measures were available for all women, further research needs to focus on understanding and improving ART adherence rates among pregnant women living with HIV during and after delivery, particularly women of young age and women suffering from a mental health diagnosis such as depression.

Parker, Walter

Project Length

Short

Prior Research Experience

No

Funding Source

NIH T35 Short Term Training Grant

Advisor

Cynthia Owsley

Co-Authors

Gerald McGwin, Jr., Joanne M. Wood, Jennifer Elgin,
Michael S. Vaphiades, and Lanning B. Kline

Title

Self-Reported Driving Difficulty by Persons with
Hemianopia and Quadrantanopia

Abstract

Background: In both monocular and binocular visual field loss, the term hemianopia is used if one half of the field is involved; quadrantanopia is used if only one quadrant is affected. Homonymous field loss is in the same relative position of each eye. No study has addressed the particular driving activities that concern persons with homonymous hemianopia or quadrantanopia. Objective: We examined self-reported driving difficulty by persons with homonymous hemianopia or quadrantanopia and how it compared to that reported by age-matched drivers with normal visual fields. We also examined how their self-reports of difficulty compared to driving performance ratings provided by a certified driving rehabilitation specialist. Methods: Participants included 17 hemianopic, 7 quadrantanopic, and 24 normal visual field persons age-matched to the drivers with hemianopia or quadrantanopia, all of whom had current drivers' licenses. We collected information regarding driving difficulty in 21 typical driving situations separated into 3 groups (reliance on peripheral vision, low visibility, and independence/mobility) via questionnaire. A certified driving rehabilitation specialist used a standard assessment scale to evaluate on-road driving performance. Results: Drivers with visual field loss (hemianopia and quadrantanopia) expressed significantly greater difficulty with driving maneuvers involving peripheral vision and independence/mobility, as compared to those with normal visual fields ($p = <0.0001$; $p = 0.0007$, respectively). Drivers with hemianopia and quadrantanopia who were rated as unsafe drivers based upon an on-road evaluation by the driving rehabilitation specialist were no more likely to report driving difficulty than those who were rated as safe. Conclusions: This study highlights aspects of driving that hemianopic or quadrantanopic persons find particularly problematic, thus suggesting areas that could be focused on driving rehabilitation. Some drivers with hemianopia or quadrantanopia may inappropriately view themselves as good drivers when in fact their driving performance is unsafe as judged by a driving professional.

Parrish, Nicholas

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Dr. Beatrice Hahn
Co-Authors	Juliet Easlick, Meagan O'Brien, Julie Decker, Weimin Liu, Hui Li, Nina Bhardwaj, George Shaw, Beatrice Hahn
Title	Envelope Content and Dendritic Cell Interaction of Transmitted/Founder HIV-1

Abstract

Background: With the identification and cloning of transmitted/founder (t/f) viruses, biological assessment of the very virus that crosses relevant bottlenecks and leads to infection is for the first time possible. 80% of heterosexually acquired infections result from a single t/f virus, which raises the question of whether or not these viruses are biologically different from viruses that are not transmitted; a phenotype conferring increased probability of transmission would offer clues concerning the mechanisms underlying transmission. Since one model of HIV transmission proposes early contact with dendritic cells, we addressed whether or not t/f viruses might interact with or infect dendritic cells more readily than controls.

Methods: Stocks of a diverse panel of infectious molecular clones, representing viruses transmitted mucosally and intravenously, along with commonly used lab strains (eg. SG3, BaL) and viruses from chronically infected patients were generated in peripheral blood mononuclear cells (PBMCs). Capsid (p24) and envelope glycoprotein (gp120) content of sucrose-pelleted virions was quantified by western blotting and ELISA. Dendritic cells (MoDCs) were derived from CD14-selected monocytes cultured with GM-CSF and IL-4. The ability of immature MoDCs to capture virus was assessed by exposing the cells to virus followed by extensive washing and quantification of cell-associated virus. Immature and mature MoDCs were infected alone or co-cultured with autologous CD4+ T cells in a *trans*-infection assay monitored by p24 ELISA.

Results: All viruses replicated to high titer in CD8+ cell-depleted PBMCs. Envelope incorporation was variable across t/f viruses. For example, the virus with the highest Env incorporation, CH106, had at least 4 times more gp120 per nanogram of p24 than another t/f virus, CH58. There was a trend towards higher Env incorporation in t/f viruses compared to controls. Interestingly, virion Env content was significantly correlated with MoDC binding. All t/f viruses replicated efficiently in immature MoDCs but only poorly in mature MoDCs. Notably, exposure of mature MoDCs to virus followed by co-culture with autologous CD4+ cells resulted in high-titer replication.

Conclusions: Envelope content of PBMC-derived t/f virions is variable but positively correlated with capture by MoDCs. While t/f viruses are not macrophage-tropic, they are capable of infecting and replicating in dendritic cells. Our results suggest that dendritic cells, through their ability to capture virus and facilitate the infection of CD4+ T cells, may select for t/f viruses with high envelope glycoprotein content.

Patterson, Derek

Project Length Intermediate

Prior Research Experience Yes

Funding Source Non-UAB Funding (External Funding Source)

Advisor Dr. Candace Floyd

Co-Authors

Title The Impact of Nicotine on Functional Recovery and Neuropathic Pain in Spinal Cord Injuries

Abstract

Spinal cord injuries dramatically alter the life of all those who are affected by both loss of function and increase of pain. It has been proposed that nicotine may be protective against loss of function in spinal cord injuries, but also that nicotine withdrawal may cause an increase in neuropathic pain in these same patients. This study examines three groups of rats all given a T13 spinal cord injury, but treated with saline, chronic nicotine, and nicotine withdrawn 14 days after spinal cord injury. Animals given nicotine before spinal cord injury experienced increased functional recovery when judged by the BBB score as compared to animals treated only with saline. However, animals with nicotine withdrawn on day 14 experienced higher levels of both mechanical allodynia and thermal hyperalgesia than the other treatment groups. These findings could be due to an increase in both TLR-4 and GFAP expression in these animals.

Pearson, Alana

Project Length Intermediate

Prior Research Experience Yes

Funding Source Departmental or Mentor Funds

Advisor Nita A. Limdi, Pharm.D, PhD, MSPH

Co-Authors Hills CE and Beasley TM

Title Influence of *ApoE* Genotype on dose, anticoagulation control and hemorrhagic complications among warfarin users

Abstract

Background: Warfarin response is highly variable and is influenced by a multitude of clinical factors. Two genes, *CYP2C9* and *VKORC1*, explain a significant portion of the variability. Polymorphisms in the gene encoding apolipoprotein E (*ApoE*) may partly explain this variability by altering hepatic uptake of vitamin K. Herein we investigate the influence of *ApoE* genotype on warfarin dose, anticoagulation control and risk of major hemorrhage.

Methods: *ApoE* genotype was assessed by interrogating two polymorphisms (rs429358 and rs7412) among participants (n=638; 46% Black) of a prospective cohort study. *ApoE* genotype was categorized based on possession of the E4 allele. The target International Normalized Ratio (INR) was 2-3 for all participants. Percent time spent in target range (PTTR) was used as the measure of anticoagulation control. Regression analysis was used to evaluate the association of *ApoE* with warfarin dose, anticoagulation control, and hemorrhage after adjusting for clinical factors (age, race, gender, weight, concurrent use of statins or *CYP2C9* inhibitors, and co-morbidity such as chronic kidney disease) and *CYP2C9* and *VKORC1* genotype.

Results: *ApoE* allelic distribution was different across race groups (p=0.0031) with *ApoE* E4 variants more common in Blacks compared to Whites. Possession of the E4 allele was associated with higher warfarin dose, however this finding was not significant in univariate (p=0.45) or multivariable analysis (p=0.3). Participants possessing the E4 allele spent less time in target INR range and more time below range (p<0.0001). After adjustment for clinical factors and *CYP2C9* and *VKORC1* genotype, carriers of *ApoE* E4 spent less time above target range (p<0.0001). Possession of the E4 allele did not influence the risk of major hemorrhage in univariate or multivariable analysis (p>0.36).

Conclusion: *ApoE* E4 genotype did not influence dose or hemorrhagic risk but may influence anticoagulation control through complex interaction with dietary vitamin K intake and other factors.

Pierce, Caleb

Project Length Short

Prior Research Experience No

Funding Source NIH T35 Short Term Training Grant

Advisor Dr. Fadi Hage

Co-Authors Dr. Sazanne Oparil

Title Blockade of the Renin-Angiotensin system reduces neointima formation in CRPtg mice

Abstract

The last decade has demonstrated that CRP is a precise and accurate marker of the risk for cardiovascular disease, but its role in pathogenesis remains controversial. Vascular injury causes excessive proliferation of the intima resulting in the formation of neointima that contributes to many types of cardiovascular disease. Using mice carrying the human CRP transgene (CRPtg), we have previously demonstrated that CRP exacerbates neointimal thickening following acute vascular injury. The renin-angiotensin system (RAS) also plays a central role in vascular proliferative disorders. We hypothesize that in the setting of acute vascular injury an inflammatory cascade initiated by CRP exacerbates the effect of the RAS on neointima formation. Interrupting this pathway with a specific renin inhibitor (aliskerin) should ameliorate neointima formation, and we speculate that combination with an ATII receptor blocker (valsartan) will show added benefit.

To model acute vascular injury, we ligate the right carotid artery of twelve week, ovariectomized female CRPtg mice. Twenty-eight days after carotid ligation, the mice are euthanized and the vasculature is flushed with sodium phosphate buffer and perfused with formalin. Both carotid arteries are then excised, fixed in formalin, and sectioned. The ligation site is identified by examining H&E stained serial sections. Additional sections taken at 200, 500, and 700 micrometers are stained with Verhoeff's stain. Digital images are then analyzed by computer assisted morphometric analysis to determine the relative areas of the intima and media. Drugs are administered by subcutaneous micropumps.

Preliminary results support our hypothesis that CRP increases neointimal formation by increasing the activity of RAS. The ratio of intima to media is significantly smaller in the experimental group indicating neointimal formation is reduced in CRPtg mice treated with antagonists to the RAS. These results support a likely mechanism by which CRP is an active participant in the pathogenesis of vascular proliferative disorders.

Planz, Virginia

Project Length Intermediate

Prior Research Experience Yes

Funding Source Departmental or Mentor funds

Advisor Mark Lockhart

Co-Authors Tatum A. McArthur, MD, Mark E. Lockhart, MD, Naomi S. Fineberg, PhD and Lincoln L. Berland, MD

Title CT Evaluation of Common Duct Diameter in Post-Cholecystectomy Patients with at Least Two-Year Follow-up

Abstract

Background: Although the common duct (CD) is commonly believed to dilate after cholecystectomy, latest research and previous studies have not confirmed this prevalent opinion. Patients with CD dilation after cholecystectomy may undergo further testing leading to increased medical costs and risk of morbidity associated with tests. We addressed the question of whether or not the CD normally dilates in post-cholecystectomy patients by CT evaluation of the CD diameter and its change over time in remote and interval cholecystectomy and non-operated patients.

Methods: This retrospective study evaluated baseline CD diameter, intrahepatic biliary dilation, and interval duct diameter change in patients (ages 17-84) with two abdominal CTs at least 2 years apart between 1/1/2002 and 12/31/2008 (n=324). The baseline, follow-up, and interval change in CD diameters of patients with remote cholecystectomy (Group 1, n= 54) were statistically compared to those who had interval cholecystectomy (Group 2, n=35) and those with no history of cholecystectomy (Group 3, n=195). Patients with acute pancreatobiliary disease by clinical and/or laboratory data and surgical complications were excluded (n=40). Clinical data and duct diameters were evaluated using chi-square, ANOVA, and Tukey's HSD tests.

Results: Group 1 had a larger mean duct diameter than the other groups at baseline CT ($p<0.001$) and follow-up CT ($p<0.001$). Group 2 showed a greater increase in duct size than other groups at follow-up ($p=0.001$). In Group 2, thirteen patients (37%) had normal-sized CDs before and after cholecystectomy, and dilated CDs were found in 7 patients (20%) before surgery and 22 patients (63%) postoperatively.

Conclusions: Greater increase in ductal diameter occurred in interval cholecystectomy patients, suggesting that dilation may, indeed, occur post-cholecystectomy. This suggests that the extrahepatic biliary system that is normal before cholecystectomy will dilate in most cholecystectomized patients without clinical evidence of pancreaticobiliary disease. These patients may require no further testing or evaluation.

