INFORMATION FOR PARTICIPANTS

Poster Presentation Sessions:
Poster sessions will be held in the Harper Student Center Gym. You are encouraged to view the posters currently on display on the walls of the Basic Science Building and at other locations around campus for examples of poster layout, design and size. For assistance with poster design and content, contact the MUSC Center for Academic Excellence. Most poster support boards are approximately 3’ 6” tall by 5’ 6” wide. Poster support boards will be available by 7:00 am on Friday, November 2nd, with numbers corresponding to the abstract numbers in this program. Posters should be in place by 8:30 am and should remain in place until 12:00 noon. The times indicated for your session in the program are the times we expect that the judges will be in attendance. Do not remove your poster before 12:00 noon in case the judges need to make a return visit to your poster. If you have a scheduling conflict and can only be in attendance at your poster for a specific time, please let the SRD2008 Chairman, Steve Kubalak, know by email (at <kubalaks@musc.edu>) immediately. You will have 10 minutes to present the information on your poster to the judges – the judges will also ask you questions. The judges will tell you when they have completed evaluating your poster: Please note, if your session is large, more than one team of judges will be operating and a second team of judges may need to visit your poster. Do not leave the area until the judges have indicated that judging of your poster is complete - if in doubt, ask them.

Oral Presentation Sessions:
The undergraduate oral session will be held in the Education Center/Library building room 107 (the EL building is adjacent to the Basic Science Building). The remaining oral sessions will be in the College of Health Professions Building A at 151-A Rutledge Avenue. This building is accessible from Rutledge Avenue and also at the 2nd floor level from the Children’s Hospital-Rutledge Tower crosswalk over Ashley Avenue. Sessions will take place in the 2nd floor lecture rooms: 201, 202, 203, 204, 205, 206, and 207. Computer projection using a PC platform will be available. You can either save your presentation on a CD, to your homeroom or on a memory stick. Ensure that your presentation loads and runs correctly before you save it. Download your presentation into the SRD2008 file for your session on the desktop of the computer in the room where you will be presenting; do this BEFORE the start time of your session on Friday, November 7th. Oral presentation time slots are 15 minutes. An oral presentation should last 10 minutes with the remaining time for questions. The 15 minute time slot will be strictly adhered to by the session judges – you will receive a warning at minus 3 minutes and again at minus 1 minute. Remember that question handling is one of the criteria being evaluated and if you leave no time for questions, you will lose points.

Judging:
Teams of 3 judges will evaluate presentations in each of the sessions. Judges will be wearing red nametags. Presentations will be scored on a scale of 1 to 10 in ten categories covering the areas a) scientific approach to the subject of the research, b) clarity and quality of delivery, and c) handling of questions. The scores for the ten categories (max 100 points) from each judge in that session will be used to compute a ranked score. 1st and 2nd place prizes will be awarded to the presentations with the highest and next highest mean ranked scores respectively. We have tried to assign judges so as to avoid possible conflicts of interest. If, however, there is a conflict, then the judge affected will not score that presentation. Scores and evaluation sheets will be available to presenters after 4:00 pm on Friday, November 14th in the Graduate Studies office on the 1st floor of the Basic Sciences Building. Any evaluation sheets not collected by November 21st will be sent out by campus mail to the address you gave when submitting your abstract. Please note, there will also be a team of judges selecting presentations for the Library's Bioinformatics prizes, for Sigma Xi prizes, for an Interprofessional Research prize, for the VA Research Prize, and for the Health Disparities Prize - these judges will be operating as separate teams, and if your presentation qualifies for one of these categories you will be visited by these additional judges.

Breaks:
Coffee, doughnuts and soft drinks will be available from 9:30 am – 12:00 pm in the Harper Center Gym. There will be a Subway catered lunch for presenters and other student attendees in the Harper Center Gym at 11:00 am. Coffee, soft drinks and cookies will also be available in the CHP Building from 12:00 pm.

Awards Ceremony:
The Awards Ceremony will follow the Keynote Lecture (4:00 pm) in the Basic Science Auditorium, starting just after 5:00 pm. In each session there will be a 1st place prize of $500 and a 2nd place prize of $200. The Bioinformatics, Sigma Xi, Interprofessional Research, VAMC Research, and Health Disparities Awards have their own cash prizes that are in addition to the regular session prizes.
Door prizes, as part of the Vendor Show in the Gym, will also be awarded – for further information and for your door prize ticket, see the individual exhibitors tables at the Vendor Show. The door prize drawing will occur at approximately 11:00 am.
ACKNOWLEDGEMENTS

The Perry V. Halushka Student Research Day Endowment

In 2006, in recognition of the many years of service given by their father, Dr. Perry V. Halushka, to the Medical University, Francine Halushka Katz, Marc Halushka, M.D., Ph.D., and Suzanne Friedman and their families have established, through the MUSC Foundation, The Dr. Perry V. Halushka Student Research Day Endowment. This endowment will help to support the activities of Student Research Day in perpetuity. Specifically, the endowment will enable the University to:

• Provide monetary awards for outstanding research presentations
• Attract world-class scientists as guest keynote speakers
• Provide funds to support the annual Student Research Day event

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The Student Research Day Committee

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SRD2008 – SCHEDULE

FRIDAY, NOVEMBER 7th – Research Presentations

POSTERS – Harper Wellness Center Gym, 8:30 am – 12:00 noon

ORALS – CHP building A, 151-A Rutledge Ave, 2nd floor: rooms 201 – 207: 11:45 am – 3:00 pm
Education Center/Library Building, 1st floor: room EL 107: 12:15 pm – 3:00 pm

Keynote Address: Basic Science Auditorium, 4:00 – 5:00pm

"Turning Pages: From Gels to Genes"
By:
Dr. Oliver Smithies
Excellence Professor
Co-Recipient of The Nobel Prize in Physiology or Medicine 2007
University of North Carolina at Chapel Hill
School of Medicine
Chapel Hill, NC.

SATURDAY, NOVEMBER 8th – Careers Workshop XVIII
‘Job Searching and Career Development’
Gazes Cardiac Research Institute, Rm 125, 10:00 am – 12:00 noon
for Graduate Students and Postdocs

Presented by College of Graduate Studies / Graduate Studies Alumni Association
Panelists: M. Scott Bowers, UC San Francisco; Jeannie M. Chapman, University of South Carolina Upstate; S. Craig Dyar, South University School of Pharmacy; P. Brian Giles, The Needle & Rosenberg IP Practice of Ballard Spahr; Ryan Monfeli, NIH; Octavia M. Peck-Palmer, University of Pittsburg Medical Center
Cynthia Wright, Associate Dean of Admissions, MUSC, College of Graduate Studies.
LOCATION OF ORAL PRESENTATIONS – SESSION 10

Education Center/Library, Building, 171 Ashley Avenue, 1st floor

Access either:
a). from Ashley Avenue side (facing the horseshoe) ground level, or
b). from President Street side (this is the side that faces the Harper Student Center direction).
LOCATION OF ORAL PRESENTATIONS – SESSIONS 11-17

College of Health Professions, Building-A, 151-A Rutledge Avenue, 2nd floor

Access either:
a). from the Children’s Hospital-Rutledge Tower crosswalk over Ashley Avenue at the 2nd floor level, or
b). through the Ashley Avenue Parking Garage to Rutledge Avenue to the main entrance on Rutledge.
Student Research Day 2008 - Program

POSTER PRESENTATIONS

Harper Wellness Center Gym

8:30 am - 12:00 noon

Session 1: Undergraduate – I #001-013
Session 2: Clinical Prof/Masters – I #014-025
Session 3: Clinical Prof/Masters – II #026-035
Session 4: Clinical Prof/Masters – III #036-048
Session 5: PhD – I #049-066
Session 6: PhD – II #067-081
Session 7: PhD – III #082-095
Session 8: Postdocs/Residents/Fellows – I #097-111
Session 9: Postdocs/Residents/Fellows – II #112-126

ORAL PRESENTATIONS

Education Center/Library Building, 1st Floor

Session 10: Undergraduate – II EL107 12:15-3:00 #128-138

College of Health Professions, Building-A - 2nd Floor

Session 11: Clinical Prof/Masters – IV CHP 203 12:00-3:00 #139-149
Session 12: Clinical Prof/Masters – V CHP 201 11:45-3:00 #150-161
Session 13: PhD – IV CHP 204 12:15-3:00 #162-171
Session 14: PhD – V CHP 207 11:45-3:00 #172-183
Session 15: PhD – VI CHP 206 12:00-3:00 #184-194
Session 16: Postdocs/Residents/Fellows – III CHP 202 12:15-3:00 #195-204
Session 17: Postdocs/Residents/Fellows – IV CHP 205 12:15-2:45 #205-213
Session 1: Undergraduate

001 Optimization of SiRNA Delivery In Vitro and In Vivo
Sabrina M Porcher1, Qiyang Li2, Keith L Kirkwood2; 1CU, Craniofacial Biology, Dental Medicine, MUSC, 2Craniofacial Biology, Dental Medicine, MUSC.

002 Does Periostin Intron 1 Regulate Periostin Transcription?
Robert W Pratt1, Russell J Norris2, Michael A Kern2; 1Dental Medicine, MUSC, 2Cell Biology and Anatomy, MUSC.

003 The Effects of Calpain Activity on Stat6 in Jurkat T Cells
Gabriel C Fitton1, Jonathan T Butler2, Naren L Banik1; 1Neuroscience, MUSC, 2MCBP, MUSC.

004 Combination of Low Dose Estrogen and Melatonin Protects VSC 4.1 Motor Neurons From Glutamate-induced Cell Death By Increasing the Estrogen Receptor Beta:Estrogen Receptor Alpha Ratio
Joshua A Smith1, Arabinda Das2, Swapan K Ray3, Naren L Banik2; 1Medicine, MUSC, 2Neurosciences, MUSC, 3Pathology, Microbiology, and Immunology, USC School of Medicine.

005 Melatonin Protects VSC4.1 Motoneurons Cells Exposed to Oxidative Stress, Glutamate Excitotoxicity, and TNF-α Toxicity Via Receptor Mediated Pathway
Misty McDowell1, Arabinda Das1, Matthew J Pava1, Russel J Reiter2, John J Woodward1, Swapan K Ray3, Narendra Banik1; 1Neuroscience, MUSC, 2Cellular and Structural Biology, UT, TX, 3Pathology, Microbiology and Immunology, USC, Columbia, SC.

006 Affect of TGFβ2 and Retinoic Acid on the Regulation of VCAM-1 During Epicardium Development
Laura E Brichler1, M. Elizabeth G Burton2, Loretta L Hoover2, Steven W Kubalak2; 1College of Charleston, Charleston, SC, 2Cell Biology and Anatomy, MUSC.

007 3D Models of the Mouse Atrio-Ventricular Node
Rebecca A Neuren1, Mary S Rackley2, Brett S Harris3; 1College of Charleston, Charleston, SC, 2Gazes Cardiac Research Institute, Ralph H. Johnson VA Medical Center, 3Cell Biology and Anatomy, MUSC.

008 Modeled Microgravity Induces the Expression of PU-1 in Preosteoclast Cells
Jeremy J Blanchard, Yuvaraj Sambandam, Sakamuri V Reddy; Charles P. Darby Children’s Research Institute, MUSC.

009 Association Between Race/Ethnicity and Glycemic Control in an Indigent Primary Care Sample with Type 2 Diabetes
Joni Strom2, Ashley Primus2, Erica Hayne1, Tremayne Mitchell1, Leonard E Egede2; 1South Carolina State University, 2College of Medicine, MUSC, Ralph H. Johnson VA Medical Center.

010 Ethnic Differences in Association Between Diabetes Knowledge and Self-Management Behavior and Glycemic Control in Adults with Type 2 Diabetes
Erica Haynes1, Ashley Primus2, Tremayne Mitchell3, Leonard Egede4; 1Biological Sciences, SCSU; Ralph H. Johnson VA Medical Center, 2Medicine, MUSC, 3Biological Sciences, SCSU, 4Medicine, MUSC, Ralph H. Johnson VA Medical Center.

011 Position of Maxillary First Molar Relative to Cranial and Maxillary Dimensions Following Cervical Traction
Katie T Stroud1, Louis M Andria2, Luis P Leite 2; 1Dental Medicine, MUSC, 2Dental Medicine, Pediatric Dentistry and Orthodontics, MUSC.
012 The Role of Impulsivity as a Predictor of Methamphetamine Self-Administration and Effects of Methamphetamine on Impulsivity, Callan Davenport¹, Kelly Banna², Ronald See², ¹University of South Carolina Beaufort, ²Neurosciences, MUSC.

012.1 Sex Differences in Nicotine Self-Administration and Relapse Using an Animal Model, Fiorela Ruiz¹, Matthew Feltenstein², Ronald See², ¹University of South Carolina Beaufort, ²Neurosciences, MUSC.

013 The Impact of Retrograde Autologous Priming on the Effectiveness of the Magovern Formula to Predict Blood Transfusions, Samantha L Kaiser¹, Anthony G Shackelford²; ¹College of Health Professions, MUSC, ²College of Health Professions, Clinical Services, MUSC.

Session 2: Clinical Prof/Masters I

014 Racial/Ethnic Differences in Diabetes Fatalism in an Ethnically Diverse Primary Care Sample with Type 2 Diabetes, Ashley Primus¹, Tremayne Mitchell², Erica Haynes², Leonard E Egede¹; ¹Medicine, MUSC, Ralph H. Johnson VA Medical Center, ²Biological Sciences, SCSU.

015 Diabetic Resources in South Carolina: Are Research Institutions, Physicians, and Prevention Programs Responding to the Diabetes Burden in South Carolina?, Jenny C McCallister¹, Andrea D Boan², Daniel T Lackland²; ¹Medicine, MUSC, ²Biostatistics, Bioinformatics, and Epidemiology, MUSC.

016 Diabetic Patients’ Access to and Preference for Patient Education, Julia Hughes¹, Carolyn Fuller², Amanda Powell², Amanda Chapman², Hon Yuen²; ¹College of Health Professions, MUSC, ²College of Health Professions, MUSC.

017 Arthritis Knowledge Among Health Professional Students At the Medical University of South Carolina: A Pilot Study, Katie E Atkinson, Nicole C Abner, Erin Gravino, Tamara B Hardee, Thomas C Head, Amber S King, Kelli C Mackie, Lauren C Shockley; College of Health Professions, MUSC.

018 Prognosis in Aphasia: What Are the Factors?, Sarah Knauff, Lacy Stephens, Brittni Carnes, Laura Shaffer, Maureen Mahan, Charles Ellis; College of Health Profession, MUSC.

019 Global Coherence in Narratives of Individuals with Parkinson’s Disease, Stephanie Smith, Kelsey Roth, Jessica Terry, Kathryn Robarge, Charles Ellis; College of Health Professions, MUSC.

020 The Influence of Parkinson’s Disease on Referential Cohesion, Brecken Hentz, Lindsay Hunt, Alissa Green, Fran Toth, Charles Ellis; College of Health Professions, MUSC.

021 The Perceived Benefits of Participation in Structured Recreational Activities Among Parents of Children with Severe Mental and Physical Disabilities, Danielle Corneille, Stacy L Lyons, Patricia Coker, Charles Ellis; College of Health Professions, Rehabilitation Sciences, MUSC.

022 Perceived Barriers to Healthy Nutritional and Physical Activity Habits Among Community Dwelling Mental Health Clients, Hope E Craddock, Tara F Hassler, Paisley C Polk, Erin L Smith, Ashley E Cunningham, Andrea D Sandifer, Nancy Carson; College of Health Professions, Occupational Therapy, MUSC.

024 A Survey of Head and Neck Cancer Curriculum in United States Speech Language Pathology Masters Programs, Brittany A Dejarnett, Michelle E Fallis, Caroline J Wylie, Hon K Yuen; College of Health Professions, MUSC.

025 Stroke Knowledge Among Speech-Language Pathology Graduate Students, Jessica Terry, Lauren Marshall, Kristen Lankford, Amanda Pittman, Charles Ellis; College of Health Professions, MUSC.

Session 3: Clinical Prof/Masters II

026 Evaluation of Global and Regional Myocardial Function Using Contrast Enhanced Cardiac CT and MRI, Kevin O Herman¹, Chris Bruno², Joseph Schoepf³, Gorka A Bastarrika³, Balazs Ruzsics³; ¹Medicine, MUSC, ²College of Medicine, University of Tennessee, ³Radiology, MUSC.

027 Regulation of Beta-Galactosidase MRNA Expression in Hypoxic And/or Electrically Stimulated Adult Cardiac Myocytes, Charlie Pickens Jr¹, Paul J McDermott²; ¹Medicine, MUSC and Ralph H Johnson VA Medical Center, ²Medicine, Cardiology, MUSC and Ralph H Johnson VA Medical Center.

028 Myocardial Infarction Induces Changes in Nkx2-5 and Connexin 40 Expression in the Peripheral Conduction System, Irissa N Wilson¹, Mary S Rackley¹, Brett S Harris², Rupak Mukherjee³, Terrence X O'Brien⁴; ¹Medicine, MUSC, ²Cell Biology and Anatomy, MUSC, ³Surgery, MUSC, ⁴Medicine, Cell Biology and Anatomy, MUSC and Ralph H Johnson VA Medical Center.

029 Comorbidities in South Carolina Stroke Patients: What Percent of Stroke Patients Also Have Combinations of Hypertension, Hyperlipidemia, and Diabetes Mellitus?, Elizabeth W McCoy¹, Andrea D Boan², Daniel T Lackland²; ¹Medicine, MUSC, ²Biostatistics, Bioinformatics, and Epidemiology, MUSC.

030 Characterization of Toll-Like Receptors 1, 2, 4, and 6 in Human Myofibroblast of the Large Intestine, Megann K Helton-Rieter¹, Titus A Reaves²; ¹Medicine, MUSC, ²Cell Biology and Anatomy, MUSC.

031 Does Sickle Trait Exacerbate Diabetic Retinopathy?, John H Johnson¹, Berdine Burger², Esther Bowie², Rosalie Crouch²; ¹Medicine, MUSC, ²Ophthalmology, MUSC.

032 Characterization of Calpain 10 Substrates, Robert E Sweeney¹, Rick G Schnellmann²; ¹Medicine, MUSC, ²Pharmaceutical Science, MUSC.

033 Impact of Acid Ceramidase Expression on Head and Neck Cancer Proliferation In Vitro, Sarah T Marrison¹, Alex S McPherson², Joseph C Cheng³, Thomas H Beckham ², Xiaoyi Zhang¹, Lorianne S Turner³, Xiang S Liu³, James S Norris³; ¹Medicine, MUSC, ²MUSC, ³Microbiology and Immunology, MUSC.

034 BDNF Processing and Signaling and Its Correlation with Aging Associated Memory Decline in Mice, Hiromi Terawaki¹, Mona Buhusi², Lotta Granholm - Bentley²; ¹Medicine, MUSC, ²Neurosciences, MUSC.

035 Regulation of an Amino-Acid Transport Protein By Oncogenic Herpesvirus, Benjamin C Kalivas¹, Chris Parsons²; ¹Medicine, MUSC, ²Infectious Diseases, MUSC.
Session 4: Clinical Prof/Masters III

036 Comparison of the Preferences of Two Types of Pill Boxes Amongst Older Adults, Leigh F Smith, Caitlyn S Butsura, Lee Ann D Gladwell, Lindsay R Hoyle, Hon Yuen; College of Health Professions, MUSC.

037 Medication Use for Diabetes, Hypertension, and Hyperlipidemia From 1988-1994 to 1999-2004, Tina M. Ellis¹, Charles G. Everett², Paul F. Jacques¹, Dana E. King²; ¹College of Health Professions, MUSC, ²Family Medicine, MUSC.

038 Pediatric Emergency Medicine, Physician Assistants, and Postgraduate Education: A Prospective Survey, Kara D Larson, Sarah E Belden, Christopher T McLaren, Meghan E McQuiston, Rebecca E Obenza, Jessie J VanDerveer, Paul Jacques; Health Professions, Physician Assistant Studies, MUSC.

039 A Study of Modified Constraint-induced Movement Therapy Used for Children with Hemiplegic Cerebral Palsy, Thomas C Head, Cameron H Corbin, Patricia C Coker; College of Health Professions, Occupational Therapy, MUSC.

040 Improvement of Ergonomic Laptop/Notebook Positioning Following Graduate Student Education, Gina Kinney Barkley, Jessica Holt, Jessica Williams, Shannon Barch, Rita Cordell, Katherine Lorenz, Peter Bowman; Health Professions, Occupational Therapy, MUSC.

041 Comparison of Intravenous Immune Globulin and High Dose Anti-D Immune Globulin As Initial Therapy for Childhood Immune Thrombocytopenic Purpura, I Kane¹, D Ragucci², I Shatat³, R Kalpathi⁴; ¹Medicine, MUSC, ²Pharmacy Services, MUSC, ³Pediatrics, MUSC, ⁴Pediatrics, Hematology/Oncology, MUSC.

041.1 The Role of Early Placentation in Recurrent Preeclampsia, Elizabeth M White, Mark M Alanis², Laura Goetz³; ¹Medicine, MUSC, ²Medicine, OB/GYN, MUSC.

042 Oral Health and Respiratory Disease in People with Scleroderma, Eric Layton¹, Hon K Yuen², Caroline Westwater³; ¹College of Dental Medicine, MUSC, ²College of Health Professions, Health Professions, MUSC, ³College of Dental Medicine, Stomatology, MUSC.

043 Long-Term Music Exposure Significantly Decreases Seizure Frequency In Subjects with Intellectual and Developmental Disabilities, Caroline E Norment¹, Robert P Turner², Mark Bodner³; ¹Dental Medicine, MUSC, ²Neurosciences, MUSC, ³MIND Institute of California.

044 C-Reactive Protein: Stabilization Versus Activation of the First Complement Component (C1), David A Bodie¹, Marcus R Duvall², Robert J Boackle³; ¹Dental Medicine, Stomatology, MUSC, ²Immunology, MUSC.

045 Cisplatin/Irinotecan Versus Carboplatin/Paclitaxel As Definitive Chemoradiotherapy for Loco-Regionally Advanced Esophageal Cancer, Bree N Ruppert¹, John M Watkins², Shirai Keisuke³, Amy Walquist⁴, Elizabeth Garrett-Mayer⁴, Carolyn E Reed⁵, Carol K Sherman³, Anand K Sharma²; ¹Medicine, Radiation Oncology, MUSC, ²Radiation Oncology, MUSC, ³Medicine, Division of Hematology and Oncology, MUSC, ⁴Biostatistics, Bioinformatics, and Epidemiology, MUSC, ⁵Surgery, Division of Cardiothoracic Surgery, MUSC.
046 Factors Affecting Participant Inaction During High-Fidelity Simulation of ACLS Megacodes, Jennifer R Matos¹, Matt Crumpler¹, Young Choi¹, Matthew McEvoy²; ¹Medicine, Anesthesia, MUSC, ²Anesthesia, MUSC.

047 High Throughput Screening for Inhibitors of Zeb-1, Brandon L Mizell¹, Matthew M Chao¹, Charles Smith², Harry A Drabkin³, Robert Gemmill³, Michael Mitas³; ¹Health Professions, MUSC, ²Pharmacology, MUSC, ³Medicine, MUSC.

048 Population-based Prevalence and Incidence of Health Conditions Over a 10-year Period After Traumatic Spinal Cord Injury, Eric J Shiroma¹, Dulaney A Wilson¹, Elisabeth E Pickelsimer²; ¹Biostatistics Bioinformatics & Epidemiology, MUSC, ²Biostatistics Bioinformatics & Epidemiology, Medicine, MUSC.

Session 5: PhD I

049 Acid Ceramidase Upregulation Following Radiation Therapy Desensitizes Cancer Cells to Taxol, Thomas H Beckham, Joseph C Cheng, Ayman EM Mahdy, Saeed Elojeimy, S. Tucker Marrison, Xiaoyi Zhang, Xiang S Liu, James S Norris; Microbiology and Immunology, MUSC.

050 Cathepsin B Is Tied to Acid Ceramidase Expression in Prostate Cancer and Mechanistically Contributes to Tumor Progression, Xiaoyi Zhang¹, Thomas H Beckham¹, Joseph C Cheng¹, Sarah T Marrison¹, Lorianne S Turner¹, Alex S McPherson¹, Alicja S Bielawska², James S Norris¹; ¹Microbiology and Immunology, MUSC, ²Biochemistry and Molecular Biology, MUSC.

051 The Use of Cationic Polymers to Improve Adenoviral Transfection of Prostate Cancer Cells, Fahmin Basher¹, Laura Kasman¹, Kaushal Rege², Christina Voelkel-Johnson¹; ¹Microbiology & Immunology, MUSC, ²Chemical Engineering, Arizona State University.

052 Estimating Long-term Placebo Effect Using Short-term Repeated Measures Data And Meta Analysis: An Example From Depression, Annie N Simpson¹, Kit N Simpson², Ziad Nahas³; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²College of Health Professions, Health Administration, MUSC, ³Medicine, Psychiatry and Behavioral Sciences, MUSC.

053 Improving the End User Experience Within ArrayQuest, a Web-based DNA Microarray Analysis Process Controller, Adrian M Nida¹, Saurin D Jani², Gary L Argraves³, W. Scott Argraves²; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²Cell Biology and Anatomy, MUSC, ³Array Genetics, Newtown, CT.

054 Hyaluronan-CD44 Interactions Aid in Stabilization of Pro-Tumorigenic Signaling Complexes and Transporters in the Plasma Membrane, George D Grass, Mark G Slomiany, Bryan P Toole; Cell Biology and Anatomy, MUSC.