Poholek, Catherine

Project Length Short

Prior Research Experience Yes

Funding Source NIH Medical Scientist Training Program Grant

Advisor Charles O. Elson, MD

Co-Authors

Title Evidence for the role of Th17 cells in the maintenance of intestinal homeostasis

Abstract

Inflammatory Bowel Disease (IBD) is a group of chronic inflammatory disorders that affects an estimated 1-2 million people in the United States. The current understanding of IBD pathogenesis is that disease results from a dysregulation between intestinal flora and the mucosal immune system in a genetically susceptible host. Humans have an estimated average of 100 trillion bacteria in their intestine comprised of at least 15,000 species. During IBD, adaptive immune responses to these microbiota are increased. Th17 cells have been shown to be protective against certain bacteria and fungi and have also been implicated in the pathogenesis of IBD. In order to understand the role of Th17 cells in the disease state, we must first understand the role of Th17 cells in the normal response to intestinal microbiota. We hypothesize that Th17 cells in the lamina propria maintain the host-microbiota homeostatic relationship by inducing intestinal epithelial cells to produce anti-microbial products. To examine this hypothesis we created an *in vitro* model whereby murine naïve CD4⁺ T cells were induced to become Th17 cells. The products of these cells were then co-cultured with Mode K cells, a murine intestinal epithelial cell line, and Mode K cells and their products were examined by ELISA and real-time PCR. Our results indicate that Mode K cells are capable of producing lipocalin-2 (LCN-2) and regenerating islet-derived protein III gamma (RegIII γ), two anti-microbial proteins, when stimulated with lipopolysaccharide (LPS). In addition, Mode K cells respond to Th17 cell products by upregulating their production of LCN-2 and RegIII γ . While interleukin-17 (IL-17) has been implicated in many of the functions of Th17 cells, we also show that IL-17 is not sufficient for the induction of these antimicrobial products. This study has provided an effective model that can be used for further studies on the interactions between gut epithelial cells and lymphocytes in murine systems. It has also provided evidence that Th17 cells play a role in maintaining normal intestinal homeostasis between the vast microbiota and the intestinal immune system.

Record, Jessica

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Randy Q. Cron
Co-Authors	Timothy Beukelman
Title	High Prevalence of Inflammatory Myositis in Patients with Pediatric Lupus in Alabama

Abstract

Inflammatory myositis is recognized as a feature in 5-11% of adult systemic lupus erythematosus (SLE) patients. The aims of this study were to determine the prevalence of myositis in a cohort of pediatric SLE patients from the Children's Hospital Alabama (CHA), to compare this rate with the reported prevalence in the medical literature, and to evaluate clinical factors for possible association with myositis. We performed a retrospective chart review of 55 patients who satisfied ≥ 4 out of 11 ACR criteria for SLE who were evaluated at the CHA since January 1, 2008. Laboratory, clinical, and serologic characteristics of all patients were collected. Patients were defined as having myositis if they satisfied one of the following categories: 1) Proximal muscle weakness on physical exam with evidence of lower extremity muscle edema on MRI; 2) Proximal muscle weakness on physical exam with an elevation in one of the following muscle enzymes: CK, AST, aldolase, or LDH; or 3) Patient reported muscle weakness or muscle pain with an elevated CK. Standard statistical tests were used to compare the rate of myositis in this cohort to previously reported rates and to determine possible associations between myositis and clinical and laboratory findings. We found inflammatory myositis present as a feature of SLE in 31% ($n=17$) with a 95% confidence interval of 19-45%, statistically different from the reported rates of 5-11% ($p<0.0001$). Positive associations with myositis were the presence of anti-ribonucleoprotein antibodies ($p=0.009$) and anti-Smith antibodies ($p=0.06$). In conclusion, pediatric SLE myositis is present at a statistically higher rate in the state of Alabama than previously published values of adult SLE myositis. The association of both anti-ribonucleoprotein and anti-Smith antibodies with myositis highlights the significant overlap SLE has with other autoimmune diseases and the challenges that come with appropriately classifying and treating these overlap patients.

Reish, Nicholas

Project Length

Intermediate

Prior Research Experience

Yes

Funding Source

Non-UAB Funding (External Funding Source)

Advisor

Alecia Gross

Co-Authors

Title

Monitoring Rhodopsin Trafficking in Transgenic Tadpoles

Abstract

Normal vision requires the proper function of rod and cone photoreceptors. Photoreceptors are highly specialized neurons which sense light in a special organelle called the outer segment. In rods, the rod outer segment (ROS) consists of a stack of membranous disks within a plasma membrane, connected to the rest of the cell via a connecting cilium. The ROS is continuously phagocytosed and renewed in healthy rods, at the rate of 10% per day. Mutations that interfere with this renewal cause retinal diseases, including the blinding disease retinitis pigmentosa (RP). A major cause of RP is mutation in the light-sensing protein in rods, rhodopsin. Previous studies on rhodopsin have revealed the carboxy-terminus of the protein as the structural element necessary for proper trafficking and disc biogenesis. While much progress has been made in understanding how the c-terminus' protein interactions guide post-golgi trafficking, the interactions (with a hypothesized second complex) responsible for rod disk biogenesis remain unclear. The goal of this study is to identify those proteins interacting with the c-terminal tail of rhodopsin in the process of disk formation, and to understand how these proteins assemble rhodopsin-containing membranes into disks. Because rod cells do not maintain their morphology in culture, it is necessary to study this process in vivo in an animal model. The African clawed frog *Xenopus laevis* has been used in vision research for decades and is easily made transgenic. We will use transgeneic *Xenopus* tadpoles expressing epitope-tagged or fluorescent-tagged rhodopsin to monitor the trafficking of rhodopsin. This monitoring will be combined with morpholino knockdown and shRNA techniques directed against candidate disk formation proteins. In each case, we will test the hypothesis that the candidate participates in disk formation.

Reynolds, Harris

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Peter D. Ray, MD
Title	Facial Contact Burns at Alabama's Major Tertiary Care Center: 2000-2009

Abstract

Background: Burn-related injuries are a significant cause of morbidity and healthcare cost in pediatric patients. We seek to characterize facial contact burns from 2000-2009 at The Children's Hospital of Alabama (TCA), the major tertiary Children's hospital with a pediatric burn unit in a 150 mile radius. Methods: Data was gathered from the admissions log of the Burn Unit at TCA from 2000-2009. Patients under 18 with contact burns to the face less than ten percent of their total body surface area (%TBSA) were analyzed. Results: Data from each patient was collated and statistical analysis was performed. The average age of patients analyzed was 3.2 years old. Of the patients analyzed, 82% were male. Caucasians represented 64% of patients. An iron was the burn agent in 55% of the cases. Patients traveled an average of 104 miles from their hometown to receive care and the longest distance traveled was 254 miles. Some type of surgery other than debridement was required in 36% of patients. The average %TBSA affected was 3%. The majority of cases (55%) were admitted between 8 pm and 4 am. The median length of stay was two days. 84% of patients with 1-2% TBSA burns stayed one day or less. Conclusion: Proper parental supervision, especially of children under age 3, could help prevent serious burn-related injuries. The majority of our cases occurred between 8 pm and 4 am, when parents are likely to leave children unattended. Incomplete records in the burn unit logbook were common. An electronic logbook could be a useful tool for TCA's burn unit. It would enable data to be entered accurately with less effort than hand written notes and accessed easily. Finally, further analysis of TCA's emergency department records should be completed to expand this data set and compare it to national averages.

Robert, Stephanie

Project Length	Short
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Harald Sontheimer
Co-Author	
Title	Mechanism underlying radio-resistance and chemo-resistance of glioma cells

Abstract

Gliomas are glial derived tumors, which make up 80% of malignant brain tumors. These tumors upregulate transport mechanisms that promote glioma cell survival. System xc⁻, one of these mechanisms, mediates the uptake of L-cystine for conversion into glutathione (GSH), and has been shown to be involved in growth progression, radiotherapy and chemotherapy resistance of gliomas. Inhibition of system xc⁻ leads to decreased L-cystine uptake, reduced intracellular GSH concentrations and slowed tumor growth. Here we examine the effect of system xc⁻ on radiation and chemotherapy resistance of glioma cells through the depletion of GSH using L-cystine depleted growth medium, while treating glioma cell lines D54-MG, U87 and U251 with radiation or chemotherapeutics (including Temozolomide (TMZ), Carmustine, and Cisplatin). Cell number was examined 1-4 days after treatment using a Coulter-Counter Cell Sizer. GSH levels and L-cystine uptake was measured using assays at specific time points, before and after radiation. xCT protein expression was examined using Western blot following radiation and chemotherapy. The cell lines showed little sensitization to radiation under GSH depleted conditions, even with verified depleted GSH levels in treated cells. However, uptake assays suggested variation in L-cystine uptake by cells over varying time points after radiation. Likewise, protein expression of xCT increased with increasing radiation doses under GSH depleted conditions. Chemotherapy treated cells showed even more promising preliminary data. U251 cells treated with Temozolomide under GSH depleted conditions showed a decreased cell number after 4 days, as compared to controls, suggesting a sensitization of cells to TMZ treatment. Future experiments are planned to further explore this sensitization of glioma cell lines to chemotherapeutics through GSH depletion and the role of system xc⁻ in the sensitization. Furthermore, radiation resistance will be further explored through examination of glioma stem cells (CD133+) possibly present in these cell lines, leading to the observed radio-resistance.

Roebuck, Natalie

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor John Grant, Michael Cunningham and Kelly Evans

Co-Author Babette S. Saltzman, Kathleen C Sie, Kelly N Evans

Title Outcomes in 200 children with RS: Does facial phenotype matter?

Abstract

BACKGROUND & PURPOSE: While Robin Sequence (RS) is a well-recognized condition, current classification systems do not account for the etiopathogenetic/phenotypic heterogeneity of RS, nor predict the optimal management course. As modalities for evaluating upper airway obstruction (UAO) in infants are limited, clinical assessment is critical. Does phenotype (specifically cleft type and mandibular involvement) affect treatment and/or outcomes in children with RS? Understanding phenotypic subtypes will guide research into etiology of RS and appreciation of the clinical course will direct prospective studies to evaluate outcomes in children with RS. The goal of this presentation is to describe the phenotype and clinical course of cohort of children born with RS, highlighting the key features.

METHODS: We conducted a retrospective review of ~200 children with RS cared for at SCH from 2000-2010. We included subjects with a diagnosis of RS or ≥ 2 of the following: micrognathia; glossoptosis; secondary cleft palate (CP); airway obstruction. Summary statistics were used to describe the distribution of infants' demographic, physical and clinical characteristics, which were then evaluated among phenotypic subgroups of RS (cleft type [CP1-3] and severity of mandibular involvement). UAO severity, medical/surgical treatments and short/long term outcomes were tabulated within the subgroups.

RESULTS: Subgroups were similar with respect to demographic characteristics. Preliminary data indicates an association between CP-2 and a milder clinical course. More severe micrognathia correlated with more severe UAO, use of assisted tube feeding, and hospital and ICU admissions. Prone positioning alone was successful in a significantly higher proportion of children with mild micrognathia (vs. severe). Further phenotypic assessments and delineation of variables analyzed will be addressed.

CONCLUSIONS:

Functional variables (work of breathing, gas exchange abnormalities, growth parameters) likely predict clinical outcomes, however cleft type and degree of mandibular involvement may relate to clinical course and outcomes. The relationship between phenotype and clinical course may provide a framework for counseling families and caring for children born with RS.

Rutherford, John

Project Length	Long
Prior Research Experience	yes
Funding Source	5K01MH077955
Advisor	Rita Cowell, Ph.D
Co-Author	Beth Lucas, Vahram Haroutunian
Title	Mechanism of PGC-1 α control of GABAergic genes

Abstract

Cortical interneuron dysfunction has been implicated in the pathophysiology of schizophrenia and affective disorders. In particular, markers of interneuronal function are reduced in schizophrenic brain, and deficits in modulation of prefrontal cortical activity – thought to be governed by the same interneuronal type – exist in schizophrenia patients. PGC-1 α , a transcriptional coactivator best known as a regulator of oxidative metabolism, is expressed specifically in a subset of interneurons. Expression of PGC-1 α in a neuronal-like cell line which normally has very low amounts of PGC-1 α results in the induction of a number of genes of relevance to interneuronal function. Parvalbumin, a calcium binding protein which marks a functional subset of interneurons of particular relevance to schizophrenia, is used here as a prototype PGC-1 α -dependent interneuronal gene. Transgenic animals deficient in PGC-1 α have a marked reduction in parvalbumin expression in the cortex and striatum. Human frontal cortex from schizophrenic patients displays a loss of correlation between RNA levels of PGC-1 α and parvalbumin seen in age-matched controls, suggesting a disruption along an axis of signaling running through PGC-1 α to the regulation of parvalbumin gene expression. By using the region upstream of the parvalbumin gene to drive luciferase expression, we identified a discrete segment of DNA responsible for induction by PGC-1 α . This segment contains putative sites for association with transcription factors of the nur subfamily, which are known to have a role in activity-dependent transcriptional changes. Nur77, a member of this family, is also known to respond to haloperidol. A more thorough understanding of the mechanism of PGC-1 α control of parvalbumin expression might enable the extension of this mechanism to the control of other genes enacted by PGC-1 α , which we propose as a coordinator of interneuronal cellular phenotype.

Sarver, David Brasfield

Project Length Intermediate

Prior Research Experience Yes

Funding Source T-35 Short Term Training Grant

Advisor Robert Lopez-Ben, MD, CCD

Co-Authors Michael J. Pitt, MD, Robert Lopez-Ben, MD, CCD, Sarah L. Morgan, MD, RD, CCD, Justin N. Duke, MD, Naomi Fineberg, PhD

Title Association of the Presence of Bone Bars on Radiographs and Hip Fracture

Abstract

Objective:

Bone bars (BB) are struts of normal trabecular bone that cross the medullary portions of the metaphysis and diaphysis at right angles to the long axis of the shaft. The purpose of this investigation was to determine whether the presence of bone bars identified on anteroposterior hip radiographs are more prevalent in patients that have suffered a hip fracture (femoral neck (FN), intertrochanteric (IT), subtrochanteric (ST) and subtrochanteric and intertrochanteric (SIT)).

Materials and methods

Inclusion criteria: 1) Women aged 65 or older 2) With an anteroposterior radiograph of the hip for reasons not associated with excessive traumas. Exclusion criteria: 1) previous conditions associated with osteopenia or fracture 2) those who ever received medications known to affect bone mineral density 3) previous hip fracture besides the one noted for the study. 121 patients known to have no hip fracture were used as a control group. 133 patients with known hip fracture as evaluated on anteroposterior hip radiograph were used as the experimental group. The radiographs were evaluated for the presence of BBs by two musculoskeletal radiologists who were blinded to the previous radiological interpretation and presence of fracture or not. A t-test was used to evaluate the relationship of BB to hip fractures and a chi-square test was used to determine if BB were equally distributed among the categories of fracture.

Results

BBs were significantly more prevalent in the fracture group compared to the normal group. Bone bars are seen similarly in patients with femoral neck and intertrochanteric fractures. There are too few SIT and ST fractures to reach a conclusion about them.

Conclusions

If BBs are noted in a hip radiograph for a female over the age of 65, proper measures should be taken in order to assess bone quality and prevent hip fracture.

Scott, Adam

Project Length Short

Prior Research Experience Yes

Funding Source

Advisor Drs. Teresa Coco and Kathy Monroe

Co-Authors Teresa Coco, Kathy Monroe, William King

Title Pediatric Injury Prevention: Baby Safety Showers to Bring Safe May Flowers

Abstract

Objective: Unintentional injuries are the leading cause of death in children. The goal of this project is to reduce the number of childhood injuries by providing first time parents with basic injury prevention knowledge in a baby safety shower format, and to demonstrate the effectiveness of this format in knowledge retention.

Methods: Participants included first time parents either in pregnancy or with an infant less than or equal to 6 months of age. Each participant received a pre-test to determine baseline knowledge of injury prevention. Health care professionals then provided several brief lectures on a variety of injury prevention topics. A follow up post-test was administered by phone one month after the shower. Analysis of the most frequent questions missed on the pre-test was compared to the percent correct increase of the same questions on the post-test, using the z test of proportions.

Results: A total of 131 caregivers participated in eleven separate safety showers. The most common question missed on the pre-test was the temperature a water heater should be set to prevent scalding, with 43% answering correctly. On the post-test, 84% correctly responded ($z=5.6$, $p<.001$). The second most commonly missed question asked if it was safe for an infant to sleep in the bed with an adult. 73% correctly answered on the pre-test. 96% answered correctly on the post-test ($z=4.0$, $p<.001$). The third question most frequently missed asked about safe positioning of infants during sleep. 76% responded correctly on the pre-test, and 96% answered correctly on the post-test ($z=3.6$; $p<.001$).

Conclusions: Improvements seen in the post-tests demonstrate the effectiveness of the baby safety shower format for providing and retaining important injury prevention information that we hope will lead to a reduced number of preventable childhood injuries. We believe the baby safety shower format is an effective educational intervention.

Shah, Nemil

Project Length

Intermediate

Prior Research Experience

Yes

FundingSource

Departmental or Mentor funds

Advisor

Dr. Hyunki Kim and Dr. Kurt Zinn

Co-Authors

Nemil Shah, Helen Zhai, Sharon Samuel, Kurt Zinn, Eban Rosenthal, Tong Zhou, Hyunki Kim

Title

Anti-EMMPRIN therapy in combination with gemcitabine for pancreatic adenocarcinoma

Abstract

Pancreatic cancer, also known as the “silent killer”, carries a significant morbidity and mortality rate. Due to the tumor’s late presentation and aggressive biology, current pharmacologic and surgical treatments only marginally improve survival. There is a continued effort to develop models that significantly decrease the morbidity and mortality associated with advanced pancreatic cancer. Advances in molecular genetics and biology have contributed to a greater understanding of the neoplastic process, thus, specific targeted molecular therapy shows great promise. A murine, monoclonal antibody (Anti-EMMPRIN) targeting human CD147(EMMPRIN) receptors was radiolabeled with Tc-99m. The specific binding affinity (Kd) and the number of EMMPRIN receptors was measured in MIA-Paca-2 derived cell lines. evaluated Tc-99m-anti-EMMPRIN retention was evaluated by single-photon emission computed tomography and X-ray computed tomography (SPECT/CT) within orthotopically implanted pancreatic tumors xenografts. Subsequent, biodistribution analyses confirmed the levels. Scatchard assays delineated specific and high binding affinity of Tc-99m-anti-EMMPRIN to CD147. The Kd for the acid-stable binding component was 4.31 ± 0.59 (mean \pm SE) nM. However, the acid-labile binding component was too small to be quantitatively assessed. The average number of EMMPRIN per cell was $582,000 \pm 56,000$. SPECT/CT imaging analyses at 4 h after injection of Tc-99m-anti-EMMPRIN revealed higher levels of uptake than in the Tc-99m-isotope-control antibody. The biodistribution study confirmed the higher rate of uptake with labeled anti-EMMPRIN antibody (26.9 ± 3.4 %ID/g in tumor) versus the labeled isotype control antibody (26.9 ± 3.4 %ID/g in tumor). The tumor uptake of Tc-99m-anti-EMMPRIN was significantly ($p < 0.001$) higher than that of the Tc-99m-labeled isotype control antibody, while no difference was detected in liver and blood uptake ($p > 0.05$). Finally, four groups of SCID mice (Group 1-4) bearing pancreatic tumor xenografts were untreated (control) or treated with gemcitabine(120mg/kg weekly for two weeks, i.p.), anti-EMMPRIN monotherapy(0.2 mg twice-weekly for two weeks) , or given combination therapy respectively. The murine models were subsequently imaged on 21, 25, and 38 days after tumor implantation. PET/CT imaging confirmed the high efficacy of anti-EMMPRIN monoclonal antibody monotherapy and synergetic efficacy when combined with gemcitabine.

Shelley, David

Project Length

Short

Prior Research Experience

No

Funding Source

NIH T35 Short Term Training Grant

Advisor

Marcas Bamman

Co-Authors

Ed Merritt, Anna Thalacker-Mercer

Title

Skeletal muscle in old vs. young humans is not more susceptible to mechanical injury but appears to be in a pro-inflammatory state even at rest

Abstract

Background: With age, skeletal muscles exhibit an impaired regenerative capacity when exposed to the same stress as young, possibly due to the body's inflammatory response. This presents a serious concern to older adults experiencing muscle loss and/or attempting to recover from joint surgery. Purpose: To elucidate the effect of age on inflammatory mediators in muscle induced by mechanical stress. Methods: Muscle and blood samples were collected before and 24 hours after high intensity knee extensor resistance loading (used to induce minor muscle damage: 9 sets, 10 repetitions, 60% of 1-repetition maximum) from young (n = 40), middle-aged (n = 25), and old adults (n = 27). Serum creatine kinase (CK) levels, a marker of muscle membrane damage, and the content and activation state of key intermediates of pro-inflammatory cytokines (IKK α , I κ B α , NF κ B, JNK, p38) were assessed. Results: Serum-CK levels increased post-exercise, but no differences existed between age groups indicating that all age groups experienced similar levels of muscle injury. Old adults had the highest resting and post-exercise levels of the inflammatory mediator NF κ B, and both the activated and total levels of the NF κ B-regulator, I κ B α . After mechanical loading, most inflammatory intermediates showed a similar response regardless of age. Conclusions: These results indicate that despite the same magnitude of muscle damage and a similar inflammatory response to mechanical load, older adults might have an impaired muscle regeneration response due to heightened resting levels of inflammatory intermediates.

Skelley, Jason

Project Length

Intermediate

Prior Research Experience

Yes

Funding Source

Cunningham Fellowship (Pediatrics)

Advisor

Joycelyn Atchison, MD

Co-Authors

Joycelyn Atchison, MD; Ambika Ashraf, MD; Edmond Kabagambe DVM, MS, PhD; Jessica Skelley, PharmD

Title

Diabetes in Alabama school systems: a survey of parental satisfaction with student care

Abstract

Background: Children with diabetes spend large amounts of time at school. Due to the frequent need to monitor blood glucose levels and administer insulin or medications, it is possible that some schools do not adequately care for and accommodate the needs of students with diabetes. The goal of this study was to assess parental perceptions of the current state of care for children with diabetes in the Alabama public school system and to determine what resources would most improve diabetes management in this setting.

Methods: We adapted our survey from a previous study based on ADA guidelines and collected the responses online via Survey Monkey. Surveys were distributed among parents of children with diabetes through the Children's Hospital endocrinology clinic, a diabetes camp, and the Alabama Association of School Nurses email list serve.

Results: We obtained survey responses from 170 parents of school-age children with diabetes in Alabama. The statewide parental satisfaction rate was 82.9%. Both parental satisfaction and the ability to participate in all school activities were significantly associated with the ability for students to conveniently check blood glucose levels at school. Parents of Caucasian students were 3.6 times more likely to be satisfied with their student's care at school. Minority students were less able to conveniently check blood glucose levels and participate in all school activities. The ability to participate in all school activities correlates with the rural nature of the school district and average median household income.

Conclusions: The accommodation and care for children with diabetes is highly variable within Alabama. Parents of minority students and students unable to conveniently check blood glucose levels at school expressed less satisfaction with the current state of diabetes care in schools. Institution of a uniform, statewide diabetes training protocol for school personnel would likely improve care and parental satisfaction.

Smith, Kenneth

Project Length Short

Prior Research Experience No

Funding Source CaRES Program

Advisor Dr. Catherine Fuller

Co-Authors

Title Adapting the LI-COR On-Cell Western Protocol to Measure Ion Channel Trafficking in Glioma Cells

Abstract

In patients with glioblastoma multiforme (GBM), migration of malignant cells to other areas of the brain presents a major barrier to the effectiveness of therapy. The treatment for these patients starts with surgery; however, at this point micrometastases have already begun to migrate to other parts of the brain. Integral to this process is a cation channel composed of ENaC and ASIC subunits located on the plasma membrane. This study has focused on establishing a method for determining the cell surface expression of this channel using the Li-COR Odyssey Infra-Red Scanner. Our overall goal is to use this technique to pinpoint specific plasma membrane targeting sequences of the glioma channel. Chinese Hamster Ovary cells (CHO) and D54-MG glioma cells were transfected to express an HA-tagged ASIC 1 subunit and plated on to 96 or 24-well plates. We then used a monoclonal rat anti-HA primary antibody followed by a goat anti-rat secondary antibody tagged with an 800nm infra-red label. Cells were then permeabilized prior to staining with TOPRO-3, a DNA stain that fluoresces at 700 nm. The plates were then scanned to obtain the fluorescence intensity at both 700 and 800 nm. While we have been able to detect high levels of the transfected protein intracellularly (in cells permeabilized prior to the antibody washes) we have experienced difficulty in obtaining fluorescent intensities above background for the cell surface labeled channels. This could be due to a failure of the subunit to traffic to the membrane, or to steric hindrance preventing antibody access to the HA-epitope. While these data do not prove that this method will become viable, it does provide a launch pad for future work to establish this technique for quick, accurate measurements of the cell surface expression of ENaC, ASICs and other ion channels.

Smola, Cassandra

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	
Advisor	Dr Tofil
Co-Authors	Nancy M. Tofil, MD, MEd; Amber Q. Youngblood RN, BSN; Terri Magruder, MD;
Title	Using High Fidelity Simulation to Prepare Caregivers of Pediatric Ventilator Dependent Children

Abstract

Introduction: Increasing numbers of children are living with home mechanical ventilation, and caregivers now have to become more knowledgeable about their children's equipment. Home ventilator programs (HVP) have been developed to educate, train and prepare caregivers to care for their child outside the hospital by teaching basic respiratory skills. HVPs must also succeed in teaching critical thinking and emergency skills needed to care for their medically complex child in the home which can be difficult to practice in real life. Medical simulators can be used to fill this gap. Our hypothesis is that simulation will improve caregivers' comfort and skill level by providing experience for real life emergencies.