055 Computer Simulation of Drug Release From Temperature-Sensitive Liposomes During Thermal Treatment, Astrid Gasselhuber¹, Dieter Haemmerich²; ¹Pediatrics, MUSC, ²Pediatrics, MUSC, Clemson Bioengineering.

056 CXC Chemokine Ligand-13 Stimulates RANK Ligand Expression in Squamous Cell Carcinoma, Alfred C Griffin¹, Yuvaraj Sambandam¹, Kumaran Sundaram¹, William L Ries², Reddy V Sakamuri¹; ¹Darby Children’s Research Institute, MUSC, ²Dental Medicine.
057 Activator of G-Protein Signaling 3: The Role of the Tetratricopeptide Repeat (TPR) Domain in Subcellular Positioning of the Protein, Ali Vural, Joe Blumer, Stephen Lanier; Pharmacology, MUSC.

058 Characterization of the AdCerS6F Adenovirus for Modulation of Ceramide Synthase 6 in Colon Cancer Cells, Tejas S Tirodkar¹, Laura M Kasman², Shai J White-Gilbertson², Christina Voelkel-Johnson²; ¹MCBP, MUSC, ²Microbiology and Immunology, MUSC.

059 Differential Roles of Sphingosine Kinase Isoenzymes in A498 Kidney Carcinoma Cells, Peng Gao, Charles D Smith; Pharmaceutical Sciences, MUSC.

060 Targeting Membrane-Associated Hsp90 Inhibits the Establishment of Latent Infection By an Oncogenic Herpesvirus, Michael R DeFee¹, Qin Zhiqiang², Jennifer Isaacs³, Chris H Parsons⁴; ¹Microbiology and Immunology, and Dental Medicine, MUSC, ²Medicine, MUSC, ³Pharmacology, MUSC, ⁴Medicine, and Microbiology and Immunology, MUSC.

061 Thermophilic Bacteria Capable of Electricity Generation in Microbial Fuel Cells, Christopher W Marshall¹, Bryan J Mathis¹, Harold D May²; ¹Microbiology and Immunology, MUSC, ²Microbiology and Immunology, MUSC, MFC Technologies LLC.

062 Intra-hippocampal Injection of Pro-NGF Increases Expression of Sortilin and P75, in Vivo: Possible Mechanism of Basal Forebrain Cholinergic Neuron Degeneration, Ashley M Fortress¹, Kris L Helke², Lotta Granholm³; ¹Neurosciences, MUSC, ²Comparative Medicine, MUSC, ³Neurosciences and Center on Aging, MUSC.

063 Dysfunctional Cognitive Performance and Blunted Prefrontal Cortex Neuronal Activity Following Chronic Methamphetamine Self-Administration in Rats, Aram Parsegian, Antonieta Lavin, Ronald E See; Neurosciences, MUSC.

064 Transdermal Dl-Methylphenidate Increases L-Isomer Absorption Relative to Oral Dosing in Mice and Yields the L-Ethylphenidate Metabolite Following Ethanol Gavage, Guinevere Bell¹, Andy Novak², Lawrence Middaugh², William Griffin², Kennerly Patrick¹; ¹Pharmaceutical Sciences, MUSC, ²Psychiatry and Behavioral Sciences, MUSC.

065 Sequential Baseline Adaptive Randomization Balancing Continuous Prognostic Factors in Stroke Clinical Trials, Jody D Ciolino¹, Yuko Palesch², Renee Martin², Wenle Zhao²; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²Biostatistics, Bioinformatics, and Epidemiology, Data Coordination Unit, MUSC.

066 Heat Shock Preconditioning Inhibits Cisplatin-induced Hair Cell Death in the Adult Mouse Utricle, Tiffany Baker¹, Mona Taleb², Shimon Francis¹, Carlene Brandon¹, Keely Morris², Lisa Cunningham¹; ¹Pathology and Laboratory Medicine, MUSC, ²Graduate Studies, Medicine, MUSC.

Session 6: PhD II

067 Factors Impacting Racial Disparities Among People with Diabetes in the Southeast United States, Kelly N Hardman¹, Kelly J Hunt¹, Rickey Carter¹, Carolyn Jenkins², Daniel T Lackland³; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²College of Nursing, MUSC, ³Biostatistics, Bioinformatics, and Epidemiology, MUSC.
068 A Bayesian Analysis of Recurrent Events Data with Dependent Termination: An Application to a Heart Transplant Problem, Bichun Ouyang¹, Debajyoti Sinha², Elizabeth H Slate¹, Adrian B Van Bakel³; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²College of Arts & Sciences, Statistics, Florida State University, ³Medicine, Cardiology, MUSC.

069 The Functional Potential of Microbial Communities Associated with the Healthy and Diseased Coral, Montastrea Faveolata, Nikole E Kimes¹, Joy D Van Nostrand², Jizhong Zhou², Ernesto Weil³, Pamela J Morris⁴; ¹Marine Biomedicine and Environmental Sciences, MUSC, ²Botany and Microbiology, University of Oklahoma, ³Marine Sciences, University of Puerto Rico-Mayaguez, ⁴Cell Biology and Anatomy, Marine Biomedicine and Environmental Sciences, MUSC.

070 Influence of Selenium and Mercury Chemistries on the Progression of Cardiomyopathy in Pygmy Sperm Whales, Kogia Breviceps, Colleen E. Bryan¹, Gregory D. Bossart², W. Clay Davis³, Guillaume Ballihaut³, Carola Neumann⁴, Wayne E. McFee⁵, Steven Christopher⁶; ¹Marine Biomedicine and Environmental Sciences Center, MUSC, ²Division of Marine Mammal Research and Conservation, HBOI, FAU, Fort Pierce, FL, ³National Institute of Standards and Technology, Hollings Marine Laboratory, ⁴Cell and Molecular Pharmacology and Experimental Therapeutics, MUSC, ⁵NOAA National Ocean Service, CCEHBR.

071 The Search for Antibiotics in Bacteria Associated with the Surface Mucopolysaccharide Layer of the Coral Pseudopterogorgia Americana, Maria I Vizcaino¹, Katherine Williams², Peter D.R. Moeller³, Pam J Morris¹; ¹MBES, MUSC, Hollings Marine Laboratory, ²Hollings Marine Laboratory, ³NOAA National Ocean Service, Hollings Marine Laboratory, MBES, MUSC, ⁴Cell Biology and Anatomy, MBES, MUSC, Hollings Marine Laboratory.

072 Celastrol, an Antioxidant and Anti-Inflammatory, Induces the Heat Shock Response and Inhibits Aminoglycoside-Induced Inner Ear Hair Cell Death, Shimon P Francis¹, Carlene S Brandon¹, Fu-Shing Lee², Lisa L Cunningham¹; ¹Pathology and Laboratory Medicine, MUSC, ²Otolaryngology – Head and Neck Surgery, MUSC.

073 Autocrine TGF-beta Signaling Regulates PP2A Levels in SSc Fibroblasts, Hazitha Samuel¹, Andreea M Bujor², Faye Hant³, Maria Trojanowska²; ¹MCBP, MUSC, ²Medicine, Rheumatology, MUSC, ³Medicine, MUSC.

074 Proportional Odds Model for Design of Dose Finding Clinical Trials with Ordinal Toxicity Grading, Emily M Van Meter, Dipankar Bandyopadhyay, Elizabeth Garrett-Mayer; Biostatistics, Bioinformatics, and Epidemiology, MUSC.

075 Cardiovascular Risk Factors and Arterial Stiffness: An Assessment of Noninvasive Measurements of Arterial Compliance, Andrea D Boan¹, William K Mountford¹, Daniel T Lackland²; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²Medicine, Biostatistics, Bioinformatics, and Epidemiology, MUSC.

076 Evaluation of Genomewide Association Study Results Through Development of Ontology Fingerprint, Lam C Tsoi¹, Michael Boehnke², Jim W Zheng¹; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²Biostatistics, University of Michigan.

077 Afferents That Regulate Lateral Hypothalamic Orexin/Hypocretin Neurons During Cocaine Conditioned Place Preference, G C Sartor, G Aston-Jones; Neurosciences, MUSC.
078 Age-Related Hippocampal Dendritic Loss is Further Aggravated By Dietary Lipids, Linnea R Freeman¹, Cheryl Stevens², Vivian Haley-Zitlin², Alfred Moore¹, Ann-Charlotte Granholm³; ¹Neurosciences, MUSC, ²Food Science and Human Nutrition, Clemson, ³Medicine, Neurosciences, MUSC.

079 Intra-dmPFC Infusion of K252a Blocks the Suppressive Effect of BDNF on Cocaine-Seeking Behavior, Timothy W Whitfield, William Berglind, Anthony Carnell, Adrian Gomez, Ron See, Jacqueline F Mcqinty; Neurosciences, MUSC.

080 Absence of Sphingosine Kinase 1 Alters Progression of TNF-alpha Induced Arthritis, DeAnna Baker¹, Lina Obeid², Gary Gilkeson³; ¹Rheumatology and Immunology, MUSC, ²General Internal Medicine/Geriatrics, MUSC, Ralph H. Johnson VA Medical Center, ³Rheumatology and Immunology, MUSC, Ralph H. Johnson VA Medical Center.

081 Sphingomyelin Synthase: A Novel Regulator of Bcr-abl Mediated Tumorigenesis, Tara Burns, Chiara Luberto; Biochemistry, MUSC.

Session 7: PhD III

082 Performance of Statistical Methods for Transitioning From a Three-Armed Superiority Trial to a Two-Armed Non-Inferiority Trial When Superiority of a Single Treatment Arm is Determined Early, Jordan J Elm, Yuko Y Palesch; Biostatistics, Bioinformatics, Epidemiology, MUSC.

083 Utilization of Beta Regression in Multivariable Analysis of Infarct Volume Measured By Diffusion-Weighted Magnetic Resonance Imaging After Acute Ischemic Stroke, Christopher J Swearingen, Joyce S Nicholas; Biostatistics Bioinformatics, and Epidemiology, MUSC.

084 Organohalogen Contaminant Exposure in Wild Bottlenose Dolphins: Cumulative Influences of Dietary Exposure, Life History and Physiology, Jennifer E Yordy¹, Randall Wells², Aurore Guichard³, Brian Balmer², Lori Schwacke⁴, Teri Rowles⁴, John Kucklick³; ¹MBES, MUSC, ²Chicago Zoological Society, c/o Mote Marine Laboratory, ³National Institute of Standards and Technology, HML, ⁴Cooperative Center for Marine Animal Health, NOAA, ⁵Marine Mammal Health and Stranding Response Program, NMFS.

085 Kruppel-like Factor 4 As a Novel Mediator of Kallistatin in Inhibiting Inflammatory Signaling in Endothelial Cells, Bo Shen, Robert S Smith, Jr., Lee Chao, Julie Chao; Biochemistry and Molecular Biology, MUSC.

086 Tumor-Secretion of VEGF-A Induces Formation of Immune Suppressive Endothelial Cells In Vivo, Jennifer Mulligan, Rita Young; Research Service, Ralph H. Johnson VA Medical Center, Otolaryngology, MUSC.

087 The Involvement of Calpain in CD4+ T Cell Bias, Jonathan T Butler¹, Naren L Banik², Craig C Beeson³; ¹MCBP, MUSC, ²Neurosciences, MUSC, ³MCBP and Pharmaceutical Sciences, MUSC.

088 The Role of NK Cells in CCL22-mediated Treg Recruitment Toward Lewis Lung Carcinoma, Adam W Mailloux¹, M Rita I Young²; ¹Microbiology and Immunology MUSC, ²Research Service, Ralph H. Johnson VA Medical Center, Otolaryngology, MUSC.

089 Locus Coeruleus Degeneration in a Mouse Model for Down Syndrome: A Potential Stimulus for Neuroinflammation, Jason P Lockrow¹, Heather A Boger¹, Ann C Granholm²; ¹Neurosciences, MUSC, ²Neurosciences and Center on Aging, MUSC.
090 Evidence of the Relationship Between Brain GDNF and Alcohol Withdrawal-Induced Convulsions in a Murine Model, Kathleen A Potter¹, C Venugopal², K S Sambamurthi², A C Granholm², L D Middaugh³, Howard C Becker⁴. ¹Neurosciences, Charleston Alcohol Research Center, Ralph H. Johnson VA Medical Center, MUSC, ²Neurosciences, MUSC, ³Psychiatry, MUSC, ⁴Psychiatry, Neurosciences, Charleston Alcohol Research Center, Ralph H. Johnson VA Medical Center, M.

091 Initial Characterization of SKAR and Its Role in Regulating Cell Size of Cardiomyocytes, Phillip C Moschella¹, Dhandapani Kuppuswamy². ¹Medicine, Cardiology, MUSC, ²Medicine, Cardiology, MUSC, Ralph H. Johnson VA Medical Center.

092 Functional Relevance of Hox-Specified Positional Identities in Adult Vasculature, Nathanael D Pruett¹, Richard Visconti², Tim McQuinn³, Alexander Awgulewitsch¹. ¹Medicine, MUSC, ²Cell Biology and Anatomy, MUSC, ³Pediatric Cardiology, Cell Biology and Anatomy, MUSC.

093 Beta3 Integrin-mediated Ubiquitination for NFkappaB Transcription is Necessary to Maintain Compensated Hypertrophic Growth, Rebecca K Johnston, Sundaravadivel Balasubramanian, Catalin F Baicu, Michael R Zile, Dhandapani Kuppuswamy; Medicine, Cardiology, MUSC and the Ralph H. Johnson VA Medical Center.

094 Sotat1 is a Regulatory Target of Hoxc13 in Both the Hair Follicle and Brain, Christopher S Potter¹, Kathleen A Potter², Nathanael D Pruett¹, Micheal J Kern³, Alan R Godwin⁴, John P Sundberg⁵, Alexander Awgulewitsch¹. ¹Medicine, MUSC, ²Neurosciences, MUSC, ³Cell Biology and Anatomy, MUSC, ⁴Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, ⁵The Jackson Laboratory, Bar Harbor, ME.

095 The Role of ALK1 and Endoglin Signaling in Scleroderma Fibrosis, Erin Morris¹, Andreea Bujor¹, Peter ten Dijke², Maria Trojanowska³. ¹Rheumatology, MUSC, ²Molecular Cell Biology, Leiden University Medical Center.

096 Retinoids Regulate TGFβ Signaling At the Level of Smad2 Phosphorylation and Nuclear Accumulation, Loretta L Hoover¹, Elizabeth G Burton¹, Megan L O'Neill², Bonnie A Brooks¹, Steven W Kubalak¹. ¹Cell Biology and Anatomy, MUSC, ²Medicine, MUSC.

Session 8: Postdocs/Residents/Fellows I

097 Sphingomyelin Synthases Regulate Production of Diacylglycerol At the Golgi and Protein Trafficking to the Cell Surface, Subathra Marimuthu¹, Maristella Villani¹, Yeong-Bin Im¹, Young Choi¹, Paola Signorelli², Maurizio Del Poeta¹, Chiara Luberto¹. ¹Biochemistry and Molecular Biology, MUSC, ²Laboratory of Biochemistry and Molecular Biology, San Paolo University Hospital, School of Medicine.

098 A Novel Signaling Pathway of Tissue Kallikrein in Promoting Keratinocyte Migration: Activation of Proteinase-Activated Receptor 1 and Epithelial Growth Factor Receptor, Lin Gao, Lee Chao, Julie Chao; Biochemistry and Molecular Biology, MUSC.

099 Regulation of G-protein Signaling Pathways By AGS3 in the Neuroblastoma-Glioma Cell Hybrid NG108-15, Sukru S Oner, Joe B Blumer, Stephen M Lanier; Cell and Molecular Pharmacology and Experimental Therapeutics, MUSC.
100 Activation of G Protein Independent Signaling Pathways Elicits a Distinct Protein Phosphorylation Profile, Ryan T Kendall¹, MiHyee Lee¹, Hesham M El Shewy¹, Michael G Janech², Deirdre K K Luttrell¹, Louis M Luttrell¹; ¹Medicine, Endocrinology, Diabetes & Medical Genetics, MUSC, ²Medicine, Nephrology, MUSC.

101 Regulation of Activator of G Protein Signaling 3 By FERM and PDZ Domain Containing 1 (Frmpd1), Ningfei An, Joe B Blumer, Stephen M Lanier; Pharmacology, MUSC.

102 Effects of Null Mutation of the Gene Encoding Dysbindin-1 on Cortical Fast-Spiking Interneurons, H Trantham-Davidson¹, J D Jentsch², A Lavin¹; ¹Neurosciences, MUSC, ²UCLA.

103 Multiple Memory Systems and Extinction: Neural Inactivation of Dorsolateral Striatum Selectively Blocks Response Extinction in a Runway, Amanda Gabriele¹, Mark G Packard²; ¹Neurosciences, MUSC, ²Psychology, Texas A&M University.

104 Photoreceptor Degeneration in Rpe65 Knockout Mice is Reduced By Opsin Phosphorylation, Jie Fan¹, Baerbel Rohrer², Bill Wu¹, Ching-Kang Chen³, Vladimir Kefalov⁴, King-Wai Yau⁴, Rosalie Crouch¹; ¹Ophthalmology, MUSC, ²Ophthalmology, NeuroscienceS, MUSC, ³Biochemistry, VCU, ⁴Neuroscience, JHU.

105 P-Glycoprotein Inhibition and Risperidone-Induced Striatal Dopamine Release, Alejandra M Pacchioni¹, Alisha Henderson¹, Amanda Gabrielle¹, Lindsay DeVane², Ronald E See¹; ¹Medicine, Neurosciences, MUSC, ²Medicine, Psychiatry and Behavioral Sciences, MUSC.

106 Behavioral Recovery From Long-term Deleterious Methamphetamine Effects is Deficient in GDNF+/- Mice, Tara S Bender¹, Emily D Denehy¹, Peng Huang², Jacqueline F McGinty¹; ¹Neurosciences, MUSC, ²Biostatistics, Bioinformatics, and Epidemiology, MUSC.

107 Pharmacologic Effect of 11-cis Retinal on Cone Photoreceptor in Mouse Retinal Explants Culture, Mausumi Bandyopadhyay, Baerbel Rohrer; Neurosciences, MUSC.

108 Differential Phosphorylation Of Phosphoproteins By Repeated Amphetamine Treatment In Rat Striatum Is Mediated By Different Types Of DA Receptors, Xiangdang Shi, Jacqueline F McGinty; Neurosciences, MUSC.

109 Combination Therapy of Lovastatin and Rolipram Provides Neuroprotection and Promotes Neurorepair in Inflammatory Demyelination Model of Multiple Sclerosis, Manjeet K Paintlia¹, Ajaib S Paintlia¹, Inderjit Singh¹, Robert B Skoff², Avtar K Singh³; ¹Pediatrics, MUSC, ²Wayne State University School of Medicine, Detroit MI, ³Ralph H. Johnson VA Medical Center.

110 Role of CXC Chemokine Ligand 13 in Squamous Cell Carcinoma Associated Osteolysis in Athymic Mice, Yuvaraj Sambandam¹, Subramaniya NM Pandravada¹, Liu Xang², James S Norris², Srinivasan Shanmugarajan¹, William L Ries¹, Steve V London³, Reddy V Sakamuri¹; ¹Charles P. Darby Children’s Research Institute, ²Microbiology & Immunology, MUSC, ³Dental Medicine, MUSC.

111 Predictors of Response to Anti-TNF-α Therapies in Two University-Based Populations with Rheumatoid Arthritis, Rodney S Daniel¹, Rae Bourne², Annie N Simpson³, Kenneth S O’Rourke², Marcy B Bolster¹; ¹Rheumatology and Immunology, MUSC, ²Wake Forest Baptist University Medical Center, Winston-Salem, NC, ³Biostatistics, Bioinformatics, and Epidemiology, MUSC.
Session 9: Postdocs/Residents/Fellows II

112 Role of HuR in Bcl-2 mRNA Stability in Human HL60 Leukemia Cells, Sivakumar Ramalingam, Daniella Ishimaru, Baby G Tholanikunnel, Daniel J Fernandes, Eleanor K Spicer; Biochemistry and Molecular Biology, MUSC.

113 DHHC20: A Potential Novel Target For the Development of Anticancer Therapeutics, Jeremiah M Draper, Charles D Smith; Pharmaceutical and Biomedical Sciences, MUSC.

114 Murine Hematopoietic Stem Cells But Not Progenitor Cells Are Highly Susceptible Towards Radiation Exposure and Are Less Proficient in the DSB Repair, Senthil Kumar Pazhanisamy, Yong Wan, Daohong Zhou; Pathology and Laboratory Medicine, MUSC.

115 An Analysis of Ceramide Levels in Neuroblastoma Tumor Tissues, Heather Escoto, Jacqueline M Kraveka; Pediatrics, Division of Pediatric Hematology Oncology, MUSC.

116 FGF-2 Stimulates RANK Ligand Expression in Paget's Disease of Bone, Kumaran Sundaram¹, Joseph Senn², Sudhahar D Rao³, Srinivasan Shanmugarajan⁴, Sakamuri V Reddy⁵; ¹Medicine, MUSC, ²Bristol Myers Squibb Pharmaceuticals, Syracuse, NY, ³Henry Ford Hospital, Detroit, MI, ⁴Pediatrics, Endocrinology, MUSC, ⁵Pediatrics, MUSC.

117 Endogenous Tissue Kallikrein Ameliorates Chronic Renal Injury By Inhibiting Oxidative Stress and Activating Matrix Degradation Pathways, Yuying Liu, Makoto Hagiwara, Yang Zhirong, Lee Chao, Julie Chao; Biochemistry and Molecular Biology, MUSC.

118 Increasing Virus Entry and Infection in Macrophages By MicroRNA Encoded By an Oncogenic Herpesvirus, Zhiqiang Qin, Chris Parsons; Medicine, MUSC.

119 Modulating Complement Activation Inhibits Radiotherapy Induced Apoptotic Cells Clearance on Breast Cancer, Quan Fang, Jennifer Schepp, Fei Qiao, Stephen Tomlinson; Microbiology and Immunology, MUSC.

120 C3 Deficiency Minimized Inflammation Against Dextran Sulfate Sodium-Induced Colitis, Jennifer Schepp-Berglind, Stephen Tomlinson; Microbiology and Immunology, MUSC.

121 Role of Cilia in Tooth Development, Evgeni Efimenko, Darwin P Bell, Courtney J Haycraft; MUSC Medicine.

122 Oxidized LDL-Immune Complexes Trigger Enhanced Production of Collagen 4 By Human Mesangial Cells, Souzan A Abdel-Razek¹, Charlyne Chassereau², Hasnae Elouardighi³, Gabriel Virella⁴, Maria Lopes-virella¹; ¹Medicine/Endocrinology, MUSC, ²Ralph H. Johnson VA Medical Center, ³MUSC/ Medicine/Endocrinology, ⁴MUSC/Microbiology and Immunology.

123 Disparity Between Two Automated Immunochemiluminescent Intact Parathyroid Hormone (iPTH) Assays, David Holloman, Laurel Willis, Robin Schreiber, Joyce Foster, Christine Papadea, Yusheng Zhu; Pathology and Laboratory Medicine, MUSC.

124 Heterophilic Antibody Interference Causing False-Positive Rapid Human Immunodeficiency Virus Antibody Testing, Deborah V Spencer, Frederick S Nolte, Yusheng Zhu; Pathology and Laboratory Medicine, MUSC.
125 The F Box Protein of Skp1-Cdc53/Cullin F Box (SCP) E3 Ubiquitin-Ligase Complex, Dia2 Promotes Genome Stability By Negative Regulation of Ty-1 Retro-Transposition in Yeast, Narendra K Bairwa, Deepak Bastia; Biochemistry, MUSC.

126 Role of Beta3 Integrin - BMX Signaling for STAT3 Activation During Compensatory and Decompensatory Cardiac Hypertrophy, Geetha Suryakumar, Rebecca K Johnston, Michael Zile, Sundaravadivel Balasubramanian, Dhandapani Kuppuswamy; Medicine, Cardiology, MUSC.
ORAL PRESENTATIONS:

Education Center/Library (EL) Building – 12:00 pm-3:00 pm

College of Health Professions (CHP) Building - 11:45 am-3:00 pm

Session 10: Undergraduate II: 12:15 am - 3 pm – Room EL107

12:15 - 12:30
129 Secretion of Acid Sphingomyelinase By Human Monocytic Cells Exposed to Oxidized LDL and Oxidized LDL Immune Complexes, Christabelle M Piansay¹, Russell W Jenkins², Kent J Smith³, Yusuf A Hannun⁴, Samar M Hammad⁵; ¹Clemson University, ²MUSC, ³Cell Biology and Anatomy, MUSC, ⁴Biochemistry and Molecular Biology, MUSC.

12:30 - 12:45
130 Regulation of NFAT Transcription Factor Gene Expression By Mutant P62 in the Osteoclasts of Patients with Paget's Disease of Bone, Danielle D Mumford¹, Sakamuri Reddy²; ¹South Carolina Governor's School for Science and Mathematics, Hartsville, SC, ²Pediatrics, MUSC.

12:45 - 1:00
131 Targeting Hyaluronan-CD44 Interaction in MPNSTs, Paul A Bomar¹, Thomas J Knackstedt², Jennie Gilg³, Lauren B Tolliver³, Bryan P Toole³, Mark G Slomiany³, Bernard Maria⁴; ¹Pediatrics - SURP, MUSC - Clemson, ²Medicine, MUSC, ³Pediatrics - Hematology / Oncology, MUSC, ⁴Pediatrics, MUSC, ⁵Cell Biology and Anatomy, MUSC.