Methods: Simulation curriculum was developed to augment the HVP curriculum. Caregivers participate in simulations with their emergency equipment bag. Simulators, closest to the patient's size, are placed on a ventilator with settings that caregivers will use at home. Scenarios focused on common complications including tracheostomy displacement, obstruction, difficult reinsertion, aspiration, ventilator alarms and cardiopulmonary resuscitation (CPR) with repetitive practice until caregivers feel comfortable.

Results: Seven home ventilator families have participated since 2009. Caregivers have been enthusiastic and report simulation allows them to think through the situation, putting their training to use in an organized fashion. It allows them to identify gaps in knowledge and develop increased confidence in their skills. Families report the session is intense, realistic and emotional. Careful debriefing is provided to reinforce successful skills, make corrections and bolster confidence.

Discussion: The addition of simulation to our pediatric HVP appears to have a significant impact on caregiver training, providing a crucial transition between learned skills and application to real life. We are currently surveying families after discharge to determine the value of simulation training in empowering them with the confidence and skills to manage their children successfully at home.

Speake, Lisa

Project Length	Short
Prior Research Experience	Yes
Funding Source	Departmental or mentor Funds
Advisor	J. Michael Straughn, Jr., MD

Co-Authors

Title: Preoperative Karnofsky performance status (KPS) as a predictor of postoperative complications in gynecologic oncology patients

Abstract

Objectives: In oncology, the Karnofsky performance status (KPS) is an attempt to quantify cancer patients' general well being. The objective of this study was to evaluate the impact of the KPS score on the perioperative outcomes of gynecologic oncology patients.

Methods: A non-randomized prospective cohort study was initiated on June 1, 2010 to evaluate the efficacy of using patients' preoperative KPS scores as a predictor of surgical outcomes. All new patients with a suspected gynecologic malignancy were eligible for the study. At the preoperative consultation visit, patients were assigned a KPS score. The KPS score ranges from 100 to 0, where 100 is perfect health and 0 is death. A score of 70 represents a patient caring for self but not capable of normal activity or work. Patient demographics, 30-day complications, and length of postoperative hospital stay (LOS) were assessed. Statistical significance was determined using the student t-test, Fishers exact test, and Chi square test.

Results: To date, 67 patients have completed the study. 76% of patients had major surgery and 67% had a final diagnosis of malignancy. 55 patients had medical comorbidities. The mean KPS score was 86 (range; 50 to 100). The most common postoperative complication was wound infection. 11 patients had a low KPS (≤ 70). Postoperative complications were higher in patients with a low KPS (≤ 70) compared to those with a high KPS (>70) (45% vs 23%; $p=0.15$). LOS was 4.5 days in patients with a low KPS (≤ 70) compared to 3.3 days in patients with a high KPS (>70) ($p=.13$). Women ≥ 65 years experienced similar postoperative complications compared to younger women (33% vs 24%; $p=.54$).

Conclusion: Although KPS may not be sufficient as a sole predictor for postoperative outcomes, it can be clinically useful as an objective scale to assess potential risks of surgery.

Staley, Elizabeth

Project Length	Short
Prior Research Experience	Yes
Funding Source	CaRES Program
Advisor	Robin G. Lorenz M.D./Ph.D.
Co-Authors	Scott M Tanner
Title	Persistence of Host Leukocytes Following Lethal Irradiation and Bone Marrow Reconstitution.

Abstract

Bone marrow reconstitution is utilized as both a clinical tool for the treatment of disease, and as a research technique to elucidate the function of bone marrow derived immune cells. In human populations success of engraftment is indicated by survival secondary to the development of a functioning immune repertoire. In research, reconstitution is considered successful if >85% of splenic leukocytes express donor antigens. We hypothesized that splenic reconstitution may be an inaccurate assessment of reconstitution in mucosal immune compartments. These mucosal sites are often where Graft versus Host Disease (GVHD) develops as result of recognition of histocompatibility antigens by donor T-cells. Recent data indicates that GVHD may be induced by incomplete chimerism, or the retention of host leukocytes. The purpose of this study was to test our hypothesis that following bone marrow reconstitution, a significant percentage of host leukocytes are maintained in mucosal tissues. Bone marrow was harvested from adult B6.SJL donor mice (CD45.1) and injected either retro-orbitally or intraperitoneally into lethally irradiated C57BL/6 (CD45.2) adult or neonatal recipients respectively. Tissue was harvested and immune cell populations were identified by FLOW cytometric analysis. Expression of the host CD45.2 molecule was used to calculate reconstitution with respect to immune compartment and cell type. In reconstituted adult animals 92.7% of splenic leukocytes expressed the donor CD45.1 antigen, while only 60.3% of intestinal lamina propria lymphocytes and 50.8% of intestinal intraepithelial lymphocytes (IELs) and were of donor origin. Reconstitution of neonatal mice did not alter this decreased reconstitution in mucosal immune compartments (splenic = 88.5%; lamina propria = 75%; IEL = 47.6%). This decreased ability to reconstitute mucosal tissues appears to most severely effect T-cell populations, as approximately half of all T-cells in mucosal immune compartments remained of host origin, while >90% of CD19+ B-cells in all compartments were of donor origin.

Stanley, Jennifer

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Christopher Willey
Co-Authors	Joshua C. Anderson, Tamara Burleson, Patricia Hicks
Title	Kinomic Assessment of Her2-amplified Breast Cancer Cells: Identifying Resistance Pathways

Abstract

Protein kinase signaling is central to many cellular processes including cancer development, progression, and treatment resistance. Until recently studying the intricacies of these pathways could prove extremely time consuming. However, using novel technology it is now possible to study global kinase activities through kinomics. By deciphering kinase signaling in given conditions and tissues, we can gain essential insight into normal and pathological cellular responses. Most importantly, we can use this information to modulate patient therapy. A quarter of invasive breast cancers over-express human epidermal growth factor receptor 2 (Her2) that promotes an aggressive phenotype with early progression and metastasis. The advent of Her2 targeted therapies including trastuzumab, a Her2 monoclonal antibody, and lapatinib, a small molecule EGFR/Her2 kinase inhibitor, have improved outcomes yet many patients will fail treatment due to inherent or acquired resistance. These resistance mechanisms are poorly understood; however, most theories suggest alternative kinase signaling as mediators. Thus, we are systematically evaluating cancer cell lines with known resistance/sensitivity to Her2 therapeutics using kinomic profiling to delineate potential resistance pathways that could be targeted with a pathway-specific inhibitor. We utilized a multiplex fluorescent-based assay platform (PamStation®12 microarray) to identify kinomic profiles of MDA-MB-361 cells (Trastuzumab-sensitive, lapatinib-resistant) and BT474 cells (universally sensitive). We found a significant difference in basal levels of tyrosine kinase activity between these two cell lines. Importantly, when these cell lines were treated with lapatinib, BT474 cells showed inhibition of numerous peptide substrates that were unaffected in resistant MDA-MB-361 cells. These peptides include substrates for focal adhesion kinase (FAK), vascular endothelial growth factor receptor 2 (KDR), and Janus kinase family (JAK). By targeting these pathways we may affect the cancer cell's ability to survive treatment. We believe this to be a comprehensive and efficient methodology for understanding resistance and identifying promising pathways for combinatorial therapy.

Stephens, Lauren

Project Length	Short
Prior Research Experience	Yes
Funding Source	American Federation for Aging Research MSTAR Fellowship
Advisor	Cynthia J. Brown, MD, MSPH
Co-Authors	Kathleen T. Foley, PhD, OTR/L and John D. Lowman, Jr. PhD, PT
Title	Frequency and Duration of Out of Bed Mobility Episodes During Hospitalization

Abstract

Background: Recent studies exploring nonexercise activity physiology have demonstrated benefits of even low levels of standing and walking activity when compared to sitting. Out of bed mobility, including sitting and standing/walking, is uncommon during hospitalization with much of the hospital stay being spent in bed. Understanding current patterns of out of bed mobility would be useful in the development of interventions to increase time spent out of bed.

Purpose: To examine the frequency and duration of out of bed mobility episodes during the first three days of hospitalization.

Methods: 46 hospitalized male veterans, age ≥ 65 years who were not delirious or demented and able to walk in the 2 weeks prior to admission were eligible. Wireless accelerometers were attached to the thigh and ankle of consented patients. Using a previously validated algorithm, the proportion of time spent sitting, and standing/walking was determined. An episode of out of bed activity was defined as either sitting or standing/walking for greater than 1 minute. Daily episodes of sitting and standing/walking were determined.

Results: Forty-six male patients (mean age 74.2 years; 74% white and 26% black), had a median length of stay of 3 days. During the first three days of measured mobility, the average length of a sitting episode was 19.7 minutes with a range of 10-120 minutes. All participants had at least one standing/walking episode. During the first measured hospital day, 16 (34%) participants had a standing/walking episode that lasted ≥ 10 minutes. The duration of these standing/walking episodes ranged between 1-49 minutes.

Conclusions: Out of bed episodes were frequent but typically of short duration. These may represent in-room mobility that has previously been unmeasured. Future interventions will need to focus on increasing time spent in standing/walking through nurse-driven or therapy led protocols.

Stevens, Erica

Project Length Short

Prior Research Experience Yes

Funding Source T-32

Advisor: Jennifer Dewolfe, MD

Co-Authors: Monika Haack PhD, Norah Simpson PhD, Janet Mullington PhD

Title: Total Sleep Deprivation and its Effects on Blood Pressure

Abstract:

Background: Sleep deprivation is on the rise with more Americans reporting less than six hours of sleep per night. An association has been observed between self-reported short sleep duration and increased risk to develop hypertension.

Objective: To determine if and when blood pressure increases during sleep deprivation in healthy adults.

Design: Randomized, prospective 7 night/6 day in-laboratory study conducted at Beth Israel Deaconess Medical Center.

Methods: 25 men and women ages 21-75 were studied for seven nights and six days. On the first and second nights the subject was instructed to sleep up to nine hours. On day three the subject was assigned to either the 64 hours of sleep deprivation or nine hours of sleep per night. Following the 64 hour period, participants in both groups were instructed to sleep for 9 hours for the remaining two nights. Continuous blood pressure measurements were taken using the Portapres system. The equipment was applied for 24-hours on days 3, 5, and 7 of the study.

Outcome Measures: The raw data collected from the Portapres system was processed using MATLAB. MATLAB made automatic corrections and this data was then combined with recorded r-r intervals (a measure of heart rate); the data was then averaged in 15 minute intervals.

Results: Data from only one subject was analyzed so far. Results demonstrated a slight increase in systolic (117mmHg vs. 129mmHg) and diastolic blood pressure (67mmHg vs. 74mmHg) during periods of sleep deprivation from baseline levels. After one night of recovery sleep on day 7 of the study, systolic and diastolic blood pressure returned to levels similar to baseline, 115mmHg and 63mmHg respectively.

Conclusion: Definitive conclusions will be determined after all of the data have been analyzed. This project demonstrates novel methodology to elucidate effects of sleep deprivation on blood pressure.

Stoddard, Mark

Project Length Short

Prior Research Experience Yes

Funding Source Non-UAB Funding

Advisor George M. Shaw, M.D., Ph.D

Co-Authors Hui Li, Truman Grayson, Shuyi Wang, Chuanxi Sun, Beatrice H. Hahn, George M. Shaw

Title Molecular Identification of Transmitted Hepatitis C Viral Genomes in Acutely Infected Patients.

Abstract

BACKGROUND: An estimated 3% of the world's population (270 – 300 million people) is infected with the hepatitis C virus (HCV), a major cause of hepatitis, cirrhosis, and hepatocellular carcinoma. HCV demonstrates broad genetic diversity and chronic infection leads to the evolution of quasispecies resistant to immunological and pharmacological pressures. HCV diversity has hampered the study of disease pathogenesis and hindered the generation of replication-competent infectious molecular clones (IMCs). Indeed, only a single IMC currently exists for HCV, further complicating basic studies and the development of new therapeutics.

METHODS: We used end-point dilution PCR (single genome amplification or SGA) of plasma viral RNA to amplify and sequence 5' half genomes containing the viral structural proteins (~5 kb fragment encoding Core, E1, E2, p7, NS2, NS3) from ten acutely and three chronically infected patients. Sequences were analyzed based on a model of random virus diversification.

RESULTS: 25 to 68 genomes per subject were analyzed. From each acutely infected subject, transmitted/founder (T/F) viral sequences were identified. The number of T/F viruses responsible for productive clinical infection was found to be from 1 - 12. Maximum sequence diversity within each patient ranged from 0.08% to 6.82%, with higher sequence diversity associated with transmission of >1 virus. Early virus evolution was random and followed a Poisson distribution of mutations, permitting unambiguous identification of transmitted viruses. Importantly, and unlike acute HIV-1 infection, there was no evidence of early virus immunological selection.

CONCLUSION: We show here for the first time that transmitted HCV sequences can be inferred by SGA analysis of viral RNA from acutely infected subjects. Transmitted HCV sequences, in principle, contain all genetic elements necessary for productive human infection. Molecular clones of transmitted viruses may represent critical new reagents for the analysis of HCV replication and for the development of new anti-HCV drugs and vaccines.