1:00 - 1:15
132 Prostate Derived ETS Factor Represses SLUG Expression in Breast Cancer Cells, M R Lauer¹, V J Findlay², D P Turner², D K Watson²; ¹University of North Texas, Denton, TX, ²Pathology and Laboratory Medicine, MUSC.

1:15 - 1:30
133 The Effects of Prostate Derived ETS Factor (PDEF) in Mammary Gland Development of Black 6 Strain Mice, Christine T Hang¹, Victoria J Findlay², Dennis K Watson²; ¹South Carolina Governor's School for Science and Mathematics, Hartsville, SC, ²Pathology and Laboratory Medicine, MUSC.

1:30 - 1:45 Break

1:45 - 2:00
134 The Effects of Different Antioxidants on MMP-1 Expression By U937 Macrophages, Sana A Ali¹, Yan Huang²; ¹Columbia College, Columbia, SC, ²Medicine, Endocrinology, MUSC.

2:00 - 2:15
135 The Role of ADAMTS-9 in Cardiac Development and Maintenance, Danielle N Geeting¹, Ebony Alston², Arno Wessels³, Suneel Apte⁴; ¹Biology, College of Charleston, ²Medicine, MUSC, ³Cell Biology and Anatomy, MUSC, ⁴Biomedical Engineering, Cleveland Clinic.
2:15 - 2:30
136 Renal Dysfunction in Cardiac Surgery: Identifying Potential Risk Factors, Jennifer L. Barnum, Joseph J. Sistino; College of Health Professions, Clinical Services, Cardiovascular Perfusion, MUSC.

2:30 - 2:45
137 In Vitro Modeling and Study of Respiration-dependent Subdiaphragmic Flow Reversal in the Fontan Circulation, Margaret A Zawaski¹, Amanda Hutchenson¹, Tiffany Camp¹, Tim Conover¹, Richard Figliola¹, T-Y Hsia²; ¹Clemson University, ²Medicine, Surgery, MUSC.

2:45 - 3:00
138 Comparison of Visual Responses and Receptive Fields in Biological and Artificial Retina, Grace M Dion¹, Prakash Kara²; ¹Clemson University, ²Neurosciences, MUSC.

Session 11: Clinical Prof/Masters IV: 12 am - 3 pm – Room CHP 203

12:00 - 12:15
139 Study on Renal Cell Carcinoma with Thrombosis Involvement of the Inferior Vena Cava, Ashok K Ramachandra¹, Justin Ellet², Ken Chavin³; ¹Medicine, MUSC, ²Microbiology and Immunology, MUSC, ³Medicine, Surgery, MUSC.

12:15 - 12:30
140 The Synthesis of a Hedgehog Pathway Inhibitor, GANT-61, Michael S Humeniuk¹, John Oatis², Alexander Krupenko³, George Cooper⁴; ¹Medicine, Cardiology, MUSC, ²Pharmacology and Experimental Therapeutics, MUSC, ³Biochemistry and Molecular Biology, MUSC, ⁴Medicine, Cardiology, MUSC and Ralph H. Johnson VA Medical Center.

12:30 - 12:45
141 Extracellular Biomarkers in Hypertensive Heart Disease; Unique Gender and Ethnicity Profiles, Adonteng A. Kwakye¹, Sheila Thompson², Catherine McClure³, Teresa Brinsa⁴, Robert Stroud⁴, John Mulcahy⁴, Michael G. Zile³, Francis G. Spinale ⁵; ¹Medicine, MUSC, ²Surgery, MUSC, ³Medicine, Cardiology, MUSC, ⁴Medicine, Surgery, MUSC, ⁵Medicine, Surgery, MUSC, Ralph H. Johnson VA Medical Center.

12:45 - 1:00
142 Myocardial Matrix Metalloproteinase Signatures with Atrial Fibrillation, Effect of Aldosterone Blockade, Charles C Peyton¹, Robert E Stroud², Martha R Stroud², Michael R Gold², David Gregg ², Francis G Spinale², Rupak Mukherjee²; ¹Medicine, MUSC, ²Division of Cardiothoracic Surgery and Adult Cardiology, MUSC.

1:00 - 1:15
143 Differential Matrix Metalloproteinase and Endogenous Inhibitor Expression in Ascending Thoracic Aortic Aneurysms Associated with Bicuspid Aortic Valve Subtypes, Stewart M Benton, Jeffrey A Jones, Robert E Stroud, Francis G Spinale, John S Ikonomidis; College of Medicine, MUSC.

1:15 - 1:30
144 Differential Proteolytic Profiles in Pediatric Cardiomyopathies, Nidhi Kumar¹, Robert Stroud², Jeremy Ringewald³, Nadia Roessler⁴, Francis Spinale², Tain-Yen Hsia²; ¹Medicine, MUSC, ²Surgery, MUSC, ³Pediatric Cardiology, MUSC, ⁴College of Medicine, Claude Bernard University, Lyon, France.
1:30 - 1:45  Break

1:45 - 2:00
145 TGF Beta Signaling in Embryonic Left-Right Axis Development, Megan Lee1, Ann Dr. Ramsdell2, Jayne Bernanke2; 1Medicine, MUSC, 2Cell Biology and Anatomy, MUSC.

2:00 - 2:15
146 Heterotaxy & Heart Field Development, David L Bowen1, Ann Ramsdell2, Jayne Bernanke2; 1Medicine, MUSC, 2Cell Biology and Anatomy, MUSC.

2:15 - 2:30
147 Novel Peptides Promote Cardiac Fibroblast Adhesion, Michael J Hinton1, Russell A Norris2; 1Medicine, MUSC, 2Cell Biology and Anatomy, MUSC.

2:30 - 2:45
148 Stathmin is Expressed in Pre-Mesenchymal Endothelial Cells and is Reduced in the V2/V0 Null Heart, Tyler C. Pierce1, Corey H. Mjaatvedt2; 1Medicine, MUSC, 2Cell Biology and Anatomy, MUSC.

2:45 - 3:00
149 Role of the Matrix Metalloproteinase ADAMTS-9 in Remodeling and Maintenance of the Cardiac Outflow Tract, Ebony R Alston1, Donald Menick2, Christine B Kern3; 1Medicine, MUSC, 2Medicine, Cardiology, MUSC, 3Cell Biology and Anatomy, MUSC.

Session 12: Clinical Prof/Masters V: 11:45 am - 3 pm – Room CHP 201

11:45 - 12:00
150 Effect of Low Salinity on the Expression of Membrane Transporter Proteins in Renal Tubular Segments of the Euryhaline Atlantic Stingray, Dasyatis Sabina, Adair Dempsey1, Eric Lacy2, Michael Janech3, Donald Miller4, David Ploth3, Wayne Fitzgibbon3; 1Grice Marine Laboratory, College of Charleston, 2Marine Biomedicine and Environmental Science Center, MUSC, 3Nephrology, MUSC, 4Cell and Molecular Pharmacology and Experimental Therapeutics, MUSC.

12:00 - 12:15
151 Signal Transduction Pathways Involved in the Development of Interstitial Kidney Fibrosis, Nicole Swavely1, Rick Visconti2, Wayne Fitzgibbon3, Sema Sivritas3, Pal Gooz4, Monika Gooz5; 1Medicine, MUSC, 2Medicine, Cell Biology and Anatomy, MUSC, 3Medicine, Nephrology, MUSC, 4Medicine, Rheumatology, MUSC, 5Medicine, Nephrology, MUSC and Ralph H. Johnson VA Medical Center.

12:15 - 12:30
152 Matrix Metalloproteinases and Non-Small Cell Lung Cancer, Sonam A Shah1, John S Ikonomidis2, Robert E Stroud3, Eileen I Chang3, Francis G Spinale3, Carolyn E Reed2; 1Medicine, MUSC, 2Medicine, Surgery, MUSC, 3Surgery, MUSC.

12:30 - 12:45
153 Systemic Treatment of Therapy-Resistant Malignant Peripheral Nerve Sheath Tumors with Hyaluronan Oligomers, Thomas J Knackstedt1, Paul Bomar2, Lauren Tolliver3, Bernard L Maria3, Mark G Slomiany4, Bryan P Toole4; 1College of Medicine, MUSC, 2Clemson University, 3Pediatrics, MUSC, 4Cell Biology and Anatomy, MUSC.
12:45 - 1:00
154 Bone Fracture Healing in Adult Mice: The Role of Periostin, Kathryn F Glenn¹, Russell A Norris², Kyle P Kokko³, Michael J Kern²; ¹Medicine, MUSC, ²Cell Biology and Anatomy, MUSC, ³Orthopaedic Surgery, MUSC.

1:00 - 1:15
155 Expanding the Female Neurologic Phenotype of Duplicated Xp Syndrome, Anna C Edens¹, Kenton R Holden², Barbara DuPont³; ¹Medicine, MUSC, ²Neurology, MUSC, ³Greenwood Genetic Center.

1:15 - 1:30  Break

1:30 - 1:45
156 Thermal Activation of Polymer Microfluidic Valves, Elizabeth A Gordon¹, Jian Liu², Daniel R Knapp²; ¹Medicine, MUSC, ²Pharmacology, MUSC Proteomics Center.

1:45 - 2:00
157 Oral Health in the Lowcountry Gullah Population, Zachary Evans, Michele Ravenel; Dental Medicine, MUSC.

2:00 - 2:15
158 The Role of Msh5 in Immune Deficiency in Systemic Lupus Erythematosus, Alexander T Page¹, Gary S Gilkeson², Hideharu Sekine²; ¹Medicine, MUSC, ²Rheumatology and Immunology, MUSC.

2:15 - 2:30
159 Gamma-interferon-Inducible-Lysosomal-Thiol Reductase Regulates Acidic Proteases and Costimulatory Molecules in Melanoma Cells, Duncan L Norton¹, Dan Zhao², William J McCravy², Peter Komlos³, Azizul Haque²; ¹Microbiology and Immunology, Hollings Cancer Center, MUSC, ²Microbiology and Immunology, Hollings Cancer Center, Darby Children's Research Institute, MUSC, ³Darby Children's Research Institute, MUSC.

2:30 - 2:45
160 Characterizing Racial Differences in Sarcoidosis Mortality — United States, 1991–2005: Results From Multiple-Cause Mortality Data, Colin B Ligon, Rose A Rudd, David B Callahan; Medicine, MUSC.

2:45 - 3:00
161 Prenatal Diagnosis of Agenesis of the Corpus Callosum and Prognosis: A Case Series, Kelly S Matmati¹, Maria G Matheus², Stephen S Glazier³, Bernard L Maria⁴, Kenton R Holden⁵; ¹Medicine, MUSC, ²Radiology, MUSC, ³Neurosurgery and Pediatrics, MUSC, ⁴Pediatrics, MUSC, ⁵Neurology and Pediatrics, MUSC.

Session 13: PhD IV: 12:15 am - 3 pm – Room CHP 204

12:15 - 12:30
162 Hydrogel-Based Sustained Delivery of 9-cis Retinal As a Novel Tool to Study Cone Photoreceptor Development and Congenital Pathophysiology, Peter H Tang¹, Jie Fan², Patrice W Goeltz², Rosalie K Crouch³; ¹Neurosciences, MUSC, ²Ophthalmology, MUSC, ³Neurosciences, Ophthalmology, MUSC.
12:30 - 12:45
163 The Neuroprotective Efficacy of Calpeptin in Acute and Chronic-Progressive EAE Retina, Amena W Smith¹, Arabinda Das², Kelly M Guyton¹, Gabriel C Fitton², Naren L Banik²; ¹Microbiology and Immunology, MUSC, ²Neurosciences, MUSC.

12:45 - 1:00
164 Acid Ceramidase Up-Regulation in Prostate Cancer Cells Confers Resistance to Radiation: AC Inhibition, a Potential Radio-Sensitizer, Joseph C Cheng, Ayman EM Mahdy, Jun Li, Saeed ElOjeimy, S. Tucker Marrison, William D Meacham, Xiang S Liu, James S Norris; Microbiology and Immunology, MUSC.

1:00 - 1:15
165 Metacaspase Expression and Activity in Karenia Brevis Cultures: Preliminary Insight Into Cellular Mechanisms Regulating Bloom Termination, Jillian G Lynch, Frances M Van Dolah; MCBP/MBES, MUSC, NOAA Center for Coastal and Environmental Health and Biomolecular Research.

1:15 - 1:30
166 Identification and Characterization of Senescence-Associated MicroRNAs in Human Fibroblasts, Melissa N Morris, Yong Wang, Jessica A Cloy, Joshua Kellner, Daohong Zhou; Pathology and Laboratory Medicine, MUSC.

1:30 - 1:45 Break

1:45 - 2:00
167 Caveolin-1 Regulates Normal and Scleroderma Monocytes Functions and Transformation Into Fibrocyte, Mathieu L Richard¹, Elena V Tourkina², Richard M Silver², Stanley Hoffman²; ¹MCBP, MUSC, ²Medicine, Rheumatology, MUSC.

2:00 - 2:15
168 Connexin 43 Gap Junction Dynamics in the Diabetic Heart, Joseph Palatinus, Robert Gourdie; Cell Biology and Anatomy, MUSC.

2:15 - 2:30
169 Exploring Protein Functional Similarities By Their Relationships in Three Dimensional Conceptual Space, Brian A Muller, Adam J Richards, Xinghua Lu; Biostatistics, Bioinformatics, and Epidemiology, MUSC.

2:30 - 2:45
170 Temporal and Gender Trends in Concordance of Urine Drug Screens and Self-Reported Use in Cocaine Treatment Studies, Megan S Schuler¹, William V Lechner², Rickey E Carter¹, Robert Malcolm²; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²Psychiatry, Center for Drug and Alcohol Programs, MUSC.

2:45 - 3:00
171 Inhomogeneous Solute Diffusion in Temporomandibular Joint Discs, Changcheng Shi¹, Christopher Bowers², Lixia Zhang², Hai Yao³; ¹Clemson-MUSC Bioengineering Program, Clemson University, ²Dental Medicine, MUSC, ³Clemson-MUSC Bioengineering Program, Clemson University, College of Dental Medicine, MUSC.
Session 14: PhD V: 11:45 am - 3 pm – Room CHP 207

11:45 - 12:00
172 Insights Into the Formation and Function of Membrane Vesicles From the Bacterium Burkholderia Vietnamiensis PR1301, Benjamin A Neely¹, Venetia D Lyles², Noelle T Garvin³, Gary L Mills³, Paul M Bertsch¹, Pamela J Morris¹; ¹Marine Biomedicine and Environmental Sciences Center, MUSC, Charleston, SC, ²South Carolina State University, Orangeburg, SC, ³Savannah River Ecology Laboratory, The University of Georgia, Aiken, SC.

12:00 - 12:15
173 The Impact of Methylmercury on Transcriptomic Patterns of the Vitamin D3 Pathway in Dolphin Skin, Blake C Ellis¹, Mark S Kindy², Sebastiano Gattoni-Celli³; ¹Marine Biomedicine and Environmental Sciences Center, MUSC, ²Neurosciences and Neuroscience Institute, MUSC; Ralph H. Johnson VA Med, ³Radiation Oncology, MUSC, Ralph H. Johnson VA Medical Center.

12:15 - 12:30
174 Post-Transcriptional Regulation of the Cell Cycle in the Florida Red Tide Dinoflagellate, Karenia Brevis, Stephanie A Brunelle¹, Frances M Van Dolah²; ¹MCBP, MUSC, ²CCEHBR, NOS, National Oceanic and Atmospheric Administration.

12:30 - 12:45
175 Hypoxic Preconditioning Increases Human Neural Precursor Cell Tolerance to Severe Cytotoxic Insult, Kevin R Francis¹, Shan Yu², Ling Wei¹; ¹Pathology and Laboratory Medicine, MUSC, ²Pharmaceutical Sciences, MUSC.

12:45 - 1:00
176 Context-Driven Relapse To Cocaine-Seeking In Abstinent Rats Increases Activity-Regulated Gene Expression In The Dorsal Hippocampus Differentially Following Short and Long Periods Of Abstinence, Matthew C Hearing¹, Ronald E See¹, Jacqueline F McGinty²; ¹Neurosciences, MUSC, ²Department of Neurosciences, Medical University of South Carolina.

1:00 - 1:15
177 Possible Role for VCAM-1 in Aberrant Epicardium Development in the RXRα-/- Model of Congenital Heart Disease, M. Elizabeth G Burton¹, Loretta L Hoover¹, Laura E Brichler², Steven W Kubalak¹; ¹Cell Biology and Anatomy, MUSC, ²College of Charleston.

1:15 - 1:30 Break

1:30 - 1:45
178 MAPKs-dependent Phosphorylation of SPF45 and Regulation of Fas Alternative Splicing, Adnan M Al-Ayoubi, Hui Zheng, Tao Bai, Scott T Eblen; Cell and Molecular Pharmacology, MUSC.

1:45 - 2:00
179 Osmotic Stress Effects on Dimethylsulfiniopropionate (DMSP) Concentrations in Fragilariopsis Cylindrus, Barbara R Lyon¹, Jennifer M Bennett², Peter A Lee², Michael G Janech³, Giacomo R DiTullio⁴; ¹MCBP, MUSC, Marine Biomedicine and Environmental Science, ²CofC, Hollings Marine Laboratory, ³Medicine, Nephrology, MUSC, Marine Biomedicine and Environmental Science, ⁴Marine Biomedicine and Environmental Science, CofC, Hollings Marine Laboratory.
2:00 - 2:15
180 Nucleic Acid Adducts of Brevetoxins, Tod Leighfield¹, John Ramsdell²; ¹MUSC, MCBP, MBES, ²NOAA National Ocean Service.

2:15 - 2:30
181 An Evaluation of Logic Forest for Identification of Disease Biomarkers, Bethany J Wolf, Elizabeth G Hill, Elizabeth H Slate; Biostatistics, Bioinformatics, and Epidemiology, MUSC.

2:30 - 2:45
182 Selection Bias Adjustment of Growth Estimates for South Carolina Bottlenose Dolphins (Tursiops Truncatus), Mary Tress¹, Wayne McFee², Elizabeth Slate¹; ¹Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²National Ocean Service, CCEHBR.

2:45 - 3:00
183 The Association Between Skin Characteristics and Sun-protection Behaviors, Lee Wheless¹, Rhoda Alani², Sandra Clipp³, Judith Hoffman-Bolton⁴, Timothy J Jorgensen⁵, Nanette Liegeios⁶, Paul J Strickland³, Anthony J Alberg⁶; Medicine, Biostatistics, Bioinformatics, and Epidemiology, MUSC, ²Dermatology, Oncology, Johns Hopkins, ³Bloomberg School of Public Health, Johns Hopkins, ⁴Bloomberg School of Public Health, Johns Hopkins, ⁵Radiation Medicine, Georgetown, ⁶Biostatistics, Bioinformatics, and Epidemiology, Hollings Cancer Center, MUSC.

Session 15: PhD VI: 12 am - 3 pm – Room CHP 206

12:00 - 12:15
184 Specific Inhibition of the Classical Complement Pathway with an Engineered Single Chain Antibody Variable Fragment, Marcus R Duvall¹, Hee Young Hwang², Robert J Boackle³; ¹Microbiology and Immunology, MUSC, ²Pathology and Laboratory Medicine, MUSC, ³Dental Medicine, Stomatology, Microbiology and Immunology, MUSC.

12:15 - 12:30
185 Characterization of Alveolar Epithelial Cells Cultured in a Hollow Fiber Model System, Christina L Grek¹, Xuejun Wen², Demetri D Spyropoulos³, John E Baatz⁴; ¹MCBP, Pediatrics, MUSC, ²Clemson-MUSC Bioengineering Program, ³Pathology and Laboratory Medicine, MUSC, ⁴Pediatrics, MUSC.

12:30 - 12:45
186 Phosphatase Regulation of Cellular Motility in the Tumor Microenvironment, Jarrett E Walsh¹, M. Rita I Young²; ¹Microbiology and Immunology, MUSC, ²Research Service, Ralph H. Johnson VA Medical Center, Otolaryngology and Medicine, MUSC.

12:45 - 1:00
187 The Dorsal Mesenchymal Protrusion (DMP), a Second Heart Field Derivative, Plays an Important Role in AV Septal Development, Brian Snarr, Jessica Oneal, Mastan Chintalapudi, Elaine Wirrig, Aimee Phelps, Thomas Trusk, Steve Kubalak, Andy Wessels; Cell Biology and Anatomy, MUSC.

1:00 - 1:15
188 Inhibition of Cx43/ZO-1 Interaction Improves Gap Junction Intercellular Communication and Reduces Connexon Hemichannel Activity, J Matthew Rhett¹, Jane Jourdan², Michael O'Quinn², Robert G Gourdie¹; ¹Cell Biology and Anatomy, MUSC, ²Medicine, Cell Biology and Anatomy, MUSC.
1:15 - 1:30
189 A Peptide Containing the Carboxy-Terminal Domain of Connexin43 Reduces Arrhythmias and Improves Cardiac Function After Myocardial Injury, Michael P O’Quinn, Brett S Harris, Kenneth W Hewett, Robert G Gourdie; Cell Biology and Anatomy, MUSC.

1:30 - 1:45 Break

1:45 - 2:00
190 Neutralizing Antibody Treatment Against Interferon-alpha in SCID Mice with HIV Encephalitis, Andrew R Sas¹, Heather A Bimonte-Nelson², William R Tyor³; ¹Microbiology and Immunology, MUSC, ²Arizona State University, ³Neurosciences, MUSC.

2:00 - 2:15
191 Capturing and Mapping the Distribution of Phosphorylated AQP0 in the Ocular Lens, Danielle B Gutierrez¹, Rosalie K Crouch², Kevin L Schey³; ¹Cell and Molecular Pharmacology and Experimental Therapeutics, MUSC, ²Ophthalmology, MUSC, ³Department of Biochemistry, Vanderbilt University.

2:15 - 2:30
192 Inflammatory Gene Expression in an Alveolar Macrophage Cell Line Following Exposure to Brevetoxin-2, Kelli M Sas¹, James C Ryan², Frances M Van Dolah², John E Baatz³; ¹Marine Biomedicine and Environmental Sciences Center, MUSC, ²NOAA, Center for Coastal and Environmental Health and Biomolecular Research, ³Pediatrics, Marine Biomedicine and Environmental Sciences Center, MUSC.

2:30 - 2:45
193 Role of Cag L in H. Pylori-induced H,K-ATPase Alpha Subunit Gene Repression, Arindam Saha¹, Adam J Smolka², Monika Gooz³; ¹MCBP, MUSC, ²Medicine, MCBP, MUSC.

2:45 - 3:00
194 awd, The Homologue of the Human nm23 Metastasis Suppressor Gene, Regulates Epithelial Integrity of Drosophila Follicle Cells, Julie A Woolworth¹, Tien Hsu²; ¹MCBP, MUSC, ²Pathology and Laboratory Medicine, MUSC.

Session 16: Postdocs/Residents/Fellows III: 12:15 am - 3 pm – Room CHP 202

12:15 - 12:30
195 Microtubules and Actin Differentially Influence Remodeling of Connexin43 Gap Junctions, Andrew W Hunter, Robert G Gourdie; Cell Biology and Anatomy, MUSC.

12:30 - 12:45
196 Activation of a Distant Replication Origin By Long Range Contact with a Replication Enhancer, Mukesh Saxena, Deepak Bastia; Biochemistry, MUSC.

12:45 - 1:00
197 Ceramide Generated By Acid Sphingomyelinase And Ceramide Synthase 5 Is Involved In Hypoxia/Reoxygenation-Induced Bax Redistribution To Mitochondria, Junfei Jin¹, Qi Hou², Thomas D. Mullen³, Youssef H. Zeidan¹, Jacek Bielawski¹, Jacqueline M. Kraveka⁴, Alicja Bielawska¹, Yi-Te Hsu¹; ¹Biochemistry and Molecular Biology, MUSC, ²Pharmacology, Peking Union Medical College, ³Medicine, MUSC, ⁴Pediatrics, MUSC.
1:00 - 1:15
198 Mechanistic Insights Into Reb1-Ter3 Complex Mediated Replication Termination in *Schizosaccharomyces Pombe*, Subhrajit Biswas, Deepak Bastia; Biochemistry and Molecular Biology, MUSC.

1:15 - 1:30
199 Assessing the Composition and Structure of Bacterial Communities Associated with the Upper Respiratory Tract of the Atlantic Bottlenose Dolphin, *Tursiops Truncatus*, Wesley R Johnson¹, Manolito Torralba², Karen E Nelson², Gregory D Bossart³, Patricia A Fair⁴, Pamela J Morris⁵, ¹Marine Biomedicine and Environmental Sciences, MUSC, ²J. Craig Venter Institute, ³Harbor Branch Oceanographic Institute, ⁴Center for Coastal Environmental Health and Biomolecular Research, ⁵Cell Biology and Anatomy, Marine Biomedicine and Environmental Sciences, MUSC.

1:30 - 1:45 Break

1:45 - 2:00
200 The Effect of Aquaporin-0 C-Terminal Phosphorylation on Plasma Membrane Surface Expression in HEK-293 Cells, Eric R Buck¹, Kevin L Schey², Rosalie K Crouch³; ¹Pharmacology, MUSC, ²Biochemistry, Vanderbilt, ³Ophthalmology, MUSC.

2:00 - 2:15
201 Transcriptional Events of PRL Gene Expression in GH3 Cells Are Temporally Linked to Pulses of the Circadian Factors, Sudeep Bose¹, Edward Tarnawa², Fredric Boockfor¹; ¹Cell Biology and Anatomy, Medicine, MUSC, ²Obstetrics & Gynecology, Medicine, MUSC.

2:15 - 2:30
202 Differential Effect of Wall Tension on Matrix Metalloproteinase Promoter Activation in the Thoracic Aorta, Jean Marie Ruddy, Jeffrey A Jones, Rupak Mukherjee, Francis G Spinale, John S Ikonomidis; Surgery, MUSC and Ralph H. Johnson VA Medical Center.

2:30 - 2:45
203 Inhibition Of Histone Deacetylase Activity Represses Matrix Metalloproteinase-9 Induction And Preserves Cardiac Function Post Myocardial Infarction, Santhosh K Mani¹, Christine B Kern¹, William T Rivers², Rebecca A Plyler², Francis G Spinale², Rupak Mukherjee², Donald Menick¹; ¹Medicine, Cardiology, MUSC, ²Surgery, MUSC.

2:45 - 3:00
204 Fibroblasts of Hematopoietic Origin Contribute to Embryonic Heart Valve Development, Zoltan Hajdu¹, Richard P Visconti²; ¹Medicine, Cell Biology and Anatomy, MUSC, ²Dental Medicine, Cell Biology and Anatomy, MUSC.

Session 17: Postdocs/Residents/Fellows IV: 12:15 am – 3 pm – Room CHP 205

12:15 - 12:30
205 Auditory Brainstem Response and Associated Morphological and Molecular Changes in a Mouse Model of Auditory Neuropathy, Vinu Jyothi¹, Bing Wang¹, Nancy Smythe², Bradley A. Schulte³, Richard A. Schmiedt², Hainan Lang¹; ¹Pathology and Laboratory Medicine, MUSC, ²Otolaryngology-Head and Neck Surgery, MUSC, ³Pathology and Laboratory Medicine; Otolaryngology-Head and Neck Surgery, MUSC.
12:30 - 12:45
206 The Effects of Oxygen Tension and Glucose Concentration on the Metabolism of Porcine TMJ Disc Cells, Lixia Zhang¹, Jonathan Kuo², Michael J Kern³, Hai Yao⁴; ¹Clemson University, Clemson, Dental Medicine, MUSC, ²Clemson University, Clemson, ³Cell Biology and Anatomy, MUSC, ⁴Clemson University, Clemson, MUSC.

12:45 - 1:00
207 Targeting Sphingolipid Metabolism to Control Gene Expression By an Oncogenic Herpesvirus, Sarumathi Mohan¹, Chris Parsons²; ¹Medicine, Infectious Diseases, MUSC, ²Medicine, Infectious Diseases, Microbiology and Immunology, MUSC.

1:00 - 1:15
208 Characterization of the Dihydroceramide Desaturase Enzyme and the Effects of Fenretinde on Enzyme Activity In-Vitro, Mehrdad Rahmaniyan¹, Yusuf A Hannun², L M Obeid³, Jacqueline M Kraveka⁴; ¹Pediatrics, Division of Pediatric Hematology Oncology, MUSC, ²Biochemistry and Molecular Biology, MUSC, ³Biochemistry and Molecular Biology, Medicine, MUSC, ⁴Pediatrics, Division of Pediatric Hematology Oncology.

1:15 - 1:30
209 Low Prevalence of Osteoporosis in Children with Sickle Cell Anemia Receiving Chronic Red Blood Cell Transfusion, Elizabeth T Walsh¹, Yaw Appiagyei-Dankah¹, Ramasubramanian Kalpatthi²; ¹Pediatric Endocrinology, MUSC, ²Pediatric Hematology and Oncology, MUSC.

1:30 - 1:45 Break

1:45 - 2:00
210 Regulation of Flt1 Expression By Ets Factors in Lymphocytes, John L Svenson, Katherine Chike-Harris, May Amria, Tamara K Nowling; Medicine, Rheumatology, MUSC.

2:00 - 2:15
211 Silencing of Abcd1 and Abcd2 Genes Sensitizes Astrocytes for Inflammation: Implication for X-Adrenoleukodystrophy, Jaspreet Singh, Mushfiquddin Khan, Inderjit Singh; Medicine, Pediatrics, MUSC.

2:15 - 2:30
212 Chronic Ethanol-Induced Homeostatic Plasticity in the Hippocampus Involves Opposing Changes in SK2 Channels and NMDA Receptors, Patrick J Mulholland¹, Howard C Becker², John J Woodward¹, Judson Chandler¹; ¹Medicine, Neurosciences, MUSC, ²Medicine, Psychiatry, MUSC.

2:30 - 2:45
213 Orexin Neurons That Project to the Ventral Tegmental Area Are Activated By Morphine Preference During Protracted Forced Abstinence, Kimberlei A Richardson, Paul T Knackstedt, Gary Aston-Jones; Neurosciences, MUSC.
001 Optimization of SiRNA Delivery In Vitro and In Vivo, Sabrina M Porcher1, Qiyang Li2, Keith L Kirkwood2; 1CU, Craniofacial Biology, Dental Medicine, MUSC, 2Craniofacial Biology, Dental Medicine, MUSC.

Periodontal inflammation drives alveolar bone destruction leading to tooth loss. Previous data from the project laboratory indicates that multiple inflammatory cell signaling pathways are critical in small animal models of periodontal disease progression. The aim of this study was to develop a silencing interference RNA (siRNA) strategy that could be utilized for intraoral applications. For the In vitro experiments, HeLa cells were plated and grown to 70% confluency for 24 hours. After 24 hours, the cells were infected with different Adenovirus containing luciferase reporter gene (Ad5-Luc). Once the cells were infected, they were allowed to incubate 4 to 5 hours. Afterwards, they were transfected with a siRNA specific for luciferase. Once this occurred the cells were then given fresh growth medium with twice the normal concentration of serum and allowed to incubate 24 hours at 37ºC. After 24 hours the cells were harvested and luciferase activity was measured by a luminometer (Molecular Devices). Transgene reporter activity was monitored to assess efficiency of gene knockdown using cell lysates and luminometer. Optimized siRNAs are going to be used for subsequent in vivo experiments. For the in vivo experiment, the data from the in vitro experiment will show the optimized MOI and siRNA to be used and demonstrate how to effectively silence a specific targeted gene, in this case the luciferase gene. The data shows that there was a 30% knockdown of gene expression. From the data, it was concluded that a continuation into the in vivo experiment would not provide conclusive data. [Summer Undergraduate Research Program, NIH, Glaxo Smith Kline, 1R21DE019272]

002 Does Periostin Intron 1 Regulate Periostin Transcription?, Robert W Pratt1, Russell J Norris2, Michael A Kern1; 1Dental Medicine, MUSC, 2Cell Biology and Anatomy, MUSC.

Abstract not available.

003 The Effects of Calpain Activity on Stat6 in Jurkat T Cells, Gabriel C Fitton1, Jonathan T Butler2, Naren L Banik1; 1Neuroscience, MUSC, 2MCBP, MUSC.

T cell activation and polarization is essential in order to properly respond to the various pathogens and challenges that the human body encounters in the natural world. The delicate balance between antibody production, cytotoxic inflammation and autoimmunity is dictated in part by the various cells responding to the challenge. The T cell contributes to the immune response by generating cytokines and providing the proper signals required to address the specific challenge that is presented. The complex signaling pathways involve various proteins acting as checkpoints and counterbalances to prevent unregulated inflammation and autoimmunity. One such protein that balances the response is the ubiquitously expressed calcium activated neutral protease calpain. Calpain contributes to various cellular responses and actions and is thought to regulate T cell bias through the Stat signaling molecules, more specifically through Stat1 and 4 for Th1 cell type and Stat6 for Th2 cell type. The purpose of this study was to demonstrate that calpain regulates the Th2 phenotype by acting as a negative repressor of STAT6 in a cellular system. In order to test this hypothesis we used the Jurkat T cell as a model cell system. Following activation with CD3 antibody in the absence or presence of calpain inhibitor cells were collected and Western blotting was performed to analyze the various transcription proteins and regulators associated with specific T cell subtypes. This preliminary study reveals that calpain acts as a negative regulator of the intracellular Stat6 levels. Further studies in more disease relevant cell types are warranted to confirm the following results. [NIH NS 041088, NIH NS 056176]

004 Combination of Low Dose Estrogen and Melatonin Protects VSC 4.1 Motor Neurons From Glutamate-induced Cell Death By Increasing the Estrogen Receptor Beta:Estrogen Receptor Alpha Ratio, Joshua A Smith1, Abadinda Das2, Swapan K Ray3, Naren L Banik2; 1Medicine, MUSC, 2Neurosciences, MUSC, 3Pathology, Microbiology, and Immunology, USC School of Medicine.

Multiple studies have shown that estrogen and melatonin exhibit neuroprotective effects in the treatment of spinal cord injury (SCI). The neuroprotective abilities of estrogen and melatonin have generally been attributed to their ability to attenuate Ca2+-mediated events including activation of calpain, oxidative stress, and activation of caspase-dependent apoptosis. Because SCI may involve a number of secondary injury mechanisms, treatment with a combination of multiple therapeutic agents may be more beneficial than any single therapy. However, to our knowledge, the use of estrogen and melatonin in combination has never been studied. One potential effect of combination treatment with estrogen and melatonin is an increase in the ratio of estrogen receptor beta to estrogen receptor alpha. Previous work has shown that activation and increased expression of estrogen receptor beta may play a greater role in estrogen-mediated neuroprotection than that of estrogen receptor alpha. Given that melatonin is a known down-regulator of estrogen receptor alpha, we wondered if treatment of neurons exposed to toxic levels of glutamate with estrogen and melatonin would increase the ratio of estrogen receptor beta:estrogen receptor alpha. We further hypothesized that an increase in this ratio following combination treatment would show greater protection of injured neurons than either treatment alone. To test our hypotheses, VSC 4.1 motor neuron cells were exposed to 25 µM L-Glutamic Acid (LGA) and subsequently treated with either 100 nM melatonin, 200 nM estrogen, or a combination of both. Cell viability and expression of estrogen receptor beta, estrogen receptor alpha, and cell death markers including caspase-3 and caspase-9 were then measured. Our preliminary results suggest combination therapy with estrogen and melatonin does increase the ratio of estrogen receptor beta:estrogen receptor alpha. Furthermore, the increase in the ratio of estrogen receptor beta:estrogen receptor alpha appears to offer greater neuroprotection and attenuation of cell death than either treatment alone. These findings suggest that combination of estrogen and melatonin shows potential as a treatment for SCI. [This work was supported in part by grants from the NIH and the State of South Carolina Spinal Cord Injury Research Fund]

005 Melatonin Protects VSC4.1 Motoneurons Cells Exposed to Oxidative Stress, Glutamate Excitotoxicity, and TNF-α Toxicity Via Receptor Mediated Pathway, Misty McDowell1, Abadinda Das1, Matthew J Pava1, Russel J Reiter2, John J Woodward1, Swapan K Ray3, Narendra Banik1; 1Neuroscience, MUSC, 2Cellular and Structural Biology, UT, TX, 3Pathology, Microbiology and Immunology, USC, Columbia, SC.

Melatonin (MT), a pineal gland hormone, may be used for the
treatment of spinal cord injuries (SCI) and neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS). Motoneurons may be prone to apoptosis in SCI and ALS. We examined whether MT, a potent antioxidant and free radical scavenger, would prevent motoneuron apoptosis following exposure to various toxic agents. Exposure of VSC4.1 motoneurons to 50 µM H2O2, 25 µM glutamate, and 50 ng/ml TNF-α for 24 h caused significant increases in intracellular free [Ca2+], as determined by fura-2 assay. Cells undergoing oxidative stress, glutamate excitotoxicity, and TNF-α toxicity for 15 min were then treated with 200 nM MT. Post-treatment with MT prevented cell death and maintained whole-cell membrane potential, indicating functional neuroprotection. Apoptotic features were evaluated by Wright staining and ApopTag assay. To examine and confirm the involvement of the MT receptor 1 (MTR1) in providing neuroprotection, the motoneurons were post-treated with 10 µM luzindole (MT receptor antagonist). Our data showed that luzindole significantly decreased the ability of MT to protect against cell death, indicating the involvement of MT receptor in providing MT-mediated neuroprotection. Our real-time polymerase chain reaction (R-PCR) and western blots analyses showed alterations in Bax and Bcl-2 expression at protein and mRNA levels during apoptosis. We also detected upregulation of calpain and down regulation of calpastatin at mRNA and protein levels. Increased caspase-8, 9 and -3 activities were also confirmed by colorimetric assays. Our data showed that MT works through a receptor mediated pathway to prevent calpain mediated proteolysis and apoptosis in VSC4.1 motoneurons. Collectively, these results suggest that MT may be used as an effective neuroprotective agent to attenuate motoneuron death in SCI and ALS. [Supported in part by funding from the NIH-NINDS.]

006 Affect of TGFβ2 and Retinoic Acid on the Regulation of VCAM-1 During Epicardium Development, Laura E Brichler1, M. Elizabeth G Burton2, Loretta L Hoover2, Steven W Kubalak2; 1College of Charleston, Charleston, SC, 2Cell Biology and Anatomy, MUSC.

The formation of the epicardium, the outer layer of cells in the heart, is key for the successful development of the rest of the heart. It contributes to the formation of vascular musculature, fibroblasts, coronary vasculature, and stimulates myocardial proliferation. The epicardium develops from the proepicardium (PE), a group of mesothelial cells. The transformation from PE to epicardium begins at embryonic day (E) 9.5 and is complete by E11 in the mouse. The retinoid X receptor a knockout mouse (RXRα-/-) is a model of congenital heart disease displaying epicardial as well as other cardiac defects. The abnormalities in the epicardium of the RXRα-/- play a causal role in cardiac defects arising later in development. In the RXRα/-, the epicardium forms slower than in the wildtype mouse, and, once formed, is detached from the myocardium, causing a bubble-like appearance. We suspect disturbances in cell adhesion to other epicardial cells, myocardial cells, or the subepicardial extracellular matrix (ECM) will result in epicardial detachment. Vascular cell adhesion molecule (VCAM-1) is a transmembrane protein involved in cell adhesion. Others have shown that VCAM-1 mRNA is decreased in the RXRα-/- at E11, and we reported that the protein transforming growth factor β2 (TGFβ2) is increased in the RXRα-/- . Therefore, we hypothesize that VCAM-1 levels are regulated by TGFβ2 and RA signaling during epicardial development. Using rat epicardial (REC) cells, we found that VCAM-1 protein levels decrease with 24 hour TGFβ2 treatment while 24 hour RA treatment produces a smaller decrease than TGFβ2 treatment. REC cells treated for 24 hours with both TGFβ2 and RA had VCAM-1 protein levels similar to TGFβ2 alone. Understanding how TGFβ2 regulates VCAM-1 during epicardium development can give us insight into the signaling mechanisms between the epicardium and the myocardium as well as insight into formation of epicardial-derived structures.

007 3D Models of the Mouse Atrio-Ventricular Node, Rebecca A Neuren1, Mary S Rackley2, Brett S Harris3; 1College of Charleston, Charleston, SC, 2Gazes Cardiac Research Institute, Ralph H. Johnson VA Medical Center, 3Cell Biology and Anatomy, MUSC.

The mechanism of function and morphogenesis of the Atrio-Ventricular node (AVN) remains largely uncharacterized. The AVN is found in the posterior/ dorsal region of the heart within the basal atrial septum. Here it forms the key part of a specialized conduction system that conveys pace-making signals through a fibrous tissue ring separating atria from ventricular tissues. The distal part of the AVN is continuous with the single His bundle which eventually bifurcates to form the left and right bundle branches. Although the AVN possesses automaticity, it is dominated by the Sino-Atrial Node (SAN) and is responsible for creating a 20ms delay between atrial and ventricular contractions. While recent developments in transgenic-based approaches have begun to make inroads to understanding the AVN, it has become important to characterize the mouse AVN and its development with greater precision. Here, the detailed spatial organization of the murine AVN is probed at high resolution using triple immunohistochemistry, confocal microscopy and 3-Dimensional reconstructions. Using definitive markers of the conduction system, working cardiomyocytes and fibrous extra cellular matrix (ECM) tissues, we unequivocally define the axis of conduction in the mouse. We show for the first time, using 3D models, the cellular organization of the AVN as well as the relationship of the AVN with the single His bundle. Finally we make volumetric measurements to quantify the various sub-compartments of the mouse conduction axis. These novel data will form the benchmark standard for future studies of AVN disease. [We thank Dr. Tom Trusk for his excellent Confocal Microscopy and Amira support. BSH is supported by Grant 5P20RR016434-07 from the National Center for Research Resources (NCRR).]

008 Modeled Microgravity Induces the Expression of PU-1 in Preosteoclast Cells, Jeremy J Blanchard, Yuvaraj Sambandam, Sakamuri V Reddy; Charles P. Darby Children’s Research Institute, MUSC.

The National Aeronautics and Space Association’s (NASA) primary problem associated with space flight is accelerated bone loss and fracture risk. Microgravity results in the uncoupling of bone remodeling between formation and resorption that could account for bone loss. This can lead to a 10-15% loss of bone mass over the duration of a mission. Bone forming osteoblasts and resorbing osteoclasts are the two main cell types responsible for bone dynamics. It has been identified that microgravity favors osteoclastogenesis, but the molecular mechanism responsible for bone loss during space flight is unclear. Due to the large cost of studying bone in space, NASA has developed the murine model based Rotary Wall Vessel Bioreactor called Rotary Cell Culture System (RCCS) to simulate microgravity. In studies utilizing the RCCS, we have cultured the RAW 264.7 osteoclast progenitor cells in simulated microgravity for 24 hrs. After the rotation period, both rotated cells and ground base cells were cultured with or without RANKL (50 ng/ml) for 24 hrs. RT-PCR analysis of total RNA isolated from the RAW cells demonstrated a significant increase in the expression levels of factors associated with osteoclast
differentiation/bone resorption activity, such as RANK, MCSF, cJun, cFOS, PU-1, OSCAR, Trem-2 TRAF-2, and TRAF-6 in microgravity compared to ground based cultures. Western blot analysis further confirmed these results, with a high level differential expression of PU-1 transcript critical for osteoclast differentiation in microgravity conditions. A microarray analysis is currently underway to further explore the gene expression profiling responsible for bone loss in microgravity. In conclusion, microgravity modulates PU-1 transcript expression at high levels and several other signaling molecules involved in osteoclastogenesis. The results indicate that PU-1 may be a therapeutic target to prevent the bone loss during space flight.

009 Association Between Race/Ethnicity and Glycemic Control in an Indigent Primary Care Sample with Type 2 Diabetes. Tremayne Mitchell1, Ashley Primus2, Erica Haynes1, Leonard E Egede1; 1South Carolina State University, 2College of Medicine, MUSC, Ralph H. Johnson VA Medical Center.

Background: This study examined the association between race/ethnicity and glycemic control after controlling for confounding patient level factors in a primary care clinic population with type 2 diabetes. Methods: Data on 139 subjects with type 2 diabetes recruited from the MUSC University Internal Medicine Clinic was examined. Race was defined as non-Hispanic White and non-Hispanic Black. Other patient level factors included age, sex, marital status, education, employment, insurance status, income, health and status. Medication adherence and health literacy were assessed by validated instruments. Glycemic control was based on the most recent hemoglobin A1c level abstracted from the medical records. Hemoglobin A1c was treated as a continuous variable. Mean hemoglobin A1c was compared across patient level factors using t-test. Multiple linear regression was used to assess the independent association between race/ethnicity and glycemic control adjusting for all patient level factors listed above. STATA V10 was used for statistical analysis. Results: In this sample, 29% were White and 71% were Black. 50% were aged 65+ years, 72% were women, 40% were married, 34% had >high school education, 21% were employed, 98% had health insurance, and 62% had income <$15,000. In the overall sample, there were no significant correlation between diabetes knowledge or individual self-management behaviors and glycemic control. Among Whites, there were no significant association between diabetes knowledge or individual self-management behaviors and glycemic control. Among Blacks, adherence to dietary guidelines was significantly correlated with glycemic control (p=0.03; p=0.008). Conclusion: The relationship between self-management behaviors and glycemic control differs significantly by race/ethnicity. There is a modest correlation between adherence to dietary guidelines and glycemic control among predominantly lower income blacks with type 2 diabetes.

010 Ethnic Differences in Association Between Diabetes Knowledge and Self-Management Behavior and Glycemic Control in Adults with Type 2 Diabetes. Erica Haynes1, Ashley Primus2, Tremayne Mitchell3, Leonard E Egede4; 1Biological Sciences, SCSU; 2College of Health Professions, MUSC, 3Dental Medicine, Pediatric Dentistry and Orthodontics, MUSC, 4Medicine, MUSC, Ralph H. Johnson VA Medical Center.

Background: This study examined whether the association between diabetes knowledge and diabetes self-management behavior and glycemic control differed by race/ethnicity in an indigent primary care clinic population with type 2 diabetes. Methods: Data on 139 subjects with type 2 diabetes recruited from the MUSC University Internal Medicine Clinic was examined. Race was defined as non-Hispanic White and non-Hispanic Black. Diabetes knowledge and diabetes self-management behaviors (adherence to guidelines for healthful eating, exercise, blood glucose testing, foot care, and smoking) were assessed as continuous variables with validated instruments. Glycemic control was based on the most recent hemoglobin A1c level abstracted from the medical records. Hemoglobin A1c was treated as a continuous variable. Mean scores for diabetes knowledge and self-management behaviors were compared by race/ethnicity. Pearson’s correlation was used to assess the association between mean hemoglobin A1c and mean scores for diabetes knowledge and self-management behaviors in the overall sample and among Whites and Blacks respectively. STATA V10 was used for statistical analysis. Results: 29% of the sample was White and 71% was Black. 50% were aged 65+ years, 72% were women, 40% were married, 34% had >high school education, 21% were employed, 98% had health insurance, and 62% had income <$15,000. In the overall sample, there were no significant correlation between diabetes knowledge or individual self-management behaviors and glycemic control. Among Whites, there were no significant correlation between diabetes knowledge or individual self-management behaviors and glycemic control. In contrast, among Blacks, adherence to dietary guidelines was significantly correlated with glycemic control (r=0.30; p=0.008). Conclusion: The relationship between self-management behaviors and glycemic control differs significantly by race/ethnicity. There is a modest correlation between adherence to dietary guidelines and glycemic control among predominantly lower income blacks with type 2 diabetes.

011 Position of Maxillary First Molar Relative to Cranial and Maxillary Dimensions Following Cervical Traction. Katie T Stroud1, Louis M Andria1, Luis P Leite2; 1Dental Medicine, MUSC, 2Dental Medicine, Pediatric Dentistry and Orthodontics, MUSC.

Abstract not available.

012 The Role of Early Placentation in Recurrent Preeclampsia. Elizabeth M Myers1, Mark M Alanis2, Laura Goetz3; 1Medicine, MUSC, 2Medicine, OB/GYN, MUSC.

Abstract not available.

013 The Impact of Retrograde Autologous Priming on the Effectiveness of the Magovern Formula to Predict Blood Transfusions. Samantha L Kaiser1, Anthony G Shackelford2; 1College of Health Professions, MUSC, 2College of Health Professions, Clinical Services, MUSC.

Abstract not available.

014 Racial/Ethnic Differences in Diabetes Fatalism in an Ethnically Diverse Primary Care Sample with Type 2 Diabetes. Ashley Primus1, Tremayne Mitchell2, Erica Haynes2, Leonard E Egede3; 1Medicine, MUSC, Ralph H. Johnson VA Medical Center, 2Biological Sciences, SCSU.

Background: Diabetes fatalism is defined as “a complex psychological cycle characterized by perceptions of hopelessness, meaninglessness, powerlessness, and social despair”. Few studies have examined racial/ethnic differences in diabetes fatalism. This study examined whether there were...
As the prevalence of diabetes rises so will the need for patient education. Managing diabetes is a daily job and often patients’ quality of life depends on the ability to manage their chronic condition (Allen, 2008). Diabetic patients need long term treatment to manage their disease and prevent possible complications. Patient education plays an important part in chronic management. The objectives of this pilot study are to determine adult diabetic patients': (1) access to patient education via various communication modes including internet, mail, hotline, video conferencing and patient handouts and (2) preference for the different modes of patient education.

Methods: Patients with diabetes will be recruited from MUSC Endocrinology Department, MUSC satellite clinics, and the community. They will be interviewed individually to explore various aspects of access to and preference for patient education. An interview guide is used. Results and Conclusion: The results of this study will help health care workers to better understand diabetic patients’ access to and preference for patient education. This will enable healthcare workers to provide education that better serves the needs of each individual patient, and promote partnership with the patients in managing their diabetes. In doing so it is hoped that as patients’ motivation and satisfaction with their resources increases, their level of participation in disease management will increase as well.

017 Arthritis Knowledge Among Health Professional Students At the Medical University of South Carolina: A Pilot Study, Katie E Atkinson, Nicole C Abner, Erin Gravino, Tamara B Hardee, Thomas C Head, Amber S King, Kelli C Mackie, Lauren C Shockley; College of Health Professions, MUSC.