Stone, Sara

Project Length	Short
Prior Research Experience	Yes
FundingSource	Departmental or Mentor funds
Advisor	Amit Gaggar
Co-Authors	Amit Gaggar, Xin Xu
Title	Differential regulation of granule release by a novel neutrophil-specific matrikine

Abstract

Cystic fibrosis (CF) is an autosomal recessive condition characterized by increased neutrophils (PMN), which are classically recruited to the lungs by chemokines. These PMNs are activated and release protease-containing granules which lead to “bystander” damage to the lung parenchyma. Damage to the extracellular matrix leads to the release of a non-canonical PMN chemoattractant, proline-glycine-proline (PGP), from collagen; both PGP and its more stable, acetylated form (Ac-PGP) act on PMN CXC receptors and are elevated in CF lung disease. PGP is generated by the activities of matrix metalloprotease-9 (MMP-9), which is activated by neutrophil elastase (NE) in vivo. Myeloperoxidase (MPO) is now thought to be involved in the acetylation of PGP through a reaction with free threonine. All of these enzymes (MPO, MMP-9, NE) are found in PMNs, suggesting a self-propagating inflammatory cycle. Therefore, we examined the release of MPO, MMP9, and NE, to determine the time course and signaling involved in the release of these proteases via a traditional chemokine (interleukin-8 (IL-8)) and Ac-PGP. Lysates and supernatants of Ac-PGP and IL-8- treated human PMNs were collected from 0 to 120 minutes. Enzyme activity was measured by zymogram as well as fluorogenic and colorimetric assays. MMP9 was increased from 15-45 minutes, consistent with tertiary granule release with both treatments. MPO and NE levels increased from 5-30 minutes, consistent with primary granules. The release of these enzymes corresponded to an increase of intracellular phospho-ERK; both the ligand-mediated MMP-9 release and increased phospho-ERK expression were blocked with CXC receptor blockade. Further examination of the activation of other intracellular pathways and impact of direct ERK inhibition on protease release is currently being investigated. Elucidation of the mechanisms of Ac-PGP and IL-8 induced PMN granule release may have implications for CF therapies, regulating the inflammation and airway damage observed in this disorder.

Strachan, Samuel

Project Length Intermediate

Prior Research Experience Yes

Funding Source NIH T35 short training grant and Children's Hospital Pediatric Simulation Center

Advisor Dr. Marjorie Lee White

Co-Authors Dr. Nancy Tofil, Lynn Zinkan, Amber Youngblood

Title Development and Implementation of Interactive High-fidelity Patient Simulation Cases for First Year Medical Student Curriculum and Testing in the Large-Group Setting

Abstract

High-fidelity patient simulation is an emerging tool in the medical education process. These advanced models can be programmed to realistically simulate a variety of cases from emergent situations to intense medical management. Students at all levels have expressed confidence in their effectiveness in aiding in the learning process. Key to this is the feeling that one's decisions have consequences. However, the common theme we receive in feedback from most students is the need for more hands on training with the simulators. Patient simulation is a resource intensive training modality; from the manikins themselves to the training center staff. This resource limitation is exacerbated by the fact that the benefits of patient simulation can be applied to many disciplines including nursing, undergraduate and graduate medical education. This project is aimed at taking the patient simulation experience into the large scale setting of the classroom while maintaining its decision making aspect.

This project focuses on the first year medical school curriculum. For each of the first seven modules (Patient doctor society, Fundamentals I and II, Cardiology, Pulmonary, Gastrointestinal and Renal) we developed clinical scenarios with a team of student actors and the use of the simulators and staff at the Children's Hospital Pediatric Simulation Center. These scenarios were then acted out and recorded in a "choose your own adventure format". This allows the class to make decisions using the audience response system that will then change the course of the video and will in effect allow the class to care for the patient.

In the future these video case presentations will be viewed by a medical school class accompanied by pre and post tests that will allow us to gauge knowledge retention. We will also collect evaluations in order to fine tune the process and to make the video presentations more realistic.

Special thanks to: Kavita Vankineni, Griffin Guice, Rachel Jones, Jennifer Eldredge, Cecily Collins and all other actors.

Sullivan, Daniel

Project Length	Short
Prior Research Experience	yes
Funding Source	NIH T-35 Short Term Training Grant
Advisor	J. Edwin Blalock, Ph.D
Co-Authors	Patricia L. Jackson, Ph.D., Amit Gaggar, MD, Ph.D.
Title	Longitudinal study examining Ac-PGP as a potential biomarker in COPD

Abstract

Chronic neutrophilic inflammation is an important factor in the progression of chronic obstructive pulmonary disease (COPD), and glutamic acid-leucine-arginine-positive (ELR⁺) CXC chemokines, including interleukin-8 (IL-8), have previously been shown to be the major chemoattractants for neutrophils in this condition. In addition to these molecules, an extracellular matrix (ECM) derived tripeptide, N-acetyl Pro-Gly-Pro (Ac-PGP), has been shown to induce neutrophil chemotaxis and to interact with the same receptors as IL-8. Ac-PGP levels have also been shown to be elevated in individuals with COPD and that exposure to PGP is capable of inducing changes in a murine model consistent with those seen in mice exposed to cigarette smoke. Despite years of effort, no reliable biomarker has been found for COPD diagnosis or prognosis. This study's aim was to evaluate the potential of Ac-PGP as such a biomarker. To do so, Ac-PGP levels in the sputum of 340 COPD patients collected over the span of three years were determined using electrospray ionization liquid chromatography/tandem mass spectrometry. Through our analysis we show that greater than 94% of COPD patients have measurable Ac-PGP in their sputum, and although not statistically significant, values appear to be highest in current smokers. By separating subjects into two populations, it was determined that the following clinical factors were statistically different between current and past smokers: two measures of airway reactivity to bronchodilators, COPD exacerbations per year, and the percentage of lung low attenuation area (indicative of degree of parenchymal emphysema). A normalized distribution was found when these factors were correlated with Ac-PGP levels in test subjects. Univariate and multivariate analyses are currently being done to correlate these factors with Ac-PGP and COPD progression. Our findings thus far strengthen the potential likelihood that Ac-PGP can be used as a biomarker in COPD.

Sultan, Faraz

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	J. David Sweatt
Co-Authors	Jennifer Tront, Dan A. Liebermann
Title	The Regulator of Active DNA Demethylation, gadd45b, Suppresses Memory Consolidation

Abstract

It is well established that long-term memory formation and synaptic plasticity depend on lasting alterations in gene expression. This hypothesis helps explain the apparent paradox that information can remain stable in the brain despite ongoing turnover of the neuronal proteome. Still, mechanisms supporting modified gene expression in the consolidation and storage of memory are poorly understood. Recent pioneering work has implicated molecular epigenetic mechanisms in memory-associated gene regulation. These phenomena include post-translational modifications of histone proteins and covalent modification of DNA. Pharmacological and genetic manipulations point to an essential role of catalytic DNA methylation in long-term synaptic plasticity and memory. However, the mechanisms and function of the active reversal of DNA methylation have long eluded epigeneticists. A recent study uncovered the role of the gadd45 (Growth arrest and DNA damage-inducible protein 45) protein family in DNA demethylation. Another study revealed the beta isoform, gadd45b, as a novel immediate-early gene expressed in the hippocampus, an essential brain region in memory consolidation and retrieval. In this study, we sought to examine the role of active DNA demethylation by gadd45b in long-term memory and synaptic plasticity. We first assessed gadd45b null animals and wildtype controls in a series of tasks in an effort to uncover a behavioral function of the gene. We found no difference in baseline locomotor activity, anxiety, sensorimotor gating and nociception. Surprisingly, mutants exhibited enhanced long-term memory in the rotarod task and contextual fear conditioning, tests of motor and associative memory, respectively. Secondly, preliminary long-term potentiation studies with hippocampal slices revealed a trend towards enhanced late-phase plasticity and the absence of a baseline synaptic function phenotype. Lastly, active DNA methylation and gene expression were studied in hippocampal pharmacology studies. Our data suggest the epigenetically regulated gene reelin is a potentially novel Gadd45b target and that its expression is augmented by gadd45b deletion, a finding that is consistent with the behavioral phenotype of the null mutants. In summary, our surprising results are consistent with a model in which experience- and activity-dependent DNA demethylation suppresses synaptic function and memory consolidation. Future studies are needed to confirm the enhancement in synaptic plasticity and to examine the role of gadd45b in regulating gene expression in hippocampus-dependent associative memory. Finally, we plan to study the complex association between DNA demethylation and associated chromatin modifications at a number of gene promoters known to be differentially regulated by neuronal activity. Pharmacological blockade of histone deacetylase complexes (HDACs) is known to regulate gene expression and promote memory, and as such, HDAC inhibitors are being studied as cognitive therapeutics. Confirmation of our results could implicate DNA demethylation as a second category of drug targets.

Tagayun, Christine

Project Length 8 weeks

Prior Research Experience

Funding Source NIH grant, Children's Hospital of Alabama Pediatric Neurosurgery Department

Advisor Dr. John C. Wellons

Co-Authors Joshua Chern, Chevis Shannon, Curtis Rozzelle, Jeffrey P. Blount, W. Jerry Oakes, John C. Wellons

Title Imaging and clinical outcomes after arachnoid cyst decompression surgery

Abstract

Introduction: Despite multiple studies, the ideal treatment of children with arachnoid cysts remains controversial. The purpose of this retrospective study is to provide longer term imaging and symptom follow up in a cohort of children treated with either fenestration or shunting. Both groups are analyzed together based on previous work from this institution.

Patients and Methods: Clinical and imaging records of 50 children were retrospectively reviewed. Symptoms and imaging were followed for up to 5 years when available.

Results: Surgical procedures included shunting, fenestration, or a combination of both. A majority of the patients reported symptomatic improvement at one-year follow up; however, a substantial number of patients experienced recurrence by year 3. This was especially true when headache was the presenting symptom. Focal neurological findings attributable to the cyst mass effect had the best response. DATA Greater than half of the cysts demonstrated a decrease in size on follow-up imaging. The decrease in cyst size was a positive prognostic factor on symptomatic improvement.

Conclusions: Headaches appear to recur after one year in the successfully treated group. Focal neurologic findings responded better. Imaging improvement may correlate with longer term success.

Talathi, Sonia	
Project Length	Short
Prior Research Experience	Yes
FundingSource	NIH T35 Short Term Training Grant
Advisor	Dr. Wayne Sullender
Co-Authors	Shobha Broor
Title	Seasonal Trivalent Influenza Vaccine given to Children in Rural India: An Ongoing Study.

Abstract

Influenza infections are classified as acute respiratory infections (ARI) and especially affect children in developing countries, resulting in 1.9 million childhood deaths per year, 20% of which are in India. Until recently, influenza surveillance in India has been insufficient and the impact of the disease has not been well defined. The aims of this research are to describe the influenza vaccine direct and indirect efficacy and define the clinical disease and outcomes. Since previous studies show that 15% of children in rural India with ARIs have influenza, we predict the vaccine will lessen the disease burden. The 3 year study has begun and is a prospective, randomized, controlled, observer blinded study in 3 rural Indian villages. All ages are in surveillance, weekly home visits collect nose/ throat samples if there is evidence of febrile ARI. Children 6 months to 10 years are randomized by household and receive the trivalent influenza vaccine or inactivated polio vaccine. Data is collected on paper performas, scanned and extracted using TeleFORM. Village participation was high for both surveillance (90%) and immunization (91%). Virology results as of August 7, 2010 have shown that out of 3636 samples tested, 14% were positive for influenza. Out of those 6.6% were 2009A/H1N1, .1% were other InfA and 7.3% were InfB. The appearance of 2009A/H1N1 emphasizes the importance of multi-year studies of influenza vaccines. Influenza B activity was present for an extended period in 2010. The second year of immunization will use TIV that includes 2009A/H1N1 virus. The results should inform policy makers on the efficiency and use of influenza childhood vaccination to protect against seasonal and pandemic influenza when resources are limited. These studies will also develop capacity for influenza virus study and management in India which can then be used as a model and applied to other developing nations.

Thomas, Evan

Project Length Long Term

Prior Research Experience Yes

Funding Source MSTP

Advisor John Fiveash

Co-Authors Richard Popple, John Fiveash

Title Utilization of Flattening Filter Free Mode for Improving Radiotherapeutic Treatment Efficiency

Abstract

Introduction: Medical linear accelerators (linacs) used for radiotherapy have traditionally employed beam flattening filters to maximize beam homogeneity. Use of the flattening filter was previously essential for minimizing normal tissue toxicity in treatment fields containing large volumes of normal tissue. Most flattened beams are limited to a dose rate of 300-600 MU/min, however later-generation linacs can produce un-flattened beams capable of delivering 2400 or higher MU/min. Increased clinical use of cranial/extracranial radiosurgery and other hypofractionated techniques has generated renewed interest in using flattening filter free (FFF) mode to decrease delivery time and improve treatment efficiency. In this study, we compare the beam-on and treatment delivery times for a variety of clinical cases including conventional, hypofractionated, and single fraction radiosurgery computer optimized plans in FFF and non-FFF modes with both conventional intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) delivery methods.