Background: Arthritis is the leading cause of disability in the United States yet little is known about risk factors, prevalence, and disparities among the general population. There is a general misconception that all arthritis is a normal part of the aging process. Early diagnosis can decrease arthritis pain and disability. Prevention, diagnosis, and treatment are the scope of practice for healthcare professionals, therefore increasing healthcare professionals’ arthritis knowledge will benefit individuals with arthritis. Currently, little is known about arthritis knowledge among health professional students. Purpose: This study examined the knowledge of rehabilitation healthcare professional students at the Medical University of South Carolina. Methods: A survey of arthritis knowledge was developed to examine general arthritis knowledge and the epidemiological impact of arthritis among health professional students. The survey was administered to 191 first, second, and third year students enrolled in graduate clinical education programs in the College of Health Professions. Results: Arthritis symptoms ~ 100% identified pain, aches, stiffness, and swelling in and around the joints as symptoms of arthritis. Risk factor knowledge ~ 72% identified obesity as a risk factor; 93% identified age; 73% identified occupation, 93% identified genetics; 87% identified joint injuries, and 66% identified gender. More than 50% of the students identified the 6 risk factors most likely to lead to arthritis. There were significant differences between clinical education programs and years of study in risk factor knowledge. Estimated cost - 45% knew the cost of arthritis in the U.S. Prevalence - 84% reported that in the U.S. women have a higher rate of arthritis. Disability impact – 73% reported arthritis as the third leading cause of disability yet it is the leading cause. Conclusions: All students recognized the symptoms of arthritis and most recognized its individual risk factors but few knew the financial and disability burden associated with arthritis.
knowledge of site and size of lesion was also critical to a more accurate aphasia prognosis. Studies of patient related factors (gender, age, handedness, education, intelligence) yielded mixed results and were less informative for determining accurate prognostic information for patients with aphasia. Conclusions: A multitude of inter-related variables must be considered when determining a prognosis for aphasia. While a prognosis may only represent a clinicians “best guess”, the current literature offers evidence that when integrated could offer novel and experienced clinicians a framework to facilitate a more evidenced-based assessment of the patients with aphasia and potential for recovery.

019 Global Coherence in Narratives of Individuals with Parkinson’s Disease, Stephanie Smith, Kelsey Roth, Jessica Terry, Kathryn Robarge, Charles Ellis; College of Health Professions, MUSC.

Background: An extensive literature exists linking diseases of the basal ganglia (BG) to deficits in motor speech performance. Fewer studies have demonstrated a relationship between BG disease and expressive language performance. Basal ganglia nuclei have extensive connections with the frontal lobes that significantly influence language use. Given these connections, diseases of the BG may result in disorders of language use. Methods: We examined the use of global coherence in 12 individuals with PD and 12 matched controls. Narratives were collected from individuals with PD in the “off” state of their parkinsonian medications. Each participant in the study produced three 3-minute discourse samples: (1) a typical day, (2) a memorable vacation, and (3) description of their family. Each narrative sample was examined for adequacy of global coherence. Measures of global coherence were completed to examine the influences of PD on global coherence among individuals with PD during discourse production. Results: No significant differences were observed on baseline cognitive and language measures (MMSE, WMS-LMI subtest, and BNT). Comparisons of global coherence indicated that the patients with PD did not differ significantly from the matched control in the average global coherence ratings across the three samples (typical day, p=.15; vacation, p=.69; family, p=.17). Individuals with PD received an average global coherence rating of 4.2 for typical day; 4.8 for memorable vacation; 4.7 for family compared to controls who received a rating of 4.6 for typical day; 4.7 for memorable vacation; 4.8 for family. Intra-group comparisons of individuals with PD by Hoehn & Yah stage also did not yield any significant differences. Conclusions: These findings suggest that global coherence is not significantly influenced by PD in the earliest stages.

020 The Influence of Parkinson’s Disease on Referential Cohesion, Brecken Hentz, Lindsay Hunt, Alissa Green, Fran Toth, Charles Ellis; College of Health Professions, MUSC.

Recent studies suggest that the basal ganglia (BG) has a critical role in both motor speech and expressive language disorders. However, expressive language disorders that occur in individuals with diseases of the BG are poorly understood and additional studies are required. Methods: We examined referential cohesion in narrative samples produced by 12 individuals with early stage PD and 12 matched controls. Each participant in the study produced three 3-minute discourse samples: (1) a typical day, (2) a memorable vacation, and (3) description of their family. Each narrative was examined for use of number and correct use of cohesive ties. Results: No significant differences were observed on baseline cognitive and language measures (MMSE, WMS-LMI subtest, and BNT). Comparisons of referential cohesion indicated that patients with PD did not differ significantly from the matched controls in the total number of referential cohesive ties produced for either of the three narratives (typical day, p=.16; vacation, p=.49; family, p=.90). Individuals with PD produced on average 20.5 referential ties on the discourse samples for “typical day”; 23.5 ties for “memorable vacation”; and 21.6 ties for “family” compared to the normal controls who produced 14.2 ties for “typical day”; 25.5 ties on “memorable vacation”, and 21.7 ties for “family”. Similarly, patients with PD did not differ significantly in cohesive adequacy or percent correct use of cohesive ties across the three narratives (typical day, p=.17; vacation, p=.15; family, p=.25). The percent correct cohesive ties for individuals with PD were 88%, 89%, and 92% correct use of cohesive ties compared to 95%, 93%, and 96% correct use of cohesive ties for the matched controls. Conclusions: These findings suggest that referential cohesion is not significantly influenced by PD in the earliest stages.

021 The Perceived Benefits of Participation in Structured Recreational Activities Among Parents of Children with Severe Mental and Physical Disabilities, Danielle Corneille, Stacy L Lyons, Patricia Coker, Charles Ellis; College of Health Professions, Rehabilitation Sciences, MUSC.

This pilot study analyzed survey data to measure the perceived benefits and satisfaction of parents of children with severe mental and physical disabilities who participated in the Charleston, SC Miracle Baseball League (CML). It is the only organized baseball league in our community that offers a program that does not exclude children based on their severity of disability, age, or their inability to communicate with peers. The games are non-competitive and the focus of the games is enjoyment of playing and being part of a team. This is clinically significant research because few studies have examined parental perceptions of the needs and benefits of recreational activities for children with severe mental and physical disabilities. Of the 98 parents with children participating in the league, 42 returned the survey. Of the parents who completed the survey, 100% reported a need for recreational activities for children with disabilities in Charleston, and that their child’s participation had a positive impact on their family. Additionally, almost all parents (97.6%) noted that participation in the CML was one of their child’s favorite activities. The specific perceived benefits to children from CML participation were reported as follows: 92.8% increased motor skills, 85.7% improved baseball skills; 97.5% increased self-confidence; 83.3% improved belief in their ability to succeed; 92.9% improved social skills; and 92.9% made new friends while participating in the league. The parent written comments were analyzed for related themes which highlights the areas most impacted by their child's participation in the league. These thematic areas were health/motor skills, motivation, self-esteem/confidence, friends/social, and family. In conclusion, participation in recreational programs help children gain mastery over their environment in response to participation in the occupational roles of childhood: player, teammate and friend. This adds to the overall quality of life for the child and the family.

022 Perceived Barriers to Healthy Nutritional and Physical Activity Habits Among Community Dwelling Mental Health Clients, Hope E Craddock, Tara F Hassler, Paisley C Polk, Erin L Smith, Ashley E Cunningham, Andrea D Sandifer, Nancy Carson; College of Health Professions, Occupational Therapy, MUSC.

Weight-gain and obesity are an ever increasing epidemic within
the U.S. population. This increase in obesity is also well-documented within the U.S. mental health population. Nutrition and exercise behaviors have not been well researched within this population. Therefore, the purpose of this study was to identify the perceptions of the potential barriers to healthy nutritional and physical activity habits among community dwelling mental health clients. A research team consisting of 6 graduate students overseen by a faculty advisor conducted approximately 30 interviews with clients at a recovery based program of the Charleston/Dorchester Mental Health Department. Clients were interviewed for approximately 20 minutes using a survey consisting of 17 frequency-based questions and 5 open-ended questions designed to identify their perceptions of the barriers to healthy nutritional and physical activity habits they encounter. Participation was voluntary. Descriptive data of each subject was collected including age, gender, diagnosis, estimated height and weight, and living environment (alone, with family or friends, or in a group, boarding, or foster home). This information was provided by the client or staff the day of the interview and was recorded on the interview form. The information was recorded in such a manner that human subjects could not be identified, directly or through identifiers linked to the subjects. Both qualitative and quantitative data were obtained regarding participants' perceptions of the potential barriers to healthy nutritional and physical activity habits. Analyses of the data were performed in order to draw inferences regarding current factors affecting nutritional and physical activity behaviors within this population. The significant findings from the analyses of these lifestyle behaviors will be presented. Implications for future research will be addressed.


This presentation will examine the effects of an oral motor stimulation program on feeding behaviors of infants born with congenital heart defects (CHD). The protocol was developed from current literature on oral stimulation, oral aversion, and the feeding difficulties of infants with CHD by a team of occupational therapists who work with high risk infants and a research group of occupational therapy students. Preliminary data from a pilot study measuring the effectiveness of this oral motor intervention will be presented. Literature has examined the link between early oral deprivation and later oral aversion in high risk infants. Oral motor deficits and oral aversion have lasting effects on chewing and swallowing skills that persist after oral feeds are introduced. Feeding problems experienced by tube fed infants have a profound effect on parent-infant bonding. Feeding difficulties interfere with this relationship, resulting in stress and anxiety thus hindering the infant’s overall development. These infants exhibit many feeding problems including swallowing dysfunction, rapid fatigue while eating, tachypnea, and delayed gastric emptying. In addition, many infants with CHD present with significant oral aversion triggered by prolonged orotracheal intubation or surgery, which results in feeding refusal behaviors. Providing oral motor stimulation prior to oral feeding has significant benefits on the development of feeding skills. Oral motor treatment has been shown to improve the rate of milk transfer and the expression component of sucking. Current literature has associated positive oral motor stimulation with accelerated transition to full oral feedings, decreased length of hospitalization, pain management, and maturation of oral feeding skills. However, there is a lack of research on use of oral stimulation programs for infants with CHD. Therefore, a positive oral motor stimulation protocol that involves occupational therapists, parents, nurses, and other healthcare professionals can be a powerful collaborative intervention for infants with CHD.

024 A Survey of Head and Neck Cancer Curriculum in United States Speech Language Pathology Masters Programs, Brittany A Dejarnett, Michelle E Fallis, Caroline J Wylie, Hon K Yuen; College of Health Professions, MUSC.

Purpose: To examine accredited master's level graduate programs in speech language pathology (SLP) in the US and to investigate the amount of education and training that is provided to students in the area of head and neck cancer and the SLP clinician’s role in the treatment of this cancer. The incidence rate of head and neck cancer continues to rise worldwide, making it the 6th most common type of cancer. Advancements in treatments are leading to higher survival rates; however, these treatments result in structural and physiological changes that often affect the patient's ability to communicate and swallow. Because of these deficits, the evaluation and treatment by a SLP clinician is directed toward optimizing the patient's quality of life. As students in SLP become clinicians, it is imperative that their education includes coursework that will prepare them to effectively treat this population. Methods: An email will be sent to program directors of all ASHA accredited masters programs for SLP in the United States. A survey containing 10 specific questions about the extent of material covering the diagnostic and treatment process of head and neck cancer in the curriculum will be administered. Results and Conclusions: Results obtained from this study may provide information for educators that may strengthen the curriculum related to head and neck cancer for SLP masters programs, and in the long run, may lead to improvements in the diagnostic and treatment competence of the graduates of SLP programs.

025 Stroke Knowledge Among Speech-Language Pathology Graduate Students, Jessica Terry, Lauren Marshall, Kristen Lankford, Amanda Pittman, Charles Ellis; College of Health Professions, MUSC.

Background: Stroke education modules have been added to medical school curriculums to improve stroke knowledge in graduate physicians resulting in positive outcomes. These findings suggest that similar strategies may be successful in graduate programs such as Communication Sciences and Disorders (CSD). The purpose of this study was to examine the impact of multiple stroke-related education opportunities on students enrolled in CSD programs. Methods: Seventy-six first and second year students enrolled in a Communication Sciences and Disorders program completed a survey of stroke risk factors and early warning signs of stroke. Results: Risk factor knowledge - 97% identified smoking as a risk factor; 61% identified diabetes; 90% identified high cholesterol; 84% identified age, and 90% identified physical inactivity. Students varied in their recognition of diabetes as a stroke risk factor based on their level of instruction. Early warning signs and first response knowledge - 83% recognized sudden confusion or trouble speaking, 83% recognized sudden facial, arm or leg weakness, 76% recognized sudden vision loss; 76% recognized sudden trouble walking; and 75% recognized sudden headache as early warning signs of stroke. Seventy-nine percent recognized calling 9-1-1 as the appropriate first action. Students varied in their recognition of sudden trouble walking and severe headache as an early warning sign of stroke based on their level of instruction. Conclusions: Most students recognized individual stroke risk factors and early warning signs, but few
recognized multiple risk factors and warning signs. Multiple education opportunities appear to enhance student recognition of risk factors and warning signs.

**026 Evaluation of Global and Regional Myocardial Function Using Contrast Enhanced Cardiac CT and MRI.** Kevin O Herman¹, Chris Bruno², Joseph Schoepf³, Gorka A Bastarrrika⁴, Balazs Ruzsics⁵; Medicine, MUSC, ²College of Medicine, University of Tennessee, ³Radiology, MUSC.

Abstract not available.

**027 Regulation of Beta-Galactosidase mRNA Expression in Hypoxic And/or Electrically Stimulated Adult Cardiac Myocytes.** Charlie Pickens Jr¹, Paul J McDermott²; Medicine, MUSC and Ralph H Johnson VA Medical Center, ³Medicine, Cardiology, MUSC and Ralph H Johnson VA Medical Center.

Hypoxia of the heart occurs when the heart does not receive an adequate amount of oxygen to its tissues, which can lead to its damage. The purpose of these studies was to examine how adult cardiac myocytes regulate expression of a Beta-galactosidase mRNA reporter under hypoxic conditions. A recombinant adenovirus infection under the control of the Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) promoter was used to drive mRNA expression. Both Beta-galactosidase and protein were measured through the use of real-time polymerase chain reaction (PCR) for analyzing Beta-galactosidase mRNA, Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNA, and 18S ribosomal RNA. 

CoCl2 (a hypoxia mimetic) was used, which increased Beta-galactosidase activity, with simultaneous electrical stimulation further increasing its levels. The lowest levels of Beta-galactosidase activity were documented in the quiescent control and the cells that were only electrically stimulated. The protein assay did not exhibit any clear trend, except that the control and electrically stimulated cells showed lower protein concentrations than the hypoxic and hypoxic, electrically stimulated cells. These results, along with an increase in the GAPDH, led to the conclusion that the hypoxic cells and especially the hypoxic and electrically stimulated cells saw an increase in their Beta-galactosidase activity and, in their protein activity. This was believed to have come about due to an increase in transcripational and translational efficiency of the adult cardiac myocytes, due to the hypoxia and electrical stimulation. [Dr. Don Menick, MUSC College of Graduate Studies]

**028 Myocardial Infarction Induces Changes in Nkx2-5 and Connexin 40 Expression in the Peripheral Conduction System.** Irissa N Wilson¹, Mary S Rackley¹, Brett S Harris², Rupak Mukherjee³, Terrence O’Brien⁴; Medicine, MUSC, ²Cell Biology and Anatomy, MUSC, ³Surgery, MUSC, ⁴Medicine, Cell Biology and Anatomy, MUSC and Ralph H Johnson VA Medical Center.

Abstract not available.

**029 Comorbidities in South Carolina Stroke Patients: What Percent of Stroke Patients Also Have Combinations of Hypertension, Hyperlipidemia, and Diabetes Mellitus?** Elizabeth W McCoy¹, Andrea D Boan², Daniel T Lackland³; Medicine, MUSC, ²Biostatistics, Bioinformatics, and Epidemiology, MUSC.

The incidence of stroke in South Carolina is continually among the highest in the US. Hypertension, hyperlipidemia, and diabetes mellitus have all been clearly shown to increase the risk of stroke. The purpose of this investigation was to determine the prevalence of combinations of these diseases in people who have had one or more strokes. Methods: Using In-patient and Emergency Department discharge data from the South Carolina Office of Research and Statistics, I examined all patients discharged from the hospital with a primary diagnosis of stroke and secondary diagnoses of hypertension, hyperlipidemia, and diabetes mellitus from 1996 to 2005. I created line graphs to show the change in percent of stroke patients with hypertension, hyperlipidemia, diabetes, hypertension and hyperlipidemia, hypertension and diabetes, hyperlipidemia and diabetes, and all three over time. Results: The most prevalent condition was hypertension, which increased from 46.24% in 1996 to 61.50% in 2005. The percent of stroke patients with hypertension, hyperlipidemia, and diabetes steadily escalated 6.8%. By 2005, the highest two-disease comorbidity in stroke patients was hypertension and hyperlipidemia, which increased drastically from 5.7% in 1996 to 24.7% in 2005. In 1996, 15.7% of stroke patients had hypertension and diabetes, and by 2005, this number had increased to 21.7%. The percent of stroke patients with hyperlipidemia and diabetes increased gradually from 2.6% in 1996 to 10.9% in 2005. Pearson’s correlation test showed statistically significant correlations between each of the comorbidity combinations. Conclusions: An increasing number of people who have had a stroke also had a deadly combination of serious chronic health problems that predisposed them to the stroke event. Therefore, the most complete and effective method for reducing stroke rates is to utilize a multi-disease approach that incorporates screening, treatment, and management of hypertension, hyperlipidemia, and diabetes both before and after a stroke event. [MUSC Summer Health Professionals Research Program]

**030 Characterization of Toll-Like Receptors 1, 2, 4, and 6 in Human Myofibroblast of the Large Intestine.** Megann K Helton-Rieter¹, Titus A Reaves²; Medicine, MUSC, ²Cell Biology and Anatomy, MUSC.

Inflammatory Bowel Disease (IBD, dysregulated intestinal inflammation with an unknown etiology) affects ~ 400/100,000 persons per year in the United States. A patho-physiological complication of IBD is intestinal fibrosis. Features include an over production of collagen, excessive contraction of intestine tissue, and intestinal stricture. The subepithelial fibroblast is the predominant cell type responsible for producing the increased collagen and therefore, associated fibrosis. Despite this information, the cause and progression of intestinal fibrosis are not well understood. Recent investigations have suggested that toll-like receptors (TLRs, which are a family of receptors that regulate the immune response to microbes) may play a role. Thus, for this study, we characterized the expression of TLRs 1, 2, 4, and 6 in human intestinal sub-epithelial fibroblasts. Additionally, we also characterized expression of Triggering Receptor Expressed on Myeloid Cells (TREM-1, a receptor known to interact with TLR-2 when activated) in fibroblast. Results indicate that fibroblasts expressed TLR’s 2, 4, 6, and TREM 1, but not TLR-1. Fibroblasts were also exposed to interleukin-6 (IL-6, inflammatory cytokine). While there was a difference in expression on TLR 2 and 4 when exposed to IL-6, expression of TLR-6 appeared to be much different. In particular, there was a reduction in expression of TLR-6 on the cell surface; suggesting that TLR 6 may be removed from the surface of the fibroblasts and internalized during inflammation. Moreover, this effect appears to be dependent on a 5 day exposure to IL-6. These data provide the basis for further
investigations into the role of IL-6 in TLR-6 expression and ultimate function in intestinal fibroblasts. Finally, also as a part of future studies, fibroblast and epithelial cells will be cultured together and exposed to microbial products and cytokines, which may allow for a better understanding intestinal fibrosis. [Tom Trusk, Ph.D., Department of Cell Biology and Anatomy David Label, Department of Cell Biology and Anatomy Graduate Student Summer Health Professions NHLBI P20 RR 16461-04]

**031 Does Sickle Trait Exacerbate Diabetic Retinopathy?**  
John H Johnson¹, Berdine Burger², Esther Bowie³, Rosalie Crouch²; ¹Medicine, MUSC, ²Ophthalmology, MUSC.

Sickle trait is often a benign condition with little impact on overall health. However, even though red blood cell sickling is reduced in sickle trait, this complication may be increased under certain hypoxic and acidic conditions such as that caused by diabetic ketoacidosis. It is the relationship between uncontrolled diabetes and increased cell sickling in those with sickle trait which leads to the belief that microvascular complications of diabetes may be exacerbated. Additionally, both diabetes and sickle trait are increased compared to national averages in the Charleston, SC area and research is certainly warranted. Currently our study is seeking to determine if there is a relationship between those with diabetic retinopathy and sickle trait. The project is ongoing and preliminary results are inconclusive. [Special thanks for funding to the College of Health Professions’ Summer Research Program.]

**032 Characterization of Calpain 10 Substrates**  
Robert E Sweeney¹, Rick G Schnellmann²; ¹Medicine, MUSC, ²Pharmaceutical Science, MUSC.

Abstract not available.

**033 Impact of Acid Ceramidase Expression on Head and Neck Cancer Proliferation In Vitro**  
Sarah T Morrison¹, Alex S McPherson², Joseph C Cheng³, Thomas H Beckham³, Xiaoyi Zhang², Lorianne S Turner³, Xiang S Liu³, James S Norris³; ¹Medicine, MUSC, ²MUSC, ³Microbiology and Immunology, MUSC.

Head and neck cancers are the sixth most common type of cancer, with both tobacco and alcohol exposure identified as risk factors. Squamous cell head and neck cancers have been shown to have acid ceramidase (AC) upregulated in 70% percent of cases as compared to the surrounding normal tissue. AC is a catabolic lysosomal enzyme that deacylates ceramide to generate sphingosine, the substrate for sphingosine kinase-1 (SK1), which forms the potent mitogen S1P. It is an important determinant of the balance between cellular levels of ceramide, sphingosine, and S1P, and therefore is integral in determining cell survival, growth, or death. In this study, we examined the role of AC and its impact on cell proliferation in head and neck cancers. UMSCC1, UMSCC14a, and UMSSC22, three independent head and neck cancer cell lines with differing levels of AC, were examined and their proliferative capacity was measured. As demonstrated by MTS assay and western blotting for AC expression, cell lines characterized with higher AC expression indicated greater proliferative capability. Decreased ceramide levels were seen in SCC14a and SCC1 cells compared to SCC22a cells consistent with higher endogenous AC levels and greater cell growth. Overexpression of AC using the AC-EGFP plasmid, either transiently or stably in cell lines with low AC (SCC22 and SCC1) were observed to have increased proliferation as compared to the respective EGFP controls. AC knock-down using a small molecule AC inhibitor, LCL385, may result in decreased cell proliferation in SCC14a cells at higher concentrations. All of the above suggest an important role for AC in head and neck cancer proliferation. As the capability of cells to proliferate impacts tumor malignancy and survival, understanding the role of AC in cell proliferation and tumorigenesis could greatly impact head and neck diagnosis and treatment. [This work was supported by the PPG NIH/NCI PO1 CA97132-01A1 and the NIH/MSTP Predoctoral Fellowship Training Grant, GM08716.]

**034 BDNF Processing and Signaling and Its Correlation with Aging Associated Memory Decline in Mice**  
Hiromi Terawaki¹, Mora Buhusi², Lotta Granholm - Bentley²; ¹Medicine, MUSC, ²Neurosciences, MUSC.

Abstract not available.

**035 Regulation of an Amino-Acid Transport Protein By Oncogenic Herpesvirus**  
Benjamin C Kalivas¹, Chris Parsons²; ¹Medicine, MUSC, ²Infectious Diseases, MUSC.

An oncogenic y-herpesvirus, the Kaposi’s sarcoma-associated herpesvirus (KSHV), is the most common cause of cancer in HIV infected patients. Recently published data revealed that KSHV binds to the transmembrane light chain, xCT, of the xc system and that this interaction mediates viral fusion and entry to host cells. The expression of xCT is upregulated in response to intracellular glutathione depletion or the generation of reactive oxygen species (ROS), and KSHV has been shown to upregulate ROS in endothelial cells and within the tumor microenvironment. Whether KSHV upregulates xCT expression through its regulation of ROS or other mechanisms is unknown. Using xCT-specific antibodies provided by our collaborator and flow cytometric assays, we quantified xCT expression on human cell lines in culture and peripheral blood monocytes from HIV-infected patients at MUSC. We determined that macrophages derived from a myelomonocytic cell line (THP-1), as well as human primary dermal microvascular endothelial cells, expressed xCT. Moreover, their expression of xCT increased following infection with KSHV. Finally, we demonstrated variable xCT expression on circulating monocytes from different HIV-infected patients. Additional experiments are underway to determine the mechanism of KSHV upregulation of xCT, and whether xCT expression on circulating monocytes correlates with KSHV infection in HIV-infected patients. [Department of Infectious DiseasesInfectious Diesase Society of America Medical Scholarship]

**036 Comparison of the Preferences of Two Types of Pill Boxes Amongst Older Adults**  
Leigh F Smith, Caitlyn S Butsura, Lee Ann D Gladwell, Lindsay R Hoyle, Hon Yuen; College of Health Professions, MUSC.

Purpose: This study is to compare two different types of pill boxes on their usability among older adults, over the age of 65, with chronic illness. Older adults with chronic illnesses take many medications. Reminder systems, such as pill boxes, allow them to manage their medications more effectively. In our study, two devices will be compared to see which device is a more effective reminder system. Methods: Each participant will be given one type of pill box. Participants will simulate the use of the pill box and be interviewed subsequently regarding their satisfaction with the pill box and their opinion whether they will be able to use it effectively at home to manage their medication. Participant will be given the other type of pill box and the same
037 Medication Use for Diabetes, Hypertension, and Hyperlipidemia From 1988-1994 to 1999-2004, Tina M. Ellis1, Charles G. Everett2, Paul F. Jacques1, Dana E. King2; 1College of Health Professions, MUSC, 2Family Medicine, MUSC.

Background: The prevalence of hypertension, hypercholesterolemia, and diabetes continues to increase among American adults. The extent to which prescription medication use has increased to control the symptoms of these underlying conditions has not been well documented. Methods: We analyzed data in the NHANES dataset from 1988-1994 and 1999-2004. We compared the rates of medication use for hypertension, hypercholesterolemia, and diabetes among individual’s 40-74 years old over the two time periods. We also compared medication use by gender and race. Results: Medication use increased for all three conditions from 1988-94 to 1999-2004. Anti-hypertension medication use increased from 23.6% to 32.3%, cholesterol-lowering medication use increased from 4.5% to 15.8%, and diabetes medication use increased from 5.3% to 8.2% (all p<.05). By race, anti-hypertension medication use was greatest among Non-Hispanic Blacks in each time period (30.8% and 39.9%). Cholesterol medication use increased the most in Non-Hispanic Whites (4.9% to 17.1%). Diabetes medication use increased the most among Hispanics (7.2% to 12.3%). Conclusion: There has been a substantial increase in medication use for hypertension, hypercholesterolemia, and diabetes between 1988-1994 and 1999-2004. Coupled with the increase in the prevalence of the underlying conditions, these findings have broad implications for future estimates of healthcare expenditures and the potential for drug-drug and drug-food interactions.

038 Pediatric Emergency Medicine, Physician Assistants, and Postgraduate Education: A Prospective Survey, Kara D Larson, Sarah E Belden, Christopher T McLaren, Meghan E McQuiston, Rebecca E Oberenza, Jessie J VanDerveer, Paul Jacques; Health Professions, Physician Assistant Studies, MUSC.

Abstract not available.

039 A Study of Modified Constraint-induced Movement Therapy Used for Children with Hemiplegic Cerebral Palsy, Thomas C Head, Cameron H Corbin, Patricia C Coker; College of Health Professions, Occupational Therapy, MUSC.

This investigation assessed the changes in adaptive function and selected biomechanical parameters of gait, balance, and posture of children with hemiplegic cerebral palsy (CP) before and after participation in a modified constraint-induced movement therapy program (mCIMT) provided in a developmentally appropriate day-camp setting. Design was a non-randomized, ABAA pre and post test design with follow-up testing used to measure the changes in adaptive function, gait, and posture. Pre and post intervention data on adaptive function was collected using the Pediatric Evaluation of Disability Inventory (PEDI) and the Pediatric Motor Activity Log (PMAL) and data concerning changes in the temporal-spatial aspects of gait and posture, were collected using the GAITRite walkway. Participants of the study were seven children, six males and one female, between 3.7 and 6.2 years of age with a diagnosis of hemiplegic CP, six with right hemiparesis and one with left hemiparesis. The mCIMT was performed for six hours a day, for five consecutive days. The schedule consisted of developmentally appropriate play for children. There was time allowed for mass practice and repetitive play in pre-designed gross and fine motor activities addressing both upper and lower extremity deficits. Children wore a resting hand splint restraint covered by a soft puppet glove on their non-affected extremity while participating in activities. Statistics were analyzed using the computer package SPSS. Because the data was not normally distributed, the non-parametric Wilcoxon’s matched pair test was used to evaluate changes in the PEDI and the PMAL. The level of statistical significance was set at p<0.05. The results suggest that the use of a mCIMT program is an effective way of improving the motor skills of children with hemiplegic cerebral palsy. [Coastal Community Foundation]
evaluate the safety of high dose anti-D and determine the utility of using wet purpura to predict treatment failure.

042 Oral Health and Respiratory Disease in People with Scleroderma, Eric Layton¹, Hon K Yuen², Caroline Westwater³; ¹College of Dental Medicine, MUSC, ²College of Health Professions, Health Professions, MUSC, ³College of Dental Medicine, Stomatology, MUSC.

Background: Scleroderma is an autoimmune rheumatic disease characterized by excessive deposition of collagen in the connective tissue. The severity and type of organ involvement may vary widely, but esophageal and pulmonary manifestations are common. Scleroderma patients have significantly reduced lung function, impaired swallowing, and esophageal motility dysfunction. Furthermore, the combination of poor oral hygiene and orofacial complications (microstomia, and xerostomia) increase the likelihood of dental caries and periodontal disease. Recently, several studies have shown an association between poor oral hygiene and the incidence of respiratory diseases such as pneumonia, especially in patients with esophageal disorders and reduced lung function. Aspiration of oropharyngeal contents has been suggested as a mechanism by which pathogens reach the lower respiratory tract. Objective: The goal of this study is to evaluate the oral cavity of scleroderma patients for the presence of potential microbial pathogens. Methods: This study is part of an ongoing cross-sectional survey of 250 scleroderma patients. Two oral specimens per participant were collected by systematically stroking the oral mucous membranes and/or dental plaque with a sterile Cytobrush. Culture and polymerase chain reaction (PCR) methods were used to detect and enumerate microbial pathogens. Upon completion of the larger study, all collected variables (including those that measure oral health status and hygiene) will be compared to the NHANES III dataset. Results and Conclusion: Preliminary analysis has demonstrated that a large percentage of patients are colonized/infected with Candida (fungal pathogen). Interestingly, Streptococcus pneumoniae, which is responsible for the majority of community-acquired pneumonia cases, can be found in the oral cavity of a number of scleroderma patients. Further studies are required to conclude whether the oral cavity acts as a reservoir for respiratory pathogens. [Supported by NIDCR grants T32 DE017551 and R21 DE017360.]

043 Long-Term Music Exposure Significantly Decreases Seizure Frequency in Subjects with Intellectual and Developmental Disabilities, Caroline E Norment¹, Robert P Turner², Mark Bodner³; ¹Dental Medicine, MUSC, ²Neurosciences, MUSC, ³MIND Institute of California.

Abstract not available.

044 C-Reactive Protein: Stabilization Versus Activation of the First Complement Component (C1), David A Bodie¹, Marcus R Duvall², Robert J Boackle³; ¹Dental Medicine, Stomatology, MUSC, ²Immunology, MUSC.

C-reactive protein (CRP) is a pentameric ring-like acute-phase plasma protein produced by the liver. Due to the action of specific cytokines acting on the liver, hepatocytes up-regulate the expression of CRP, which is regarded as a marker of many pathological conditions including inflammatory periodontal disease. Thus, the concentration of CRP can increase dramatically within a matter of hours. Considering the importance of CRP and its correlation with many pathological conditions, the goal of this research was to investigate the effect of CRP on the first complement component (C1). The working hypothesis was that CRP in the fluid phase would help to conserve complement by binding C1q enhancing the action of C1 inhibitor on C1 and thereby limiting C1 consumption and C1-mediated C4b deposition. The latter scenario would result in the better control and conservation of serum complement. To test this hypothesis, a series of ELISA assays were initiated. After determining the concentration of immobilized human IgG required for optimal C4 deposition, CRP was mixed with serum complement in the fluid phase to see if CRP would inhibit C1-mediated C4 deposition. Although a trend was observed towards conservation of the first complement component by CRP in the fluid phase, a statistically significant conservation of C1 was not observed. Additional refined techniques will be needed to confirm the hypothesis that CRP in the unbound state can mediate a stabilizing effect on complement. If CRP is determined to stabilize C1 and enhance the action of C1 inhibitor in controlling fluid C1 function, it may be possible to devise substances or methods to enhance or mimic the action of CRP in order to prevent or reduce inadvertent complement-mediated host tissue damage in a variety of inflammatory diseases (e.g. auto-immune diseases and periodontal disease). Perhaps in the future, peptides could be synthesized resembling regions of CRP that could emulate the CRP stabilizing function on C1 and control inadvertent complement deposition on normal host tissues. As a result, healthy host tissues would be spared from a complement mediated attack, which would better allow for the healing of damaged tissues. [This research was supported by NIH, National Institute of Allergy and Infectious Diseases AI069957.]

045 Cisplatin/Irinotecan Versus Carboplatin/Paclitaxel As Definitive Chemoradiotherapy for Loco-Regionally Advanced Esophageal Cancer, Bree N Ruppert¹, John M Watkins², Shirai Keisuke³, Amy Walquist³, Elizabeth Gerret-Mayer³, Carolyn E Reed³, Carol K Sherman⁴, Anand K Sharma⁴; ¹Medicine, Radiation Oncology, MUSC, ²Radiation Oncology, MUSC, ³Medicine, Division of Hematology and Oncology, MUSC, ⁴Biostatistics, Bioinformatics, and Epidemiology, MUSC, ⁵Surgery, Division of Cardiothoracic Surgery, MUSC.

Objective: To compare toxicities, disease control, and survival outcomes for patients treated with either cisplatin/irinotecan versus carboplatin/paclitaxel concurrent chemoradiotherapy for locally advanced esophageal cancer. Methods: Single-institution retrospective comparison between treatment groups: the cisplatin/irinotecan group was treated with two cycles of induction chemotherapy followed by concurrent chemoradiotherapy, while the carboplatin/paclitaxel group began with chemoradiotherapy followed by 2 additional cycles of chemotherapy. Acute toxicities, response rates, disease control, survival outcomes, and patterns of failure were compared between the groups. Results: Between January 2000 and December 2007, 57 patients were identified for inclusion in the present study (38 cisplatin/irinotecan and 19 carboplatin/paclitaxel). Groups were well-balanced by clinical-, pathologic-, staging-, and treatment-related factors. Thirty-five patients (92%) in the cisplatin/irinotecan and 18 patients (95%) in the carboplatin/paclitaxel group completed all planned therapy. There were no significant differences in hematologic or non-hematologic toxicities between the groups. At a median survivor follow-up of 37.6 months (range 7.3 – 59.3 months) for the entire population, 22 patients are alive (16 without evidence of disease). The median and 4-year overall survival estimates were 14.5 months and 15.8% for the cisplatin/irinotecan group, compared with 54.2 months and 56.1% for the
Factors Affecting Participant Inaction During High-Fidelity Simulation of ACLS Megacodes, Jennifer R Matos1, Matt Crumpler1, Young Choi1, Matthew McEvoy2; 1Biostatistics Bioinformatics & Epidemiology, Medicine, MUSC, 2Anesthesia, MUSC, 3Anesthesia, MUSC.

High Throughput Screening for Inhibitors of Zeb-1, Brandon L Mizell1, Matthew M Chao1, Charles Smith2, Harry A Drabkin3, Robert Gemmill3, Michael Mitas3; 1Health Professions, MUSC, 2Pharmacology, MUSC, 3Medicine, MUSC.

The development of metastatic disease is the most common cause of death among cancer patients and results from dissemination of malignant cells. The ability of cells to gain metastatic potential requires transition of tumor cells that are largely non-motile, adhesive, and epithelial in nature, to cells that are motile, non-adhesive, and mesenchymal in nature. Recent studies have shown that this epithelial-to-mesenchymal transition (EMT) is stimulated by specific transcription factors (eg., Zeb1) which inactivate epithelial-specific genes. Identification of agents that inhibit EMT might be useful for stopping the spread of cancer. We used a novel microarray/bioinformatics approach to identify a set of 22 epithelial- and cancer-specific genes, four of which (E-cadherin/CDH1, Map7, F11R, and Spint1) exhibit reciprocal expression in the NCI60 CGAP microarray database compared to Zeb1 (p=3.7E-10). A bioinformatics analysis of the promoter region of the 22 genes allowed us to deduce a potential high affinity binding site from the genomic sequence) and amplified an 800 bp fragment site (primer contains a single mismatch compared to its cognate gene. Our study goal is to perform a high throughput screening of cloning this and other fragments upstream of the luciferase promoter region of E-cadherin. We are currently in the process containing the deduced Zeb1 high affinity binding site from the genomic sequence) and amplified an 800 bp fragment site (primer contains a unique HindIII restriction enzyme (YCACCTGRN<60CACCTG) in 7 of the 22 genes, including the tumor suppressor E-cadherin. We hypothesize that placement of this high affinity site immediately upstream of a reporter luciferase gene will result in repression of luciferase activity upon Zeb1 activation. To test this hypothesis, we used a primer containing a unique HindIII restriction enzyme site (primer contains a single mismatch compared to its cognate genomic sequence) and amplified an 800 bp fragment containing the deduced Zeb1 high affinity binding site from the promoter region of E-cadherin. We are currently in the process of cloning this and other fragments upstream of the luciferase gene. Our study goal is to perform a high throughput screening using a ChemBridge drug library (n=50,000) and identify a compound that is able to inhibit Zeb1 function and restore luciferase activity. A summary of the screening results will be presented. [NIH Lung SPORE]

Population-based Prevalence and Incidence of Health Conditions Over a 10-year Period After Traumatic Spinal Cord Injury, Eric J Shiroma1, Dulaney A Wilson1, Elisabeth E Pickelsimer2; 1Biostatistics Bioinformatics & Epidemiology, MUSC, 2Biostatistics Bioinformatics & Epidemiology, Medicine, MUSC.

Abstract not available.

Acid Ceramidase Upregulation Following Radiation Therapy Desensitizes Cancer Cells to Taxol, Thomas H Beckham, Joseph C Cheng, Ayman EM Mahdy, Saeed Eliejeemy, Tucker S Marrison, Xiaoyi Zhang, Xiang S Liu, James S Norris; Microbiology and Immunology, MUSC.

Abstract not available.

Cathepsin B Is Tied to Acid Ceramidase Expression in Prostate Cancer and Mechanistically Contributes to Tumor Progression, Xiaoyi Zhang1, Thomas H Beckham1, Joseph C Cheng1, Sarah T Marrison1, Lorianne S Turner1, Alex S McPherson2, Alicja S Bielawska2, James S Norris1; 1Microbiology and Immunology, MUSC, 2Biochemistry and Molecular Biology, MUSC.

Prostate cancer is the second most common cancer and the second leading cause of cancer-related death among American men. Acid ceramidase (AC), a ceramide-metabolizing enzyme, is up-regulated in 60% of primary prostate cancer tissues and in over 80% of prostate cancers with a Gleason score of 8 - 10. Although acid ceramidase activity has been tied to enhanced cell growth and suppression of apoptosis, the exact role of acid ceramidase in the progression of these diseases is not well-defined. The cysteine protease cathepsin B, up-regulated in a variety of cancers, has been shown to play a key role in tumor development and progression, greatly increasing cancer cell growth and invasion. In this study, we observed, by immunoblotting, that cathepsin B levels are also elevated in prostate tumor tissue samples that express higher levels of acid ceramidase compared to normal tissue. Further data indicated that acid ceramidase expression directly influences cathepsin B levels as shown in stable clones of numerous prostate cancer cell lines including PPC-1, DU145, DuPro, and PC3. Additionally, this increase in cathepsin B can be reversed by siRNA knockdown of acid ceramidase expression, further confirming genetically that expression of cathepsin B is regulated by acid ceramidase levels. As previously shown, prostate cancer cells over-expressing acid ceramidase display a survival advantage. In this study, we further examined this effect in malignant tumors and show that PPC-1 cells with elevated acid ceramidase levels indicates a phenotype characteristic of aggressive cancers by displaying higher rates of proliferation, migration, and invasion through collagen. More importantly, these increases were mitigated by the inhibition of cathepsin B. These data indicate cathepsin B plays a key mechanistic role in the pathway by which acid ceramidase over-expression leads to development of an aggressive, metastatic cancer. Further exploration of this link will provide a more detailed understanding of this progression and uncover new therapeutic targets for these and other complex diseases associated with acid ceramidase. [This work was supported by PPG NIH/NCI P01 CA97132-01A1 and the NIH Medical Scientist Training Program grant.]
expressed in the tumor cells. Gene therapy using recombinant adenoviral vectors for the introduction of LIGHT into the tumor environment has been effective in several cancer cell lines, including breast and colon cancer cells. However, gene delivery can be enhanced with the use of non-viral vectors in addition to viral transfection to increase efficiency of targeting and duration of expression as well as reduce inflammatory responses. We are thus studying the use of several cationic polymers, including ethyleneglycol diglycidyl ether (EDE), polyethylene imine (PEI), and 1,4-bis(3-aminopropyl) piperazine (1,4-Bis) to determine if modification of adenoviral vectors improves transfection of the transgenic mouse prostate cancer cell line TRAMP. [Medical Scientist Training Program, College of Graduate Studies, MUSC]

052 Estimating Long-term Placebo Effect Using Sort-term Repeated Measures Data And Meta Analysis: An Example From Depression, Annie N Simpson1, Kit N Simpson2, Ziad Nahas3, Biostatistics, Bioinformatics, and Epidemiology, MUSC, 2College of Health Professions, Health Administration, MUSC, 3Medicine, Psychiatry and Behavioral Sciences, MUSC.

Results from long-term placebo-controlled studies are critical for comparing treatments for depression, but they are ethically problematic due to the poor quality of life and high rates of suicide in depression. Objective: To estimate depression remission rates at 12-months for placebo-controlled depression therapy from open label data for competing treatments. Methods: Markov simulation based on transitions observed in repeated measures data from Vagus Nerve Stimulation (VNS) and drug trials, adjusted by placebo failure rate from meta-analysis. Results: We defined Markov health states that were mutually exclusive and jointly exhaustive based on the values of the IDSSR depression scale and estimated a quarterly matrix for VNS and drug therapy for 1 year of clinical trial data from 3 studies. We found no effect of time on transitions for VNS (p=.77) or drug therapy (p=.53), supporting our choice of a Markov model. There were inadequate amounts of data to estimate a 25-cell transition matrix for placebo, so the transition matrix for placebo was generated by adjusting the drug treatment failure transitions by the relative risk of failure on placebo found by meta-analysis. Use of the HAM-D measure produced similar results. Assumptions related to failure distributions and uncertainty in parameters was tested by Bootstrap and sensitivity analysis. The Markov simulation reproduced the observed trial values and estimated a reduction of 5% in remissions for drug therapy due to blinding at 12-months. Conclusions: Markov simulation may be combined with meta-analysis of published studies to estimate long term outcomes when placebo controlled studies become infeasible. [Study Funded by Cyberonics Inc. and The Mood Disorders Program at MUSC]

053 Improving the End User Experience Within ArrayQuest, a Web-based DNA Microarray Analysis Process Controller, Adrian M Nida1, Saurin D Jani2, Gary L Argraves3, W. Scott Argraves2, Biostatistics, Bioinformatics, and Epidemiology, MUSC, 2Cell Biology and Anatomy, MUSC, 3Array Genetics, Newtown, CT.

To assist researchers with meeting the ever-increasing challenges of analyzing DNA microarray data, we created a web-based application called ArrayQuest. ArrayQuest was designed to apply various types of analysis scripts including R based Bioconductor algorithms to DNA microarray data stored either in the MUSC DNA Microarray Database, the NCBI Gene Expression Omnibus (GEO) or data uploaded to the ArrayQuest center-point web server. As with any software system, improvements can be made to increase the ease at which end users are able to perform operations and obtain results. In an effort to improve the ArrayQuest system we have engineered a point and click style graphical user interface that facilitates multiple file uploads and replaces the previous free-text parameter input architecture with a series and pull-downs and radio button options. In addition, the output file download system has been modified to allow batch downloading of files. The resulting enhancements to ArrayQuest are expected to permit greater usage of an already robust platform for analysis of DNA microarray data.

054 Hyaluronan-CD44 Interactions Aid in Stabilization of Pro-Tumorigenic Signaling Complexes and Transporters in the Plasma Membrane, George D Grass, Mark G Slomiany, Bryan P Toole; Cell Biology and Anatomy, MUSC.

Hyaluronan (HA), a predominating extracellular matrix constituent, has a large role in hydration and structural integrity of tissue architecture. In addition, HA has been found to aid in cancer progression by establishing an optimal environment for cell division and by directly influencing cell signaling pathways via binding to its main receptor, CD44. Recent work by our lab and others has shown that HA-CD44 interactions regulate or stabilize receptor tyrosine kinase signaling complexes and transporters in the plasma membrane. Oligosaccharides of HA (o-HA) compete with endogenous, high affinity, multivalent CD44 polymeric HA interactions by establishing low-affinity, monovalent o-HA-CD44 interactions, thus decreasing stabilization of cancer-promoting complexes at the plasma membrane. Populations of CD44 have been shown to reside in Triton X-100 insoluble fractions, thus indicating interactions with lipid microdomains. Previously, CD44 was shown to associate with Annexin II, a molecule thought to regulate receptor distribution into lipid rafts, in which cholesterol depletion with methyl-beta-cyclodextrin (MBCD) dissociated this complex. CD44 has also been shown to interact with the underlying actin cytoskeleton either directly or indirectly via adaptor proteins, in which pre-treatment with Latrunculin A, an inhibitor of actin polymerization, inhibits actin-dependent internalization of CD44. Here we begin to elucidate the interrelated relationships of HA-CD44 dependent signaling and complex stabilization at the plasma membrane through interactions with lipid microdomains, the cytoskeleton, and co-receptors at the plasma membrane. Furthermore, we continue to establish a possible therapeutic use of o-HA, which are non-toxic and non-immunogenic, in cancer therapy.

055 Computer Simulation of Drug Release From Temperature-Sensitive Liposomes During Thermal Treatment, Astrid Gasselhuber1, Dieter Haemmerich2; Pediatrics, MUSC, 2Pediatrics, MUSC, Clemson Bioengineering.

Introduction/rationale: Several recent studies indicate an advantage when low temperature sensitive liposomes (LTSLs) containing chemotherapy drug (doxorubicin) are administered in combination with heating therapies. LTSLs release the drug only in the heated region (above ~40 degrees Celsius) thereby considerably reducing systemic toxicity while increasing local drug concentration. In the current project we combine a computational model of thermal treatment with a pharmacokinetic model. Methods: A computer model was used to simulate the spatio-temporal drug release. A 2-compartment model was employed to describe the transport of LTSLs and doxorubicin (DOX) between the tumor vascular and extracellular
space as well as the concentration in the whole body circulation of blood. The results of our simulations were compared with the results of a published in-vivo study. Results: The concentration of DOX in the total blood volume was 26.2ug/g. Maximum DOX concentration in the tumor occurred adjacent to the heating probe (the region of highest temperature) and decreased with the distance from the electrode. The maximum value of DOX concentration in the tumor extracellular space was 444ug/g and the minimum was 39.7ug/g. Qualitatively, our results were comparable with the published concentration profile from a previous study, while quantitatively our concentration values were the same order of magnitude. Conclusions: Our computational results correlated well with published in-vivo data. The simulation showed that tissue heating leads to a coagulation of the vasculature, which in turn results in a declined perfusion in the heated region. The reduced blood flow causes on the one hand an increased drug concentration in the tumor vascular space due to reduced removal of drug by tumor perfusion. On the other hand the volume transfer constant (Ktrans) decreases with reduced perfusion, which influences the drug diffusion into the tumor tissue. Our computer model may facilitate maximization of tumor drug concentration via modulation of tumor perfusion and heating regimen.


Head and neck squamous cell carcinoma (SCC) is the most common malignant neoplasm estimated to be more than 40,000 cases per year in the US. These malignant tumors are known to have a potent activity for local bone invasion; however the molecular mechanisms of SCC associated osteolysis is unclear. We showed subcutaneous injection of SCC 14a cells onto the surface of calvaria in NCr-nu/nu athymic mice develop tumors in 4-5 weeks. Histochemical staining demonstrated tumor cell invasion/osteolysis with a significant increase in the numbers of multinucleated TRAP positive osteoclasts at the tumor/bone interface. We identified high levels of chemokine ligand, CXCL13 and RANK ligand (RANKL), a critical osteoclastogenic factor, expression in SCC derived cell lines. Real-time PCR analysis demonstrated that recombinant hCXCL13 treatment (0-25 ng/ml) to SCC 14a cells for 48 hours (4-fold) RANKL expression in a dose dependent manner. Interestingly, CXCL13 also induced (2.4-fold) CXCR5 receptor expression in these cells. Western blot analysis further demonstrated that anti-CXCR5 receptor antibody inhibits CXCL13 stimulated RANKL and CXCR5 expression in SCC 14a cells. These results indicate an autocrine regulatory function for CXCL13 in SCC tumor cell invasion/osteolysis. We further examined the molecular mechanism by which CXCL13 regulates RANKL expression. CXCL13 stimulation of SCC14a cells transfected with hRANKL gene promoter-luciferase reporter plasmid demonstrated a significant increase (3.0-fold) in RANKL gene promoter activity. Transcription factors array (super array) screening by real-time PCR identified a 3.2-fold increase in c-Jun mRNA expression in CXCL13 stimulated SCC 14a cells. Also, CXCL13 significantly increased phospho-c-Jun levels in these cells. We further show that JNK (c-Jun N-terminal Kinase) inhibitor suppressed CXCL13 stimulated RANKL expression. These results suggest CXCL13 signaling stimulates RANKL expression and implicates a potential therapeutic target to prevent osteolysis associated with SCC in vivo.

057 Activator of G-Protein Signaling 3: The Role of the Tetratricopeptide Repeat (TPR) Domain in Subcellular Positioning of the Protein. Ali Vural, Joe Blumer, Stephen Lanier; Pharmacology, MUSC.

AGS3 is a receptor independent activator of G-protein signaling involved in unexpected functional diversity for G-protein signaling systems. AGS3 has 7 TPR motifs upstream of 4 G-protein regulatory (GPR) motifs, each of which bind and stabilize the GDP bound conformation of Gic. The TPR domain is postulated to play an important regulatory role in subcellular positioning of AGS3 and influence its interaction with G-protein. We asked which regions of the TPR domain may be of particular importance regarding this regulatory role by determining the subcellular distribution of a series of AGS3-GFP constructs in COS-7 cells. We generated constructs with progressive truncations of individual TPR motifs or single amino acid substitutions in conserved residues in individual TPR motifs. Modification of individual TPR motifs redistributed AGS3 to a constellation of punctuate structures throughout the cytoplasm. These structures do not co-localize with markers for mitochondria, endoplasmic reticulum, peroxisomes, lysosomes, golgi, clathrin-coated vesicles or early endosomes, but rather exhibit the properties of aggresomes. Indeed, cellular stress induced by proteosome inhibitors resulted in movement of the cytoplasmic punctuate structures to a perinuclear region where they assemblled within a vimentin aggresome “cage”. The distribution of AGS3-GFP TPR mutants to the aggresome was rescued by coexpression of an AGS3 binding partner Gialpha3 suggesting that there is conformational communication between the TPR and GPR domains of the protein. The punctuate structures may represent a protein degradation pathway or define a specific address within the trafficking pathway for AGS3 with functional implications. Analysis of AGS3 single nucleotide polymorphisms (SNP) at the NCBI site, revealed a SNP that resulted in codon change within the TPR domain. AGS3-GFP constructs with the SNP codon change also distributed to the aggresomal structures. The aberrant accumulation of AGS3 in such structures also may contribute to cellular stress and associated pathologies.