Methods: A variety of frequently encountered radiation therapy cases were selected for study. Each case was re-planned to clinically acceptable standards and the beam and treatment times for standard 6MV non-FFF dMLC (600 MU/min) mode was compared to those of the four available FFF modes: 6MV FFF dMLC (1400 MU/min), 6MV FFF VMAT (1400 MU/min), 10MV dMLC (2400 MU/min), and 10 MV VMAT (2400 MU/min).

Results: Dramatic treatment efficiency improvements (as high as 500%) were realized in FFF mode for the hypofractionated and the radiosurgery cases. Cases with low dose conventional fractionation exhibited little or no treatment efficiency improvement.

Conclusion: Flattening filter free beams improved the clinical efficiency of a subset of radiation treatments including those with a high dose per fraction. This improvement in treatment efficiency should be more comfortable for the patient and be associated with a lower risk of intrafraction patient motion (delivery error).

Thorpe, J. Bannon

Project Length Short

Prior Research Experience Yes

Funding Source Departmental or Mentor funds

Advisor Brent A. Ponce

Co-Authors Richard D. Meyer, M.D., Brent A. Ponce, M.D., Seth D. Rosenzweig M.D., Janet P. Tate MPH, Kevin J. Thompson M.D.

Title Pectoralis Major Height as an Anatomic Reference for Shoulder Fracture Hemi-Arthroplasty

Abstract

Background:

Shoulder replacement may be indicated for complex fractures of the proximal humerus. Historically, pain relief has been satisfactory following fracture arthroplasty, but functional outcomes have frequently been poor. The primary reason for disappointing results is the non-anatomic position of the prosthesis as the normal anatomic landmarks are disrupted with the fracture. An anatomic reference outside of the zone of injury would greatly aid positioning of arthroplasty reconstruction for fractures.

Hypothesis:

The measurement from the top of the pectoralis major tendon (PMT) to the top of the humeral head height is related to patient height.

Methods:

Following IRB approval, PMT measurements were performed with a manual caliper upon twelve pairs of shoulders. A second group of PMT measurements were performed on 107 patients receiving a shoulder MRI for a diagnosis other than fracture or arthritis. A third PMT group was included using historical measurements from twenty pairs of shoulders. All heights, genders and ages were known. Statistical analysis utilized mixed effects linear regression models to properly account for replicate measurements on the same subject.

Results:

A consistent association between height and PMT was found. For a 1.7 m (67 inches) person the PMT is found to be 5.7 cm (2.2 inches), with a 2.9 mm (0.11 inches) increase in PMT for every 1 cm (0.39 inches) increase in patient height ($p < 0.0001$). The mean distance from the top of the pectoralis major tendon to the top of the humeral head was 5.74 cm (2.26 inches).

Conclusions

A predictable measurement from the upper portion of the pectoralis major tendon to the top of the humeral head exists and may be approximated using patient height. Such a measurement may greatly assist surgeons in determining the correct humeral prosthesis height in the reconstruction of fractures.

Ting, Yu

Project Length	Short
Prior Research Experience	Yes
FundingSource	NIH T35 Short Term Training Grant
Advisor	David Kimberlin, M.D.
Co-Authors	Gretchen Cloud
Title	Abnormalities in Cerebrospinal Fluid Indices in Neonatal Herpes

Abstract

Objectives

Because of the potentially severe outcomes of neonatal herpes simplex virus (HSV) disease involving the central nervous system (CNS), it is imperative to diagnose the infection as early and rapidly as possible. In this retrospective study, we examined how cerebrospinal fluid (CSF) indices vary across HSV disease classes [CNS disease; skin, eyes, and mouth (SEM) disease; and disseminated disease] and whether advances in viral diagnostics and antiviral therapies have affected CSF abnormalities.

Methods

From 1973 to 2006, the Collaborative Antiviral Study Group conducted a series of clinical trials of antiviral drugs for neonatal HSV. These seminal studies have been merged into a large database at the University of Alabama at Birmingham (UAB), containing data from over 400 subjects; this represents the largest such database of neonatal HSV in the world. Baseline data on subjects' demographics and CSF indices were pulled from the database. CSF indices were analyzed by disease class; time period of study trials; disease class within time periods; and prematurity using the non-parametric Kruskal-Wallis test.

Results

CSF protein and white blood cell counts of HSV-infected babies have decreased by 23.51% and 71.25%, respectively, since 1973. Both are highest in CNS babies and lowest in SEM babies. CSF red blood cell count has decreased by 91.58% since 1973 and is highest in disseminated babies. CSF glucose levels were consistent across the three disease classes, remaining relatively unchanged over time. Premature neonates (<37 weeks) had more CSF abnormalities than term babies.

Conclusions

CNS and disseminated babies demonstrate more CSF abnormalities than SEM babies. Overall, CSF abnormalities have become less severe since 1973. This may be due to more advanced diagnostic techniques such as PCR, as well as greater awareness and index of suspicion of neonatal HSV. Additionally, the documented safety of acyclovir treatment of neonatal HSV may hasten physicians' consideration of neonatal herpes, since there is a proven therapy readily available

Tonks, Stephen

Project Length Intermediate

Prior Research Experience

Funding Source Departmental or Mentor Funds

Advisor

Carlos A. Estrada, MD, MS

Co-Authors

Sohil Makwana, Amanda H. Salanitro, MD, MS, MSPH,
Monika M. Safford, MD, Thomas K. Houston, MD, MPH, Jeroan J. Allison, MD, MSc, William Curry, MD,

Title

Influence of Rurality on the Health of Patients with Diabetes Mellitus

Abstract

Background: Diabetes mellitus (DM) is the leading cause of new cases of blindness, kidney failure, and non-traumatic lower-extremity amputations among adults, which affects 23.6 million in the U.S. While it has been estimated that people living in rural areas are 17% more likely to develop DM, little is known about how these patients differ from their urban counterparts. We propose that there are differences in the characteristics, co-morbidities, and outcomes of rural patients with diabetes.

Methods: We conducted secondary analyses of data collected during the Rural Diabetes Online Care (R-DOC) study, which included over 1,000 patients from 11 southeastern states. Degree of rurality was defined using Rural-Urban Commuting Areas (RUCA) codes and the home zip-code of each patient, to assign them into 4 groups: 1) urban, 2) large rural, 3) small rural, or 4) isolated small rural. Using chi-squared and analysis of variance, we looked at differences across a number of patient characteristics and co-morbidities, as well as HbA1c, blood pressure (BP), and low-density lipoprotein (LDL) outcomes.

Results: Across the 4 groups (urban, large rural, small rural, isolated small rural), there were statistically significant ($P < 0.05$) differences seen in the number of African American (7.3%, 23.9%, 17.7%, 17.1%) and obese patients (30.0%, 39.4%, 46.9%, 41.7%), the prevalence of hyperlipidemia (14.0%, 6.1%, 10.9%, 13.7%) and peripheral vascular disease (3.0%, 3.0%, 8.4%, 9.1%), and the number of patients with poorly controlled hypertension (BP $\geq 140/90$ mmHg) (12.0%, 4.9%, 10.5%, 17.7%).

Discussion: While this study provides a greater understanding of fundamental differences in rural patients with DM, as well as identifying disparities in co-morbidities and DM outcomes, more work needs to be done to understand the causes and ways to improve these disparities.

Tsay, Sharon

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Marsha Sturdevant, M.D.
Co-Authors	Dayna Cook-Heard, Gwendolyn Childs
Title	Predictors of Condom Self-Efficacy in an Incarcerated Juvenile Population

Abstract

Purpose: STDs are a major problem for incarcerated adolescents in the US. Recent research reports that incarcerated adolescents are infected with STDs two to three times more than non-incarcerated adolescents. Fortunately, the consistent use of condoms can effectively decrease transmission. This has prompted researchers to investigate predictors of condom use to better develop interventions. Recent research has suggested that self-efficacy can successfully predict condom use.

Methods: This study investigated predictors of self-efficacy in 662 incarcerated adolescents ages 13 to 18 participating in the Making Proud Choices! HIV/STD intervention program. Participants completed a pre-intervention questionnaire eliciting information about knowledge and ideas about sexual behaviors. Predictors of condom self-efficacy were determined by factor analysis and included STD knowledge, correct condom use knowledge, and intent to use condoms. The researchers hypothesized that all three of these predictors would predict condom self-efficacy.

Results: Consistent with past research, adolescents reported high levels of risky activities. 71.9% reported heterosexual sex in the past six months, 21% reported sex with anonymous partners and 13.2% reported sex with a member of the same sex. Also consistent with past findings, incarcerated adolescents showed a higher percentage of STDs: 9.0% of the males and 30% of the females (19.3% total). Additionally, 44.9% reported having sex while "high" or "drunk" in the past six months. Bivariate and multivariate regression showed that correct condom use knowledge and intent to use condoms were significant predictors of condom self-efficacy ($p < .000$) in this population. STD knowledge did not act as a predictor in multivariate analysis.

Conclusions: These data are consistent with studies of incarcerated adolescents and reiterate the need to affect attitudes and intent rather than increase knowledge alone. Future intervention programs may be more effective if they consider including drug and alcohol prevention messages in addition to information on safer same sex sexual encounters.

Tucker, Jesse

Project Length Short

Prior Research Experience Yes

Funding Source Departmental or Mentor funds

Advisor Elizabeth Turnipseed

Co-Authors

Title Development of a Comprehensive Tool for Tuberculosis Contact Investigation

Abstract

BACKGROUND: In recent years, molecular genotyping in state and federal public health laboratories has become a powerful tool in tuberculosis (TB) control. However, the fundamental limitations of genotyping analysis and the inadequacies of traditional contact-tracing methods inherent in the epidemiology of TB make elimination of the disease practically impossible, especially in low-prevalence jurisdictions such as Jefferson County, Alabama. The missing piece of the epidemiologic puzzle of TB transmission is often overlooked social networks. Unfortunately, few local and state jurisdictions have implemented tools for TB investigation that reliably capture data relative to time, person, place, and behavior.

OBJECTIVE: I researched optimal practices for data collection in local health jurisdictions with the goal of improving the current toolkit for TB investigation used by the Jefferson County Department of Health.

METHODS: I collected forms and guidelines from various state and local public health agency websites. When not available online, I contacted local TB controllers in those jurisdictions whose population and disease burden characteristics are similar to Jefferson County, Alabama. To ensure fulfillment of federal recommendations for TB control practices, I met with several stakeholders at the Division of Tuberculosis Elimination's Outbreak Investigation Team at CDC and conducted a comprehensive literature review in PubMed to identify the appropriate variables to be collected in the improved toolkit.

RESULTS & CONCLUSION: The final product developed is a ten-section electronic data collection instrument that collects valid exposure information from either a TB patient or a personal contact. Areas of potential transmission assessed include household, school, work, social behaviors, locations of social aggregation, and medical risk factors. Implementation of this tool will not only enhance real-time situational awareness in the setting of a TB outbreak, but also enable powerful retrospective analyses of emerging transmission networks for the purposes of program improvement.

Turnham, Jennifer

Project Length Intermediate

Prior Research Experience Yes

Funding Source

Advisor Craig A. Elmetts

Co-Authors W. Cantrell, A. Andea, R. Shafi, M. Athar, C.A. Elmetts

Title Loss of Membrane E-cadherin and Expression of p53 are Molecular Markers of Progression of Sun-damage

Abstract

Actinic keratoses are premalignant lesions with a 6-10% lifetime risk of developing into invasive squamous cell carcinomas. In a previous study, we found that 43% of AKs clinically regressed without reoccurrence within an 11 month period of time, and that 32% regressed but then recurred, indicating that natural course of AKs is exceedingly variable. The purpose of this study was to identify molecular events associated with persistence and progression of actinic keratoses. E-cadherin, a marker of epithelial-mesenchymal transition (EMT), and p53, which plays a pivotal role in apoptosis and the repair of potentially carcinogenic UV-induced DNA damage, were examined in 35 clinically present AKs, 4 regressed AKs, and 43 sun exposed skin samples from 26 individuals. Clinically present AKs expressed significantly less membrane E-cadherin than sun-exposed skin (1.89 ± 1.81 , AKs vs. 3.07 ± 1.75 , sun-exposed skin; $p < 0.005$). When specimens from clinically present AKs and sun-exposed skin were examined for p53, both expressed p53 (2.89 ± 1.45 , AKs vs. 2.58 ± 1.68 , sun-exposed skin, $p=0.40$). Less p53 was observed in regressed AKs than in clinically present AKs (0.75 ± 0.96 , regressed AKs vs. 2.89 ± 1.45 , clinically apparent AK; $p < 0.01$). These data suggest that loss of E-cadherin expression is a key feature associated with the persistence of AKs, whereas loss of p53 is associated with regression. Procedures which enhance membrane E-cadherin expression and/or diminish p53 expression may therefore be effective in the prevention of non-melanoma skin cancers.