058 Characterization of the AdCerS6F Adenovirus for Modulation of Ceramide Synthase 6 in Colon Cancer Cells. Tejas S Tirodkar, Laura M Kasman, Shai J White-Gilbertson, Christina Voelkel-Johnson; 1MCBP, MUSC, 2Microbiology and Immunology, MUSC.

The creation of the right tools is critical to a scientific investigation. Here we describe in part the making, and the characterization of the adenovirus AdCerS6F for the investigation of the role of the sphingolipid C16-ceramide in TRAIL mediated apoptosis of colon cancer cells. Previous studies from our lab have shown that when ceramide synthase 6 (CerS6), the enzyme responsible for making C16-ceramide is downregulated in a TRAIL sensitive human colon cancer cell line SW480, the cells are rendered resistant to TRAIL mediated apoptosis. On the other hand, when an isogenic TRAIL resistant colon cancer cell line, SW620 is transfected with a CerS6 cDNA plasmid, the cells are sensitized to TRAIL mediated apoptosis. In order to further investigate the mechanism of TRAIL sensitization in the SW620 cells, we sought to create an adenovirus that would express the CerS6 protein so as to allow efficient modulation of C16-ceramide in the cells. The AdCerS6F adenovirus was created using the AdEasy system by subcloning the CerS6 cDNA fused to a FLAG tag. The virus is now being tested for three basic requirements: CerS6 upregulation, sensitization to TRAIL, and detection of the FLAG
tag in the SW620 cell line. If the virus tests positive for these three conditions it can be used for studying the role of C16-ceramide in TRAIL mediated apoptosis of SW620 cells.

059 Differential Roles of Sphingosine Kinase Isoenzymes in A498 Kidney Carcinoma Cells, Peng Gao, Charles D Smith; Pharmaceutical Sciences, MUSC.

Two isoenzymes of sphingosine kinase (SphK), i.e. SphK1 and SphK2, are expressed in human cells. The SphKs are key enzymes that catalyze the formation of sphingosine-1-phosphate (S1P) that plays important roles in cell proliferation, apoptosis and angiogenesis. The different functions of the isoenzymes in tumor epithelial cells are not fully understood. We have investigated their roles in cell proliferation, cell cycle progression, sphingolipid metabolism and cell migration in A498 human kidney adenocarcinoma cells by manipulating their expression using isoenzyme-selective siRNAs to knockdown SphK1 and/or SphK2. Both double and single SphK isoenzymes depletion strongly suppressed cell proliferation, with accumulation of cells in G1 phase and decrease of G2/M phase cells compared to the negative control siRNA treated cells. The phosphorylation of AKT and expression of total ERK were decreased dramatically after depletion of SphK1 and/or SphK2, indicating the isoenzymes have similar effects on A498 cells proliferation. However, the two SphK isoenzymes are not entirely redundant. SphK2-selective-depletion induced the expression of SphK1 and increased the production of S1P. In contrast, whereas SphK1-selective-depletion did not affect SphK2 expression but decreased S1P level and elevated the levels of most pro-apoptotic ceramide species. Additionally, SphK1-selective-depletion induced p21 expression; whereas slight decreases were observed in SphK2 depleted cells, even though the effects on cell cycle disruption were same. Depletion of either SphK1 or SphK2 enhanced the phosphorylation of ERK1; whereas, SphK2 depletion decreased the phosphorylation of ERK2. SphK2 depletion seemed to inhibit the glycosylation of vascular cell adhesion molecule 1 (VCAM1), whereas SphK1-selective-depletion resulted in slight decreases in its expression. In agreement with this result, SphK2 depletion reduced cell migration more than depletion of SphK1. Overall, these data indicate that SphK1 and SphK2 have only partially overlapping functions in tumor cell signaling and proliferation. Consequently, optimal targeting of this pathway in cancer chemotherapy will likely require inhibitors for both SphK isoenzymes. [This project is supported by NIH 1R01 CA 122226.]

060 Targeting Membrane-Associated Hsp90 Inhibits the Establishment of Latent Infection By an Oncogenic Herpesvirus, Michael R DeFee1, Qin Zhiquiang2, Jennifer Isaacs3, Chris H Parsons1; 1Microbiology and Immunology, and Dental Medicine, MUSC, 2Medicine, MUSC, 3Pharmacology, MUSC, 4Medicine, and Microbiology and Immunology, MUSC.

Abstract not available.

061 Thermophilic Bacteria Capable of Electricity Generation in Microbial Fuel Cells, Christopher W Marshall1, Bryan J Mathis1, Harold D May2; 1Microbiology and Immunology, MUSC, 2Microbiology and Immunology, MUSC, MFC Technologies LLC.

The majority of organisms discovered to be capable of electrode reduction within a microbial fuel cell to produce electricity are mesophilic bacteria. Microorganisms that thrive in thermophilic environments, on the other hand, have not been studied extensively and may prove to be more effective biocatalysts in microbial fuel cells due to their higher metabolic rates. Furthermore, no single organism has been shown to produce an electric current at thermophilic temperatures. The purpose of this study was to begin the process of discovering a thermophilic isolate capable of electrode reduction. Thermophilic organisms from marine sediment in the Charleston, South Carolina harbor were shown to produce a current ten times higher in a sediment fuel cell than the mesophilic organisms taken from the same environmental source (60°C ranged from 209 to 254 mA/m2 vs 22°C ranging from 10 to 22 mA/m2). Current generation could be sustained at high levels when the anode from the sediment fuel cell was transferred to a single-chamber thermophilic fuel cell and exchanged over several months. Amplified ribosomal DNA restriction analysis of the community of organisms present in the biofilm on the anode revealed that the majority of clones were similarly related to the Gram-positive iron-reducing bacteria Thermocina ferriacetica based on the 16S rRNA gene sequence. The clones present in the community analysis in lesser quantities were similar to uncultured Deferribacteres isolated from thermophilic environments. The organisms with similarity to known iron-reducing bacteria are currently being investigated for thermophilic electricity production. [This work is supported by the Department of Energy and SC Launch! through grants (STTR# DE-FG02-07ER68319) to MFC Technologies.]

062 Intra-hippocampal Injection of Pro-NGF Increases Expression of Sortilin and P75, in Vivo: Possible Mechanism of Basal Forebrain Cholinergic Neuron Degeneration, Ashley M Fortress1, Kris L Helke2, Lotta Granholm3; 1Neurosciences, MUSC, 2Comparative Medicine, MUSC, 3Neurosciences and Center on Aging, MUSC.

Learning and memory impairments occurring with normal aging and Alzheimer’s disease are associated with degeneration of the basal forebrain cholinergic neurons (BFCNs). BFCNs extend their axons to the hippocampus (HPC) and are dependent on nerve growth factor (NGF) for survival and maintenance. Cholinergic terminals in the hippocampus bind NGF at its high-affinity receptor, trkA, and the trkA-NGF complex is transported to the BFCN cell bodies via classical retrograde transport mechanisms. Absence of NGF transport to the BF is correlated with both cognitive deficits and BFCN degeneration. The precursor to NGF, pro-NGF, is capable of binding to the low-affinity NGF receptor, p75; this binding has been demonstrated to induce cell death in vitro. Previous work in our laboratory has shown that systemic administration of NGF increases the expression of trkA in the BF and enhances memory performance. Currently, the working hypothesis is that disrupted retrograde signaling of NGF with aging (i.e. diminished pERK) results in reduced trkA activation and elevated p75 response, resulting in a propelling degeneration of the cholinergic neurons. To test this hypothesis, 24-month-old rats were given bilateral stereotaxic intra-hippocampal injections of pro-NGF (10µg) were then sacrificed 24h or 1 week post-injection. Twenty four hours after pro-NGF injection, immunohistochemical assessment of basal forebrain sections revealed: 1) pERK-ir was reduced, 2) p75 was elevated and 3) p75 and sortilin were co-localized. One week following the pro-NGF injection, western blots revealed a two-fold increase in p75, sortilin and pro-NGF. Combined, these data represent the first evidence of the effects of pro-NGF in vivo and provide new insight in the field of aging and neurodegeneration. We propose that pro-NGF-induced up-regulation of p75 and sortilin are correlated with memory deficits following the pro-NGF administration, and that this alternative...
receptor activation may contribute to the basal forebrain cholinergic neuron degeneration. [Supported by AG10755.]

063 Dysfunctional Cognitive Performance and Blunted Prefrontal Cortex Neuronal Activity Following Chronic Methamphetamine Self-Administration in Rats, Aram Parsegian, Antonieta Lavin, Ronald E See; Neurosciences, MUSC. Abstract not available.

064 Transdermal Dl-Methylphenidate Increases L-Isomer Absorption Relative to Oral Dosing in Mice and Yields the L-Ethylphenidate Metabolite Following Ethanol Gavage, Guinevere Bell1, Andy Novak2, Lawrence Middaugh3, William Griffin2, Kennerly Patrick1; 1Pharmaceutical Sciences, MUSC, 2Psychiatry and Behavioral Sciences, MUSC.

Introduction: d,l-Methylphenidate (MPH) is used to treat ADHD. In 2006, the MPH Transdermal System (MTS; Daytrana®) was approved as an alternative to oral formulations. Concern exists that a significant interaction with ethanol may exist when using MTS. The l-MPH enantiomer exhibits only 1% oral bioavailability. Even so, l-MPH appears to be responsible for a 40% increase in plasma d-MPH Cmax when humans are given a single drink of ethanol. However, when dosing with MTS plasma concentrations of l-MPH are 50 times higher than that following oral d-MPH. To test the hypothesis that MTS accentuates the MPH-ethanol drug interaction, a mouse model was used. Methods: Drug naive C57BL6/J mice were dosed with half of a 10mg MTS and 3g/kg ethanol gavage 30 min later. Urine was collected in metabolic chambers for 1.5 hrs, then blood was collected for ethanol analysis. The time course was determined from an earlier experiment showing peak locomotor activity 1.5 hrs after MTS application. Blood alcohol levels were determined using the Analox® system. Urine was analyzed by enantiospecific gas chromatography-mass spectrometry using electron impact ionization, selected ion monitoring of trifluoroacetylprolylpiperidyl fragment ions of MPH and ethylphenidate, with d5-MPH as an internal standard. Results: Both d-MPH and l-MPH were found in concentrations exceeding 10 ug/mL urine. Only l-ethylphenidate was detectable, and in ug/mL concentrations. Blood alcohol levels fell within the expected range (151 - 165 mg/dl). Conclusions: The high bioavailability of transdermal l-MPH in humans generalizes to mice. Further, like humans the transefferentification metabolite l-ethylphenidate was formed enantioselectively. This metabolic pathway likely results in the competitive inhibition of carboxylesterase-1 to impede metabolic clearance of the active d-MPH isomer. Because the effects of l-ethylphenidate are unknown, this metabolic interaction potentially has profound implications regarding use of MTS during social alcohol consumption or especially during MTS-ethanol co-abuse. [This work was supported by the Center for Drug and Alcohol Program and NIH grant R01 AA 016707.]

065 Sequential Baseline Adaptive Randomization Balancing Continuous Prognostic Factors in Stroke Clinical Trials, Jody D Ciolino1, Yoko Palesch2, Renee Martin2, Wenle Zhao2; 1Biostatistics, Bioinformatics, and Epidemiology, MUSC, 2Biostatistics, Bioinformatics, and Epidemiology, Data Coordination Unit, MUSC.

Subject Randomization provides the foundation for the validity of statistical analysis of clinical trial results. It is also the most important method of controlling potential biases caused by known or unknown prognostic factors in a clinical trial. Currently, stratified randomization is the most commonly used method to control baseline confounding factors by balancing treatment assignment within each stratum created by the combination of all confounding factors. This strategy is limited to categorical variables only, and its efficiency of controlling treatment distribution balance decreases when the number of factors and categories increase. We propose a new method of subject randomization in which the prognostic factors to be controlled can be continuous variables or categorical variables. Bootstrapping simulation studies were conducted on a stroke dataset involving 624 subjects. Baseline age and disease severity level (NIHSS, which ranges from 0 to 42) are both believed to affect the primary outcome (functional outcome at 90 days using Modified Ranking Scale), and need to be controlled. Traditionally these two confounding variables are dichotomized and a stratified randomization is used. In the proposed new randomization method, both age and NIHSS are considered as continuous variables and a minimization algorithm is developed for the subject randomization to balance the distribution of these two variables between the two treatment groups. Results from the computer simulation study suggest a benefit in the overall power for the test of the primary outcome using the proposed continuous balancing method over the stratified balancing.

066 Heat Shock Preconditioning Inhibits Cisplatin-induced Hair Cell Death in the Adult Mouse Utricle, Tiffany Baker1, Mona Taleb2, Shimon Francis3, Carlene Brandon1, Keely Morris4, Lisa Cunningham1; 1Pathology and Laboratory Medicine, MUSC, 2Graduate Studies, Medicine, MUSC.

Cisplatin is a chemotherapeutic drug which has proven successful in treating a wide variety of cancers; however a significant proportion of patients receiving this drug suffers from significant permanent hearing loss. The ototoxic side effects of cisplatin result in part from damage to sensory hair cells of the inner ear, leading to the apoptotic death of those cells. We previously showed that upregulation of heat shock proteins (HSPs) inhibits cell death in the inner ear caused by another class of ototoxic drugs, the aminoglycoside antibiotics. We have now examined whether HSP induction can inhibit cisplatin-induced hair cell death. Adult mouse utricles were cultured for use in immunohistochemistry, QRT-PCR, and TEM. Our results indicate a protective effect of heat shock preconditioning on hair cells against cisplatin-induced hair cell death. However, our preliminary data indicate that Hsp70, the most inducible and widely-conserved heat shock protein, does not account for the protective effect of heat shock against cisplatin-induced hair cell death. Thus we are currently examining the roles of other heat shock proteins, including Hsp32, in mediating the protective effect of heat shock preconditioning.

067 Factors Impacting Racial Disparities Among People with Diabetes in the Southeast United States, Kelly N Hardman1, Kelly J Hunt1, Rickey Carter1, Carolyn Jenkins2, Daniel T Lackland3; 1Biostatistics, Bioinformatics, and Epidemiology, MUSC, 2College of Nursing, MUSC, 3Biostatistics, Bioinformatics, and Epidemiology, MUSC.

The prevalence of diabetes has dramatically increased over the past few decades, disproportionately affecting minority races. The southeast United States is a region of unique race and culture composition with a high percentage of African Americans. Black individuals have higher diabetes prevalence rates, higher rates of comorbidities, and worse diabetes outcomes. Due to the diabetes epidemic, it is important to understand the trends in diabetes, prevention, and
management. The aims of this study were to examine the trends in obesity, hypertension (HTN), and dyslipidemia prevalence and determine the trends in diabetes management, including personal care factors, physician care factors, and vaccination rates, by race and gender among individuals with diabetes in the southeast U.S. from 2000 to 2007. Data was taken from the CDC’s BRFSS, where health data is collected through telephone survey. In this study, disparities narrowed in obesity, HTN, and dyslipidemia between the race/gender groups. Black women maintained the highest obesity rates from 2000 (60.8%) through 2007 (63.3%). Obesity rates increased greater in black males, white males, and white females than in black females, thus narrowing the disparity. HTN prevalence decreased in black females and dyslipidemia decreased in black males but increased in all other race/gender groups. Diabetes management was greatest in white females (14.2% in 2007) and least in black females (8.0% in 2007) with the largest increase seen in black males (1.2% in 2000 to 10.5% in 2007). Personal and physician care factors increased slightly in all race/gender groups. A large disparity was maintained between black and white individuals with diabetes in vaccinations over the study time period. In these data, the disparities in obesity, HTN, and dyslipidemia among individuals with diabetes decreased. Racial disparities appear to be narrowing, due to greater increases in lower-risk population rates rather than decreases in higher-risk population rates. [Diabetes Initiative of South Carolina]

068 A Bayesian Analysis of Recurrent Events Data with Dependent Termination: An Application to a Heart Transplant Problem, Bichun Ouyang1, Debajyoti Sinha2, Elizabeth H Slate1, Adrian B Van Bakel3; 1Biostatistics, Bioinformatics, and Epidemiology, MUSC, 2College of Arts & Sciences, Statistics, Florida State University, 3Marine Biomedicine and Environmental Sciences, MUSC.

Abstract not available.

069 The Functional Potential of Microbial Communities Associated with the Healthy and Diseased Coral, Montastrea Faveolata, Nikoloe E Kimes1, Joy D Van Nostrand2, Jizhong Zhou3, Ernesto Wei4, Pamela J Morris5; 1 Marine Biomedicine and Environmental Sciences, MUSC, 2Botany and Microbiology, University of Oklahoma, 3Marine Sciences, University of Puerto Rico-Mayaguez, 4Cell Biology and Anatomy, Marine Biomedicine and Environmental Sciences, MUSC.

Microbial communities are ubiquitous across ecosystems and often live symbiotically within eukaryotic organisms. For example, the human gut houses an abundant and diverse population of microorganisms essential for digestion and metabolism. Moreover, variations in the human gut microbiome are thought to play a role in human health by influencing disease etiology. Likewise, coral-associated microbial communities are increasingly recognized as important components of the coral holobiont that influence coral health; however, few studies directly address the functional role of these communities. We hypothesize that variations between the phylogenetic structure of coral-associated microbial communities found in healthy and diseased corals results in a shift of functional potential associated with the microbiome. In the present study, we examine the functional potential of the coral-associated microbial community found in the surface mucopolysaccharide layer (SML) and tissue of a Caribbean coral, Montastrea faveolata. The samples were collected from visually healthy and yellow band (YB)-infected colonies off the coast of La Parguera, Puerto Rico. Community DNA was used in the functional gene array, GeoChip 2.0, which targets 10,000 functional genes involved in biogeochemical processes. We identified 6732 genes present in the microbial communities associated with M. faveolata. The relative percentage of genes found in each biogeochemical process surveyed for all samples were similar and are as follows: carbon degradation/fixation (16.5%, +/- 1.04), dissimilatory sulfate reduction (7.2%, +/- 0.73), metal homeostasis (21.15%, +/- 1.33), methane generation and oxidation (3.45%, +/- 0.37), nitrogen processing (17.57%, +/- 0.97), and organic chemical degradation (31.75%, +/- 1.16). Interestingly, principal component and cluster analyses revealed a clear distinction between the microbiome associated with SML and tissue, as well as, trends distinguishing healthy and YB-infected M. faveolata. Our data suggests that the microbial communities associated with healthy and YB-infected M. faveolata use different mechanisms to fulfill similar functional niches. [-National Science Foundation Biodiversity Surveys and Inventories Grant (DEB0516347) to PJM -National Science Foundation Graduate Research Fellowship to NEK -The efforts of JZ and JVN were supported by The United States Department of Energy under the Genomics: GTL program through the Virtual Ins]

070 Influence of Selenium and Mercury Chemistries on the Progression of Cardiomyopathy in Pygmy Sperm Whales, Kogia breviceps, Colleen E Bryan1, Gregory D. Bossart1, W. Clay Davis1, Guillaume Ballilhaut1, Carola Neumann2, Wayne E McFee3, Steven Christopher4; 1Marine Biomedicine and Environmental Sciences Center, MUSC, 2Division of Marine Mammal Research and Conservation, HBOI, FAU, Fort Pierce, FL, 3National Institute of Standards and Technology, Hollings Marine Laboratory, 4Cell and Molecular Pharmacology and Experimental Therapeutics, MUSC, 5NOAA National Ocean Service, CCEHBR.

Abstract not available.

071 The Search for Antibiotics in Bacteria Associated with the Surface Mucopolysaccharide Layer of the Coral Pseudopterogorgia Americana, Maria I Vizcaino1, Katherine Williams1, Peter D.R. Moeller2, Pam J Morris3; 1MBES, MUSC, Hollings Marine Laboratory, 2Hollings Marine Laboratory, 3NOAA National Ocean Service, Hollings Marine Laboratory, MBES, MUSC, 4Cell Biology and Anatomy, MBES, MUSC, Hollings Marine Laboratory.

Antibiotics, an important defense against pathogenic bacteria, are most often microbial natural products or their analogs. Due to the increased emergence of antibiotic-resistant bacteria, the search for novel antibiotics has prompted research in different ecosystems, including coral reefs and the diverse microbial community found in the coral surface mucopolysaccharide layer (SML). Degradation of the coral habitats worldwide increases the urgency to characterize their associated microbial communities that might produce novel antibiotics due to their suggested chemical defense role against pathogens. In our studies, we have been characterizing the chemical ecology of the microbial community in the gorgonian coral, Pseudopterogorgia americana. We hypothesize that P. americana SML-associated bacteria produce antibiotics against known human and coral pathogens. For these studies, we first conducted an anti-microbial assay on 142 bacteria isolated from P. americana's SML using seven test strains known to be human or coral pathogens. Our results showed that 70% (99/142) of the coral isolates inhibited at least one test strain. One coral isolate, with 99% 16S rDNA similarity (1200 b.p.) to
Pseudovibrio spp., demonstrated antibiotic potential against all seven test strains. To further study it, the isolate was mass cultured and extracted using dichloromethane and methanol. The methanol extract, which inhibited Gram-positive Bacillus subtilis and Gram-negative Vibrio harveyi and V. corallilyticus, was purified using high performance liquid chromatography. The bioassay-guided fractionations suggest the presence of at least two antibiotics, one inhibiting Gram-negative and another inhibiting Gram-positive bacteria. Work is being conducted to isolate, purify, and structurally characterize any novel antibiotics using chromatographic and spectrometric techniques, and nuclear magnetic spectroscopy. Pseudovibrios have been previously isolated from marine sponges but are not widely studied for production of antibiotics. These results highlight the potential of P. americana and other corals as sources of bacteria to investigate potential for the production of bioactive natural compounds. [South Carolina Sea Grant, National Ocean Service (NOS), NIH's Initiative for Maximizing Student Diversity, and the National Science Foundation Biodiversity Surveys and Inventories Program]

072 Celastrol, an Antioxidant and Anti-Inflammatory, Induces the Heat Shock Response and Inhibits Aminoglycoside-Induced Inner Ear Hair Cell Death, Shimon P Francis1, Carlene S Brandon1, Fu-Shing Lee2, Lisa L Cunningham1; 1Pathology and Laboratory Medicine, MUSC, 2Otolaryngology – Head and Neck Surgery, MUSC.

Aminoglycosides are expensive and effective in the treatment of bacterial infections, but as a side effect can cause death of mechanosensory hair cells of the inner ear, resulting in irreversible hearing and balance disorders. Aminoglycoside-induced hair cell death is associated with the induction of apoptotic signaling pathways, including JNK phosphorylation, cytochrome c release from the mitochondria, and activation of caspases -9 and -3. In addition, treatment with aminoglycosides has been shown to result in a spike in the formation of reactive oxygen species (ROS). Our previous work has shown that heat shock inhibits aminoglycoside-induced hair cell death in the adult mouse utricle in vitro. Heat shock leads to the robust upregulation of several heat shock proteins in mouse hair cells, including HSPs -27, -70, and -90. The mechanism(s) by which HSPs inhibit aminoglycoside-induced hair cell apoptosis are unknown. A recent screen for molecules that induce the heat shock response resulted in identification of celastrol, a triterpene used in Chinese herbal medicine, as a potent inducer of the heat shock response (Westerheide et al. 2004 J Biol Chem. 279 (53):56053-60.). Celastrol has also been found to have antioxidant and anti-inflammatory properties. We examined the effect of celastrol on aminoglycoside-induced hair cell death and found that treatment with celastrol results in robust upregulation of Hsp70 and Hsp32. In addition, celastrol resulted in significant inhibition of aminoglycoside-induced hair-cell death. Utricles were cultured in 1.5 µM celastrol for 3h and allowed to recover in culture media for 5h. Utricles were then exposed to 1 mM, 2 mM, 3 mM, 4 mM, or 5 mM neomycin for 24h. Neomycin significantly reduced hair cell viability (t-test, p<0.05, n=20). Celastrol inhibited neomycin-induced hair cell death across the neomycin dose-response curve (Two-way ANOVA, F1,39 = 13.12, p<.001, n=25). These data suggest that induction of heat shock proteins and/or antioxidants may represent a viable approach to clinical prevention of aminoglycoside-induced hair cell death and hearing loss. Heat shock factor-1 (Hsf-1) is the major transcription factor that regulates Hsp induction in cells. We have used Hsf-1/- mice to examine whether Hsp induction is necessary for the protective effect of celastrol. The protective effect of celastrol was partially retained in utricles from Hsf-1/- mice (t-test, p< .05, n=20). These data indicate that other, possibly antioxidant, mechanisms are involved in celastrol-mediated protection against aminoglycoside-induced hair cell death. [This work was supported by NIH R01 and NIH/NCRR extramural research facilities construction (C06) grants C06 RR015455 and C06 RR14516 from the Extramural Research Facilities Program of the National Center for Research Resources, and Initiative for Maximizing Student Diversity (IMSD) Program.]