Vankineni, Kavita

Project Length	Intermediate
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Nancy M. Tofil M.D., MEd
Co-Authors	J. Lynn Zinkan R.N. MPH, Amber Q. Youngblood R.N., Kathy Harrington Phd, MPH, Marjorie Lee White M.D., MPPM, MEd
Title	High-Fidelity Simulation Enhances Learning During a Third Year Pediatric Clerkship

Abstract

Introduction: Simulation allows for hands on learning as well as medical decision-making. We discuss the first use of simulation in a pediatric clerkship and how the simulation experience affects knowledge, skills, and attitudes (K, S, and A). Our hypothesis was that our simulation course would improve student K, S, and A. **Methods:** Students participated in 4 one-hour simulations, focusing on supraventricular tachycardia, croup, diabetic ketoacidosis, and hyponatremic seizure. We used a pre/post test study design to evaluate K, S, and A learned during the course. Statistical analysis was done using SPSS Version 11.5 and Wilcoxon Signed Ranks test. Themes were identified for qualitative data from student evaluations. **Results:** 140 third year medical students participated over twelve months. Student knowledge significantly increased from $71 \pm 16\%$ pretest to $90 \pm 9\%$ post test ($p < 0.001$). Students' self-assessment of their ability to perform medical skills improved significantly: intravenous line placement ($p=0.036$), administering medications ($p=0.001$), using a defibrillator ($p=0.001$), and administering oxygen using different devices ($p=0.001$). Self-assessed attitudes included working in medical teams, communication with families without using medical jargon, family at bedside during patient care, and family in the room during emergencies. Students were significantly more likely to want family to stay in the room in an emergency after the simulation course than before ($p < 0.001$). Student evaluations of the simulation experience were overwhelmingly positive; the most common themes were the value of "hands on learning" and the "ability to make decisions." **Conclusion:** Medical students benefit from simulation experience. In addition to an increased knowledge base, our data show that students feel more comfortable with medical skills and feel more comfortable with parents' presence during their child's emergent situation. By using simulation to create real-life scenarios, students are given the opportunity to actively make decisions, administer medical therapies, and learn without compromising patient care.

Wahl, Tyler

Project Length Short

Prior Research Experience No

Funding Source NIH T35 Short Term Training Grant

Advisor Michael J Mugavero, MD

Co-Authors

Title HIV Peer Interventions Influencing Adherence to Medications and Clinical Care

Abstract

OBJECTIVE: The focus of this study was to conduct a systematic review of HIV peer interventions influencing antiretroviral medication and appointment adherence among HIV-infected patients.

METHODS: Standardized search terms were employed to search databases for English language peer reviewed manuscripts, published between 1999 and 2010, pertaining to peer mentor interventions for HIV antiretroviral and/or appointment adherence. Databases included CINAHL, PSYCHinfo, PubMed, and Web of Science. Excluded studies pertain to prevention, risk reduction, pediatrics, or those conducted in regions other than United States, Canada, Europe, or Australia. Two independent coders reviewed abstracts for eligibility with discrepancies arbitrated by a third investigator.

RESULTS: Keyword combination search terms yielded a total of 2,629 abstracts. Further investigation revealed 724 studies involving HIV peer interventions with 42 peer interventions addressing attendance adherence. Preliminary analysis suggested that interventions utilizing peers to improve medication and appointment adherence is desired among HIV care providers and patient populations. This study also demonstrated that peers provide a cost-effective way to address barriers to care, increase clinical care access and care re-uptake, reduce antiretroviral medication resistance, decrease disease progression, improve quality of life, and increase patient-provider trust and communication.

CONCLUSIONS This study suggests that a strategy that includes peer involvement improves adherence to prescribed antiretroviral medication and appointments in HIV-infected patients. Further investigation of this approach is warranted.

Warmus, Brian

Project Length	Short
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Faculty Advisor	Erik Roberson
Title	Ventral Striatum Neurodegeneration is Linked to Behavioral Symptoms in Frontotemporal Dementia

Abstract

Frontotemporal dementia is one of the most common dementias and is characterized by behavioral problems such as obsessive-compulsive behaviors, personality changes, and social disturbances. Currently, there are no disease-modifying treatments for this progressive and lethal disease. Several mutations in the gene for microtubule-associated protein tau have been found to cause FTD, and tau accumulates in about half of all FTD cases. Our lab studies a transgenic mouse model of FTD expressing the V337M tau mutation. We found that this mouse line (Tg-hTau-V337M) displays age-dependent obsessive-compulsive behavior and thus models a key behavioral phenotype seen in human FTD. Many human patients with OCD show significant improvement when deep brain stimulators are placed in the ventral striatum; this suggests obsessive-compulsive behaviors are related to abnormal activity in networks involving the ventral striatum. We have obtained preliminary data linking compulsive grooming behaviors in Tg-hTau-V337M mice to ventral striatum dysfunction; excitatory synaptic transmission is depressed as early as 14 months, and dendritic spine density is decreased by 24 months. We hypothesize that the loss of dendritic spines and synaptic transmission in ventral striatum of Tg-hTau-V337M mice is a progressive, degenerative change which leads to compulsive grooming behavior. In order to determine if these abnormalities are caused by a degenerative as opposed to a developmental process, it is essential to examine younger Tg-hTau-V337M mice. Here, we test this hypothesis by quantifying dendritic spines using Golgi staining and measuring excitatory synaptic transmission by electrophysiological recordings in ventral striatum of 4 month-old Tg-hTau-V337M mice. We predict that spine density and synaptic transmission in Tg-hTau-V337M mice are the same as non-transgenic mice at 4 months, yet significantly increased as compared to 24 month-old Tg-hTau-V337M mice, indicating a degenerative disease process.

Watkins, Stacey

Project Length Long

Prior Research Experience Yes

Funding Source MSTP

Advisor Harald Sontheimer, Ph.D.

Co-Authors

Title Biophysical and Biomechanical Aspects of Glioma Invasion

Abstract

Grade IV glioblastoma multiforme (GBM) are the most common primary brain tumor. Diffuse migration and invasion into the surrounding brain, often migrating along white matter tracts or brain vasculature, makes complete surgical resection limited. Invading cells encounter tortuous extracellular spaces necessitating profound cell shape and presumably cell volume alterations. Currently, it is uncertain whether glioma cells undergo global volume changes as they invade and migrate. Based on prior findings, it is hypothesized here that ion channels and cotransporters expressed in gliomas flux Cl^- and K^+ along with obligated water to facilitate global volume alterations. To examine this, an ex-vivo chemotactic migration model that mimicked the spatial constraints of glioma invasion while allowing imaging in real time, was established. Data obtained thus far shows that total cell volume changed an average of 32.1% via a common pattern of volume decrease followed by volume recovery, as the cells traverse the barrier. This is compared to non-migrating (static) cells that exhibited dynamic 14.5% volume fluctuations. In addition, the invasive migration of glioma cells along blood vessels in brain slices either after seeding on top or implanting tumors *in vivo* were imaged. These studies also showed 33.2% and 29.7% dynamic cell volume alterations, respectively. Current efforts are focused on imaging glioma invasion *in vivo* through multi-photon imaging through a cranial window. Transwell assays performed in the presence of pharmacological inhibitors of Cl^- channels and transporters involved in cell volume regulation demonstrated the necessity of global volume changes for invasion. Unequivocal identification of the underlying channels will be achieved by the use of glioma cells lines stably expressing channel specific shRNA silencing constructs. Data obtained from this proposal will hopefully aid in the understanding of glioma biology while providing a more specific molecular target for future therapy.

Webers, Carolyn

Project Length	Short
Prior Research Experience	No
Funding Source	NIH T35 Short Term Training Grant
Advisor	Namasivayam Ambalavanan
Co-Authors	Scott Ballinger, Arlene Bulger, Brian Halloran, David Krzywanski, Stephanie Larson
Title	Preterm birth is associated with decreased endothelial cell proliferation

Abstract

Despite medical advances, preterm birth remains a significant source of neonatal mortality and perinatal and life-long morbidity. Preterm birth exposes an infant to a higher oxygen-containing environment than that of normal intra-uterine development, which is relatively hypoxemic. Exposure of endothelial cells to higher than normal oxygen tension leads to oxidant stress, which may be responsible for many of the sequelae associated with preterm birth. This study evaluates the susceptibility of preterm endothelial cells to oxygen-induced injury by assessing the effect of preterm birth on the proliferation of endothelial cells. Human umbilical venous endothelial cells (HUVEC) were chosen for analysis because they are easily obtained without invasive procedures and represent a subset of cells that lack exposure to the numerous variables introduced by the extrauterine environment. HUVEC were isolated from umbilical cord segments collected during vaginal and operational deliveries. Isolates were obtained from 40 neonates, 11 preterm and 24 full term, and were passaged in M199 medium with 20% Fetal Bovine Serum. Proliferation was assessed using the Vybrant MTT Cell Proliferation Assay kit (Invitrogen) on confluent, third-passage cells, and all absorbance values were normalized as a percentage of a Caucasian, term infant. Statistical analysis was performed using Analysis of Variance (ANOVA). Spearman Rank Order Correlation revealed a positive relationship between gestational age in weeks and proliferation ($r=0.340$, $p=0.0454$). These findings indicate increasing proliferation with more maturity, suggesting that endothelial cells of preterm neonates may be exposed to increased oxidant stress or other stress that leads to decreased proliferation. This correlation provides an important insight into a possible mechanism for preterm-birth associated morbidity. Studies with larger sample sizes are needed to confirm findings, and future research is necessary to elucidate the exact mechanisms by which endothelial cells undergo oxygen-induced injury so that therapeutic strategies can be developed.

Wells, Ryan

Project Length	Long
Prior Research Experience	Yes
Funding Source	NIH Medical Scientist Training Program Grant
Advisor	Michael Niederweis
Co-Authors	Chris Jones
Title	MmpS4 and MmpS5 are outer membrane proteins of <i>M. tuberculosis</i> involved in siderophore secretion

Abstract

Mycobacterium tuberculosis (*Mtb*), the causative agent of tuberculosis, is able to survive in macrophages by preventing phagosomal maturation to phagolysosomes. In spite of this ability, the microenvironment within phagosomes remains inhospitable due to low pH, the presence of reactive nitrogen and oxygen species, as well as a paucity of nutrients and trace elements required for mycobacterial growth. Iron acquisition by pathogenic bacteria is necessary for their survival and bacteria compete with the host for limited iron stores by producing and secreting low molecular weight, high affinity iron chelators called siderophores. The ability of *Mtb* to acquire and utilize iron within iron limiting phagosomes is a virulence factor; however, the mycobacterial siderophore secretion system remains unknown.

This research focuses on *mmpS4* and *mmpS5* which were predicted to be outer membrane proteins (OMPs) and have been shown to be upregulated under low iron conditions. Single deletion mutants lacking *mmpS4* ($\Delta mmpS4$) and *mmpS5* ($\Delta mmpS5$), as well as the double deletion mutant lacking both *mmpS4* and *mmpS5* ($\Delta mmpS4/S5$) were constructed in *Mtb*. Under low iron conditions, $\Delta mmpS4/S5$ has a severe growth defect, while *Mtb* wt, $\Delta mmpS4$, and $\Delta mmpS5$ grow equally well in low versus high iron media. Furthermore, media that has been conditioned by growing either *Mtb* wt, $\Delta mmpS4$, or $\Delta mmpS5$ is able to partially rescue the low iron growth defect of $\Delta mmpS4/S5$. Liquid CAS assays and radiolabeling experiments indicate that although $\Delta mmpS4/S5$ retains the ability to synthesize siderophores, their secretion is abrogated. Subcellular fractionation along with proteinase K surface accessibility assay show that MmpS4 and MmpS5 are OMPs. Taken together, this data supports the hypothesis that MmpS4 and MmpS5 are OMPs involved in the secretion of mycobacterial siderophores.

Whitley, Sarah

Project Length

Long

Prior Research Experience

Yes

Funding Source

MSTP

Advisor

Casey T. Weaver

Co-Authors

Robin D. Hatton, and Casey Weaver

Title

Regulation of IL17 Transcription in CD4+ T Cells

Abstract

Proper cytokine expression and commitment to CD4+ T helper (T_H) lineages is regulated at the level of transcription. It is clear that distal *cis*-regulatory elements aid in the chromatin remodeling that establishes and maintains lineage-specific patterns of gene expression. Here we used a PCR-based approach to map DNase-hypersensitive sites spanning almost 1Mb up- and downstream of the *Il17a* and *Il17f* cytokine loci. Using this method we have identified many regions with Th17-specific epigenetic modifications. A subset of these sequences enhanced IL-17 expression in primary Th17 cells, indicating that they represent functional *Il17* enhancers. Two distal *cis*-elements bind the insulator-associated factor CTCF and are likely to function as boundary elements for the extended *Il17a/f* locus. Further studies have employed chromatin immunoprecipitation to map the binding pattern of the Th17 lineage-specific transcription factor STAT3 to these sites upon IL-23 stimulation. We show that the addition of IL-1 β enhances and sustains STAT3 activation as well as augments STAT3 binding to *cis*-regulatory elements. Our findings suggest a functional cooperation between STAT3 and IL-1 β -induced NF κ B factor RelA in promoting *Il17* gene transcription and Th17 differentiation. Our studies indicate that mice with a CD4+ T cell-specific deficit in RelA exhibit reduced IL-17 production, and studies examining the consequences of this in host defense are underway.

Wilson, Erica

Project Length	Short
Prior Research Experience	No
Funding Source	Diabetes Research and Training Center
Advisor	Edmond Kabagambe
Co-Authors	Edmond Kabagambe and Gerado Vallejo
Title	Hyperglycemia and associated risk factors in pregnant women in Tegucigalpa, Honduras

Abstract

Maternal hyperglycemia during pregnancy increases the risk of short- and long-term adverse pregnancy outcomes, but has not been studied in Central American populations. We estimated the prevalence of hyperglycemia (fasting blood glucose (FPG) ≥ 92 mg/dL) and associated risk factors in 242 pregnant women (age 24 ± 5 y) attending Las Crucitas Clinic in Tegucigalpa, Honduras. Women were recruited on their first antenatal visit (11 ± 4 weeks of gestation), during which anthropometric measurements were taken and blood drawn for FPG measurement. An interviewer-administered questionnaire was used to assess medical history, physical activity and other lifestyle attributes. We used logistic regression to calculate odds ratios for hyperglycemia. Several women were underweight (7%), overweight (28%) or obese (13%) and some had a family history of diabetes (43%) or hypertension (45%). Among women with FPG data, 20% (38/188) had FPG ranging from 92-125 mg/dL while 2% (4/188) had FPG ≥ 126 mg/dL. In models containing age, BMI, family history of diabetes and pre-pregnancy physical activity, total number of hours slept per week was significantly associated with hyperglycemia (OR for each additional hour of sleep was 1.04; 95% CI: 1.01-1.07). None of the other variables in the model was significant at $p=0.05$. These preliminary data highlight the high prevalence of hyperglycemia and obesity, known risk factors for adverse pregnancy outcomes, and call for intervention programs to prevent these risk factors.

Witte, Steven

Project Length	Short
Prior Research Experience	Yes
Funding Source	Non-UAB Funding (External Funding Source)
Advisor	Dr. Stefan Muljo
Co-Authors	Thelma Escobar
Title	Discrete Targets of miR-155 During B Cell Activation

Abstract

microRNAs (miRNAs), a class of small regulatory RNAs, are crucial for lymphocyte development and function. MicroRNA-155 (miR-155) has recently been directly implicated in memory B cell differentiation, including IgG1 antibody production and germinal center proliferation. In order to assay for miR-155 mediated control of these processes, we measured expression of several candidate miR-155 targets following stimulation of mature B cells with LPS and IL4. Higher levels of expression of the transcription factors MYB, nfe212, and CEBPb was seen in miR-155 deficient B cell cultures compared to controls, suggesting that these genes may be regulated by miR-155 *in vivo*. These findings may explain why miR-155 KO mice display decreased B cell activation and reduced antibody class switching.

Yang, Sherry

Project Length Long

Prior Research Experience Yes

Funding Source MSTP

Advisor Selvarangan Ponnazhagan

Co-Authors Sherry W. Yang, James J. Cody, Angel A. Rivera, Reinhard Waehler, Diptiman Chanda, Minghui Wang, Kristopher J. Kimball, Ronald A. Alvarez, Gene P. Siegal, Joanne T. Douglas and Selvarangan Ponnazhagan

Title A TIMP2-Armed Conditionally-Replicating Adenovirus for the Treatment of Ovarian Cancer

Abstract

Ovarian cancer remains the most lethal gynecological malignancy in the U.S. Conventional therapies have limited therapeutic value due to advanced stage of the disease at diagnosis. Among new therapies, conditionally replicating adenoviruses (CRAds), designed to selectively lyse cancer cells, hold promise. In clinical trials, CRAds exhibited limited efficacy thus far. Second generation CRAds are being developed to express a therapeutic protein to enhance antitumor efficacy. One attractive target in the tumor microenvironment is the matrix metalloproteinases (MMPs). MMPs are endogenous proteases that degrade extracellular matrix and are upregulated in ovarian cancer. Tissue inhibitors of metalloproteinase 2 (TIMP2) is an endogenous inhibitor of MMPs.

The present study developed a CRAd, Ad5/3-CXCR4-TIMP2 that uses the CXCR4 promoter for selective replication in ovarian cancer cells combined with the delivery of TIMP2. We first confirmed the production and secretion of functional TIMP2, as demonstrated by the inhibition of gelatin degradation by MMPs. In addition, arming with TIMP2 did not inhibit viral replication nor oncolytic potency, as the TIMP2-armed viruses showed enhanced killing of cancer cells when compared to the unarmed viruses. Further validation of this virus on primary ovarian cancer tissues from patients with stage III and IV ovarian cancer revealed a consistent high level of viral replication with Ad5/3-CXCR4-TIMP2. The therapeutic efficacy of the TIMP2-armed CRAd was then evaluated in a murine model of orthotopically disseminated ovarian cancer. Results demonstrated that the TIMP2-armed CRAd delayed tumor growth and significantly increased survival when compared to the unarmed CRAd. This effect was mediated through inhibition of MMPs. Collectively, the study demonstrated the enhanced therapeutic efficacy of the dual-action, TIMP2-armed CRAd *in vivo* and the translational potential of using Ad5/3-CXCR4-TIMP2 for treatment in patients with advanced ovarian cancer.

Zimmerman, Jacquelyn

Project Length	Intermediate
Prior Research Experience	Yes
FundingSource	NIH Medical Scientist Training Program Grant
Advisor	Boris Pasche, MD/PhD
Co-Authors	Frederico P. Costa, Ivan Brezovich, Michael Pennison, Ryne Ramaker, Devin Absher, Richard M. Myers, Alexandre Barbault, Boris Pasche
Title	Low Levels of Amplitude-Modulated Electromagnetic Fields Inhibit Cell Growth and Mitotic Division in Hepatocellular Carcinoma Cells

Abstract

Hepatocellular carcinoma (HCC) is a rapidly progressing malignancy, and impaired liver function often prevents patients from receiving effective treatment. Intrabuccal administration of electromagnetic fields, amplitude-modulated at discrete frequencies (AM-EMF) is a novel, minimally invasive treatment approach for HCC. Phase II data for patients treated with AM-EMF demonstrate outcomes no worse than outcomes following other treatment approaches, and AM-EMF caused few adverse effects. Promising clinical data prompted in vitro studies to dissect the molecular mechanism, with the initial hypothesis that clinical observations resulted from frequency-specific resonance effects on tumor cell proliferation. HepG2 and HuH7 cells, common HCC cell lines, were exposed to either a program of HCC-specific frequencies ranging from 400Hz-21kHz or to a program of randomly-chosen frequencies in the same range but at least 2.5Hz away from any tumor-specific frequency. Following AM-EMF exposure, proliferation, gene expression, morphology, and cell cycle were assessed. Tritium-incorporation assay revealed growth inhibition in cells exposed to HCC-specific frequencies when compared to cells exposed to randomly chosen frequencies, suggesting that AM-EMF has in part a direct effect on proliferation. We identified with RNA-Seq and validated with qPCR the downregulation of PLP2, a gene functioning in chemotaxis, in HCC cells exposed to HCC-specific frequencies. PLP2 downregulation was not seen in non-malignant cells, suggesting effects are limited to tumor cells. Fluorescence microscopy revealed cytoskeletal disruption in cells exposed to HCC-specific frequencies; this was most apparent in cells in mitosis, in which we saw centrosomal distortion and poor chromosomal separation at anaphase. Preliminary flow cytometry data supports this observation, suggesting that HCC-specific frequencies increase the number of cells with increased nuclear content as seen in cells just prior to mitotic cell division. Though further investigation is necessary, current data supports the hypothesis that frequency-specific resonance, markedly affecting cytoskeletal components, is impairing mitotic division and consequently inhibiting HCC cell proliferation.

Abroms, Sarah	20
Akinsiku, Olusimidele	21
Aksut, Baran.....	22
Alberti, Michael.....	23
Albertson, Asher	24
Allen, Heather.....	25
Alvarez, Mitchell	26
Azbell, Christopher	27
Bailey, Lisa	28
Bansal, Swati.....	29
Barr, Eleanor	30
Baxley, Sarah	31
Bishop, Elliot.....	32
Black, Jonathan.....	33
Blake, Courtney	34
Blosser, Emily.....	35
Boohaker, Hikel	36
Bradley, Jerry, Jr	37
Brennard, Megan.....	38
Brosius, Stephanie	39
Brossier, Nicole	40
Byekova, Yevgeniya.....	41
Calix, Juan.....	42
Carstarphen, Kathy Jo.....	43
Chen, Zsu-Zsu.....	44
Chestnut, Michael.....	45
Ciszak, Tadeusz.....	46
Clark, Eva.....	47
Clifford, William	48
Corrick, Ryan.....	49
Cuddapah, Vishnu.....	50
Davis, Brian	51
Deep, Nicholas	52
Dinsmore, Amanda.....	54
Dobbin, Zachary C	55
Donnithorne, Katherine.....	56
Doo, David.....	57, 58
Elkhetali, Abdurahman	59
Elsamadicy, Emad.....	60
Flowers, Grace Powell.....	61
Foster, Christy	62
Gaston, David.....	63
Gladden, James	64
Griffin, Drees Jr	65
Griffith, Zachary.....	66
Grochowsky, Angela	67
Gunnells, Drew.....	68

Guzman Karlsson, Mikael.....	69
Hadley, Jennifer	70
Hammond, John	71
Harbin, Lindsay	72
Harris, Shaundra	73
Hatch, Neal.....	74
Hendrixson, Taylor	75
Hixon, Brian.....	76
Ho, Christina.....	77
Hollis, Robert.....	78
Honasoge, Avinash	79
Huff, Kayci	80
Hull, Travis	81
Huynh, Thy	82
Jaleel, Tarannum.....	83
Jarboe, John.....	84
Johnson, Joffre.....	85
Johnson, Stephen	86
<i>Keith, Charles</i>	87
Kennedy, Christopher.....	88
Kentros, Jonathan, II	89
Kezar, Carolyn.....	90
Khan, Farah.....	91
Kirkman, Jennifer	92
Kumbla, Pallavi.....	93
Kumbla, Rekha.....	94
Kundukulam, Joseph.....	95
Land, Andrew	96
Larson, Stephanie	97
Lawal, Taoreed.....	98
LeGrand, Jason.....	99
Lewis, Travis	100
Lin, Victor	101
Lopker, Michael	102
Ma, Jing-Yuan	103
Mai, Karen	104
McAnnally, John-Ryan	107
McCormick, Don, III.....	105
McDonald, Andrew	106
McPheeters, Meghan	108
Meadows, Jarrod.....	109
Merino, Aimee Marie	110
Miller, Jonathan	111
Modi, Sarika	112
Molony, Elizabeth	113
Moseley, Carson	114
Murthy, Rajini Krishna	115
Nwaobi, Sinifunanya.....	116

Odom, Carl	117
Ogorek, John	118
Oliver, James	119
Owen, Matthew	120
Owens, Milner	121
Parchman, Michelle	122
Parker, Walter	123
Parrish, Nicholas	124
Patterson, Derek	125
Pearson, Alana	126
Pierce, Caleb	127
Planz, Virginia	128
Poholek, Catherine	129
Record, Jessica	130
Reish, Nicholas	131
Reynolds, Harris	132
Robert, Stephanie	133
Roebuck, Natalie	134
Rutherford, John	135
Sarver, David Brasfield	136
Scott, Adam	137
Shah, Nemil	138
Shelley, David	139
Skelley, Jason	140
Smith, Kenneth	141
Smola, Cassandra	142
Speake, Lisa	143
Staley, Elizabeth	144
Stanley, Jennifer	145
Stephens, Lauren	146
Stevens, Erica	147
Stoddard, Mark	148
Stone, Sara	149
Strachan, Samuel	150
Sullivan, Daniel	151
Sultan, Faraz	152
Tagayun, Christine	153
Talathi, Sonia	154
Thomas, Evan	155
Thorpe, J. Bannon	156
Ting, Yu	157
Tonks, Stephen	158
Tsay, Sharon	159
Tucker, Jesse	160
Turnham, Jennifer	161
Vankineni, Kavita	162
Wahl, Tyler	163
Warmus, Brian	164

Watkins, Stacey.....	165
Webers, Carolyn.....	166
Wells, Ryan	167
Whitley, Sarah.....	168
Wilson, Erica	169
Witte, Steven.....	170
Yang, Sherry	171
Zimmerman, Jacquelyn	172