073 Autocrine TGF-beta Signaling Regulates PP2A Levels in SSc Fibroblasts, Hazitha Samuel1, Andreea M Bujor2, Faye Hant3, Maria Trojanowska2; 1MCBP, MUSC, 2Medicine, Rheumatology, MUSC, 3Medicine, MUSC.

Scleroderma (SSc) is an autoimmune disease of the connective tissue that is characterized by deposition of excess collagen in skin and internal organs, leading to tissue fibrosis. During this process, fibroblasts are altered and behave differently from normal fibroblasts by producing excess collagen and other ECM proteins. The pro-fibrotic cytokine TGF β is proposed to play a major role in the development of the SSc phenotype. Previous studies have shown that SSc fibroblasts are also characterized by higher levels of phosphorylated Akt and Erk and increased resistance to apoptosis. Protein Phosphatase 2A is a major serine-threonine phosphatase, involved in dephosphorylation of Akt, Erk and other signaling molecules. Since SSc fibroblasts show constitutive activation of Akt and Erk signaling pathways, the purpose of the present investigation was to determine whether PP2A is dysregulated in SSc fibroblasts and could contribute to the SSc phenotype. In order to examine the role of PP2A in SSc fibroblasts we tested levels of PP2A both in vivo (IHC analysis of patient skin biopsies) and in vitro (qPCR and Western analysis of cultured SSc fibroblasts). These experiments show for the first time that PP2A expression levels are decreased in SSc fibroblasts at the protein and mRNA levels. We observed that normal dermal fibroblasts stimulated with TGF-beta showed decreased PP2A levels at the mRNA and protein levels suggesting that PP2A is regulated by TGF-beta signaling. Since autocrine TGF-beta signaling is constitutively activated in SSc fibroblasts, and is responsible for maintenance of the SSc phenotype, we next examined whether autocrine TGF-beta signaling could contribute to PP2A down-regulation seen in SSc fibroblasts. To determine whether TGF-beta signaling is responsible for the decreased levels of PP2A in SSc fibroblasts, we blocked autocrine TGF-beta signaling using soluble recombinant TGF-beta receptor II (SRII), which binds TGF-beta ligand, preventing it from activating TGF-beta signaling. SSc dermal fibroblasts treated with SRII showed at least partial restoration of PP2A levels. These studies suggest that PP2A is under the regulation of TGF-beta signaling and decreased PP2A levels in SSc may be a result of constitutively activated autocrine TGF-beta signaling in SSc fibroblasts.

074 Proportional Odds Model for Design of Dose Finding Clinical Trials with Ordinal Toxicity Grading, Emily M Van Meter, Dipankar Bandyopadhyay, Elizabeth Garrett-Mayer; Biostatistics, Bioinformatics, and Epidemiology, MUSC.

Currently there are many dose finding clinical trial designs including the continual reassessment method and the standard 3 + 3 design that dichotomize toxicity based on pre-specified dose-limiting criteria. Since phase I trials tend to have a small sample size, much information is lost by not accounting for different toxicity grades seen in a trial. This study aims to extend the continual reassessment method to include ordinal toxicity outcomes using the proportional odds model and to compare the results with the traditional CRM design. This proposed
design incorporates toxicity grades 1 and 2 not currently considered in the standard designs while also allowing a life-threatening toxicity sometimes seen in a phase I trial to be weighted more than a less severe toxicity. A simulation study using the statistical package R shows that the proposed proportional odds CRM does as well or better than the standard CRM while incorporating more toxicity information. We also prevent a sensitivity analysis of the new method comparing various initial weights, sample sizes, and cohort sizes. These findings suggest that it is beneficial to incorporate ordinal toxicities into dose finding trial designs, and future studies will compare this proposed design to other phase I trial designs and will include writing an R library so that this new design can be freely accessible to other biostatisticians for use in future phase I trials.

075 Cardiovascular Risk Factors and Arterial Stiffness: An Assessment of Noninvasive Measurements of Arterial Compliance, Andrea D Boan1, William K Mountford1, Daniel T Lackland2, 1Biostatistics, Bioinformatics, and Epidemiology, MUSC, 2Medicine, Biostatistics, Bioinformatics, and Epidemiology, MUSC. Abstract not available.

076 Evaluation of Genomewide Association Study Results Through Development of Ontology Fingerprint, Lam C Tsoi1, Michael Boehnke*, Jim W Zheng1; Biostatistics, Bioinformatics, and Epidemiology, MUSC, Medicine, Biostatistics, Bioinformatics, and Epidemiology, MUSC. Abstract not available.

077 Afferents That Regulate Lateral Hypothalamic Orexin/Hypocretin Neurons During Cocaine Conditioned Place Preference, G C Sartor, G Aston-Jones; Neurosciences, MUSC. Abstract not available.

An increasing amount of evidence suggests that lateral hypothalamic (LH) orexin neurons are importantly involved in reward and addiction. In particular, our lab has shown that LH orexin afferents to the ventral tegmental area (VTA) are Fos-activated by conditioned stimuli associated with drugs or food (Harris et al 2005; Harris et al. 2007), and that chemical stimulation of LH orexin neurons or injection of orexin in the VTA reinstated an extinguished morphine preference (Harris et al. 2005). However, the circuitry that regulates orexin neurons during reward seeking behaviors remains unknown. Here we investigated the inputs that gate the activation of LH orexin neurons during cocaine conditioned place preference. Methods: Sprague-Dawley male rats (325-350 g) received a unilateral microinjection of the retrograde tracer cholera toxin b (CTb) in the LH orexin field (30nl). One week later, animals were subjected to cocaine or saline conditioned place preference (CPP). After the CPP test (drug-free) rats were perfused with 4% PFA, and the whole brain was sectioned and stained for c-Fos and CTb. The accuracy of the CTb injection was verified, and only rats with CTb injections in the orexin field were further analyzed. CTb injections outside of the LH but within the prefrontal/dorsomedial (PeF/DMH) orexin field were used as topographical controls to illustrate a functional dichotomy for medial vs. lateral orexin inputs. The percentage of CTb neurons that were Fos-positive in each brain region were quantified in each group. In addition, correlations between preference scores and percent of CTb neurons that were Fos-positive in each brain region were analyzed. Results: Immunohistochemical analysis revealed that the LH orexin field receives strong afferents from many brain regions (preflimbic, infralimbic, nucleus accumbens shell, amygdala, lateral septum, bed nucleus of the stria terminalis, preoptic area,) consistent with previous reports (Yoshida et al. 2006). However, only LH inputs from the lateral septum (LS) and ventral bed nucleus of the stria terminalis (vBNST) were significantly activated during the expression of cocaine CPP. Significant positive correlations were also observed between the preference score and the percentage of CTb/c-Fos double labeling in LS and vBNST. In addition, LS and vBNST afferents to the LH, rather than PeF/MH, were preferentially activated during the expression of cocaine CPP. Discussion: These data revealed that LS and vBNST afferents to the LH orexin field are activated during cocaine CPP. Using a bilateral disconnection technique, future studies will determine if these areas are necessary LH orexin inputs during the expression of cocaine CPP. References: Harris, G. C., M. Wimmer, et al. Nature 437(7058): 556-9 (2005); Harris, G. C., M. Wimmer, et al. (2007). Behav Brain Res 183(1): 43-51 (2007); Yoshida, K., S. McCormack, et al. J Comp Neurol 494(5): 845-61 (2006). [Funding was provided by NIH grants R01DA017289 and T3207288-16.]

078 Age-Related Hippocampal Dendritic Loss is Further Aggravated By Dietary Lipids, Linnea R Freeman1, Cheryl Stevens1, Vivian Haley-Zitlin2, Alfred Moore2, Ann-Charlotte Granholm3; Neurosciences, MUSC, 2Food Science and Human Nutrition, Clemson, 3Medicine, Neurosciences, MUSC. Numerous factors contribute to age-related cognitive decline including genetics, sex hormones, and environment. The focus of this study was to determine the role of a high fat diet on age-related changes to hippocampal morphology, the primary site for learning and memory. Previous studies have shown a loss of neurons, overall volume, and dendritic integrity in the hippocampus. Here, we reveal an even greater loss of dendrites in the CA1 region of the hippocampus following a short-term exposure to various high fat diets. Forty middle-aged male Fischer 344 rats were fed a 12% fat diet for 8 weeks; the animals were randomly divided into four groups and fed the following types of lipids: 12% soybean oil, 12% hydrogenated soybean oil, 10% soybean oil + 2% cholesterol, and 12% lard. Map 2 immunohistochemistry of the hippocampus from the right hemisphere of each animal revealed a much greater loss of expression in those animals fed hydrogenated soybean oil (“trans fats”), cholesterol or lard (saturated fat), compared to soybean oil (un saturated fatty acid) treatment. Further investigation suggested that this was a loss of neuronal function involving inflammation but not oxidative stress and reduced neurogenesis (as measured by hematoxylin-eosin staining, OX-6 immunoreactivity, 5-LOX immunoreactivity, and doublecortin immunoreactivity, respectively). These results indicate an important role of diet in age-related hippocampus degeneration even though a biological mechanism for these findings has not been revealed. With additional studies, the mechanisms by which these particular lipids affect brain structure and function, an area normally protected by the blood brain barrier, can be determined. This will have a major impact on treatment strategies for Alzheimer’s disease and other degenerative disorders of aging, since dietary intake has been found to play a major role in the onset and progression of these severe disorders. [Supported by AG04418, AG12122, AG023055, and AG022103.]
079 Intra-dmPFC Infusion of K252a Blocks the Suppressive Effect of BDNF on Cocaine-Seeking Behavior, Timothy W Whitfield, William Berglind, Anthony Carnell, Adrian Gomez, Ron See, Jacqueline F Mcginty; Neurosciences, MUSC.

Addictive cocaine-seeking behavior arises from persistent neuroadaptations in mesolimbic dopaminergic circuitry during acquisition of cocaine self-administration and corticostriatal glutamatergic circuitry during relapse. Neuroplasticity in these pathways can be regulated by the expression and availability of growth and neurotrophic factors such as brain-derived neurotrophic factor (BDNF). BDNF has been characterized as an essential regulator of neuroplasticity underlying learning and memory (Tyler et al., 2002), goal-oriented and motivated behaviors (Nestler and Carlezon, 2006), and addictive cocaine-seeking (Shaham & Hope, 2005). We have previously demonstrated that direct intracranial infusion of exogenous BDNF into the dorsomedial prefrontal cortex (dmPFC), an origin of glutamatergic cortico-accumbens projections, attenuates cocaine-seeking during an extinction test 6 days postinfusion and for up to 21 days in tests of cue-induced and cocaine prime-induced reinstatement of cocaine-seeking (Berglind et al., 2007). Here we aimed to determine the extent to which the attenuation of cocaine-seeking following intra-dmPFC BDNF depends upon TrkB signaling in the prefrontal cortex. Using the Trk antagonist, K252a, we have characterized the functional antagonism of BDNF’s persistent suppressive effect on cocaine-seeking behavior. Infusion of K252a 15-20 minutes prior to intra-dmPFC BDNF blocked BDNF's suppressive effect on cocaine-seeking behavior following 6 days of abstinence from cocaine-taking and in tests of cue and cocaine-prime induced reinstatement. Animals pre-infused with K252a showed a typical enhancement of cocaine-seeking in each test regardless of BDNF infusion. Nevertheless, intra-dmPFC infusion of K252a alone was not sufficient to significantly induce cocaine-seeking compared to vehicle infused controls. Future studies will aim to more specifically identify the mechanism of action of exogenous BDNF by using inhibitors of the PLC-γ, PI3K, and MAPK cascades prior to intra-dmPFC BDNF to assess the contribution of each cascade to BDNF’s suppressive effects on cocaine-seeking. This work provides further evidence that cortico-accumbens BDNF expression regulates addictive cocaine-seeking behavior in animal models of relapse. [NARC- P50-DA015369 NRSA- F31-DA023743-01]

080 Absence of Sphingosine Kinase 1 Alters Progression of TNF-alpha Induced Arthritis, DeAnna Baker1, Lina Obeid2, Gary Gilkeson3, 1Rheumatology and Immunology, MUSC, 2General Internal Medicine/Geriatrics, MUSC, Ralph H. Johnson VA Medical Center, 3Rheumatology and Immunology, MUSC, Ralph H. Johnson VA Medical Center.

Sphingolipid metabolism is critical in the development of chronic inflammatory diseases. (hTNF/SphK1−/−) will have less synovial inflammation than those mice that overexpress human TNF with functional SphK1 (hTNF/SphK1+/+). Transgenic hTNF mice were crossed with SphK1−/− mice and genotyped. The mice were observed for disease activity, while histological sections and serum were collected to evaluate disease activity and measure systemic sphingolipid levels, respectively. FLS were isolated from the knee joints of WT and SphK1−/− mice, cultured, and stimulated with TNF. hTNF/SphK1+/+ mice had significantly decreased arthritis scores from hTNF/SphK1−/− mice. The serum levels of S1P in hTNF/SphK1+/+ mice also differed significantly from hTNF/SphK1−/− mice. Histological sections showed less inflammatory infiltrates and preservation of the joint space of hTNF/SphK1+/+ mice compared to hTNF/SphK1−/− mice. FLS, stimulated with TNF alpha, from SphK1−/− mice produced less PGE2 than FLS from SphK1+/+ mice. Genetic deletion of SphK1 significantly delays progression and severity of hTNF induced arthritis. Synovial proliferation and inflammatory infiltrate are both decreased in hTNF/SphK1−/− mice. Lack of SphK1 results in decreased PGE2 production by synoviocytes in response to TNF alpha. Therefore, inhibiting SphK1 is a potential novel therapeutic agent for treatment of inflammatory arthritis. [R01GM062887 from the National Institute Of General Medical Sciences and a grant from the ACR REF]

081 Sphingomyelin Synthase: A Novel Regulator of Bcr-abl Mediated Tumorigenesis, Tara Burns, Chiara Luberto; Biochemistry, MUSC.

Sphingomyelin synthase (SMS) is an important class of enzymes regulating sphingolipid metabolism. In particular, SMS transfers the phosphorycholine moiety from phosphatidylcholine (PC) onto ceramide forming sphingomyelin and diacylglycerol. Because of the ability to modulate in opposing directions the level of ceramide, a negative regulator of cell growth, and DAG, a well-established mitogenic factor, SMS activity has been proposed to play a significant role in the regulation of those processes associated with aberrant cell proliferation. Through analysis of a variety of different cell lines, a chronic myelogenous leukemia/Bcr-abl positive cell line (K562) was identified displaying a dramatic upregulation of SMS activity. Furthermore, stable transfection of Bcr-abl causes a dramatic increase of SMS1 activity, expression, and translation. Functionally, inhibition of SMS activity in blast crisis cells significantly reduces cell proliferation and causes a change in morphology consistent with differentiation. Further studies will focus on inhibition of SMS as a possible method of sensitizing blast cells to chemotherapy. [COBRE Grant and Abney Grant]

082 Performance of Statistical Methods for Transitioning From a Three-Armed Superiority Trial to a Two-Armed Non-Inferiority Trial When Superiority of a Single Treatment Arm is Determined Early, Jordan J Elm, Yuko Y Palesch; Biostatistics, Bioinformatics, Epidemiology, MUSC.

Background: With group sequential multi-armed clinical trials, there is an increased chance of finding a winning treatment before the planned end of the trial (e.g. before all patients have completed follow-up) because either of the treatments could show overwhelming efficacy at an interim analysis. Both adaptive and non-adaptive testing methods can allow for transitioning from a 3-armed superiority trial (e.g., active treatment A, active treatment B, and placebo) to a 2-armed non-inferiority trial when efficacy of one treatment arm (A) relative to the placebo arm is determined at an early interim analysis. Methods: Monte Carlo Simulation was used to compare the following statistical methods: (1.) cumulative t-test with the data
pooled across stages (non-adaptive); (2.) Fisher’s adaptive combination test; and (3.) Weighted-Inverse Normal adaptive combination test. The power and average sample size were compared with and without sample size inflation based on interim information. Results: Empirical power was highest for the cumulative t-test. Adaptive approaches achieved nominal power for the joint hypothesis, but not for the individual non-inferiority hypothesis alone. Conclusions: Applying a standard t-test and committing upfront to a larger sample size will maximize power to declare treatment B non-inferior to A. The adaptive methods allow for a possible reduction in total sample size but have reduced power for the individual non-inferiority hypothesis (compared to non-adaptive approach). [NIH (National Institute of Neurological Disorders and Stroke), U01NS043127]

083 Utilization of Beta Regression in Multivariable Analysis of Infarct Volume Measured By Diffusion-Weighted Magnetic Resonance Imaging After Acute Ischemic Stroke, Christopher J Swearingen, Joyce S Nicholas; Biostatistics Bioinformatics, and Epidemiology, MUSC.

Introduction – Diagnostic assessment of acute ischemic stroke has greatly improved with the advancement of imaging technologies. The volume of the stroke infarct, the necrotic brain matter not receiving blood flow, can also be measured. However, the relationship between infarct volume and clinical outcome remains unclear. Statistical assessment of this relationship is difficult due to the analytical challenges presented by the underlying distribution of volumes, which is ill-behaved, characterized as a skewed boundary mass distribution. Beta regression may provide an analytical solution to this problem. Method – Medical records for all ischemic stroke patients admitted to the Medical University of South Carolina Hospital from March 2002 to March 2006 were abstracted. Due to the skewed distribution of the infarct volumes, a multivariable logistic regression was developed, defining the dependent variable as a dichotomy based upon the median of the stroke volume(1). Given that dichotomizing volume causes a loss of information, results from the final logistic model were reassessed using beta regression, a method based on the highly flexible beta distribution that can model volume as a continuous variable. Logistic and beta regression models were compared to assess if beta regression more adequately modeled the association between baseline measurements and infarct volume. Results – The infarct volumes were adequately described as a beta distributed variable. The beta regression model confirmed the original results of the logistic model. Additionally, the estimation of two covariates in the original logistic model, Prior Stroke by Imaging (p=0.059) and Atrial Fibrillation (p=0.068), was improved in the beta regression model (p=0.003 and p=0.001 respectively). Conclusion – Beta regression can be utilized to model ill-behaved data and improved upon nonparametric methods for this dataset. Reference – (1)Nicholas JS, Swearingen CJ, Thomas JC, Rumboldt Z, Tumminello P and Patel SJ. “The effect of statin pretreatment on infarct volume in ischemic stroke.” Neuroepidemiology 2008; 31:48-56. [This work is supported by NINDS/NIH Biostatistics Training with Application to Neuroscience Grant 1 T32 NS48007-01A1 (PI: Yuko Y. Palesch, Ph.D.) Data were originally collected under an independent research grant 2004-0361 from Pfizer (PI: Joyce S. Nicholas, Ph.D.)]
lungs of tumor-bearing mice or normal controls and examined for secretion of immune modulatory products. It was observed that endothelial cells isolated from tumor-bearing lungs had elevated secretion of the immune suppressants PGE2, IL-6, IL-10 and VEGF as compared to endothelial cells isolated from the lungs of normal controls. Tumor-isolated endothelial cell also had diminished production of the immune stimulatory product IL-12. Conditioned media from endothelial cells isolated from tumor-bearing lungs were found to suppress CD8+ T-cell IFN-gamma and CD4+ T-cell IL-2 production in response to anti-CD3 stimulation. Studies were also conducted to determine if inhibition of VEGF signaling could block the in vivo induction of suppressive endothelial cells. Treatment of mice with the VEGF receptor tyrosine-kinase inhibitor, SU5416, blocked tumor-induced increases in endothelial cell production of immune suppressive products compared to control treatments. SU5416 also prevented tumor-derived products from inducing endothelial cells to suppress T-cell functions. Taken together, these studies provide support for the use of VEGF targeting therapies as an immunotherapeutic agent to block induction of suppressive endothelial cells isolated from tumor-bearing lungs. This work was supported by the Research Service of the Department of Veteran’s Affairs and by grants R01CA85266 and R01CA97813 from the National Institutes of Health to MRIY.

087 The Involvement of Calpain in CD4+ T Cell Bias, Jonathan T Butler1, Nathan L Banik2, Craig C Beeson3; 1MCBP, MUSC, 2Neurosciences, MUSC, 3MCBP and Pharmaceutical Sciences, MUSC.

089 Locus Coeruleus Degeneration in a Mouse Model for Down Syndrome: A Potential Stimulus for Neuroinflammation, Jason P Lockrow1, Heather A Boger1, Ann C Granholm2; 1Neurosciences, MUSC, 2Neurosciences and Center on Aging, MUSC.

Individuals with Down syndrome (DS), or trisomy 21, develop the neuropathological hallmarks of Alzheimer’s disease (AD), including amyloid deposition, cholinergic neuron degeneration, and early-onset dementia. A mouse containing a partial trisomy of murine chromosome 16, the Ts65Dn mouse, expresses a triplication of many of the genes implicated in DS pathology. These mice recapitulate several of the salient features of DS, including cholinergic neuron loss and age-dependent memory dysfunction. In addition, there are indications that Ts65Dn mice exhibit attentional and anxiety-related deficits, which led us to assess morphological alterations in noradrenergic neurons of the locus coeruleus (LC) in this model. LC neurons, which project heavily to cortical and hippocampal regions and may modulate inflammatory gene expression, show premature degeneration in several neurodegenerative diseases, including DS and AD. The present study analyzed LC neurons in the Ts65Dn mouse and assessed whether changes in the LC may contribute to increases in neuroinflammation. We found a depletion of noradrenergic neurons at 10 months in Ts65Dn mice, primarily in the rostral LC. In addition, the hippocampus of Ts65Dn mice at this age exhibited morphological changes to microglia and astrocytes consistent with inflammation, as well as increased gene expression of inflammatory markers such as iNOS and COX-2. We are currently evaluating the inflammatory response to an LC lesion in Ts65Dn mice. These changes to the noradrenergic system, which appear to precede the rise of inflammation in Ts65Dn mice, may influence the progression of pathology that results in the impairment of brain function in DS. [Supported by NIH Grant AG2122 and the Sie Foundation for the study of Down syndrome.]

088 The Role of NK Cells in CCL22-mediated Treg Recruitment Toward Lewis Lung Carcinoma, Adam W Mailloux1, M Rita I Young2; 1Microbiology and Immunology MUSC, 2Research Service, Ralph H. Johnson VA Medical Center, Otolaryngology, MUSC.

Regulatory T-cells (Tregs) are one of the most potent mediators of tumor induced immune suppression. Their levels are significantly increased in most cancer types, including mice bearing Lewis Lung Carcinoma (LLC). Chemokines that bind with high affinity to the chemokine receptor CCR4 have been shown to induce selective Treg migration. Here we use a combination of ELISA and transwell migration techniques to measure the levels of these chemokines and find that CCL22 is secreted in large amounts by LLC-bearing lungs. Moreover, this chemokine induced the selective recruitment of Tregs toward media conditioned with LLC-bearing lung tissue. Interestingly, CCL22 is not produced by the tumor itself, but rather is upregulated by some other component of the microenvironment. Using a series of immunomagnetic fractionations coupled with FACS, we identify resident NK cells as the major producers of CCL22, and indeed when NK cells are depleted from ex-vivo lung dissociates levels of CCL22 drop accordingly. However, when NK cells are depleted in-vivo, and LLC is grown in their absence, CCL22 and Treg levels paradoxically rise. This suggests that not only do NK cells play a positive role in the regulation of CCL22 secretion, but that they represent a huge negative regulatory element in the tumor microenvironment, which has a large impact on selective Treg recruitment and subsequent tumor-induced immune suppression. [The work presented was funded by the Medical Research Service of the Veteran’s Affairs and by NIH grants MRIY CA97813 and CA8566]
A major feature of the alcohol withdrawal syndrome that ensues following cessation of excessive, long-term alcohol consumption is CNS hyperexcitability that may culminate in life-threatening seizures. Among a large number of neuroadaptive changes in brain, evidence suggests that Gli1 cell-line Derived Neurotrophic Factor (GDNF) may play a role in withdrawal seizures. Previous studies have demonstrated that seizures can alter brain GDNF levels and that GDNF activity in the CNS may serve to modulate seizure susceptibility and/or expression. The present studies were conducted to examine the potential role of GDNF in mediating and/or modulating alcohol withdrawal-related seizure activity in a mouse model of dependence. The first set of experiments examined whether brain regional changes in GDNF protein levels occur following chronic alcohol exposure, withdrawal, and/or alcohol withdrawal-induced convulsions. Adult male DBA/2J (“seizure sensitive”) and C57BL/6J mice (“seizure resistant”) inbred mice were exposed to either 64-h continuous alcohol vapor (or control air) in inhalation chambers. Brain samples (cortex, hippocampus, striatum, and cerebellum) were collected and GDNF protein levels were determined by ELISA. The second set of experiments examined whether alterations in brain GDNF levels influence the severity of alcohol withdrawal-induced convulsions. Adult GDNF deficient (+/-; ~40% reduction in CNS GDNF) and wildtype mice were tested for withdrawal convulsions following chronic alcohol exposure. Additionally, withdrawal convulsions were examined in C57 and DBA mice given 1 mg/kg cabergoline (shown to increase CNS GDNF). Results indicate that alcohol withdrawal-induced convulsions markedly reduced GDNF levels in DBA mice 8-h following seizure expression. Additionally, reducing brain GDNF levels results in significantly increased seizure severity, while increasing GDNF levels lessened seizure severity. These data suggest that brain GDNF may play a role in both response to and prevention of alcohol withdrawal-related seizure activity. [This research was generously supported by the Department of Veterans Affairs, the Ralph H. Johnson VA Medical Center, and the Charleston Alcohol Research Center. Supported by NIAAA grants AA10761, AA013885, training grant AA007474, NIA grant AG023630, and VA Medical Research.]

093 Beta3 Integrin-mediated Ubiquitination for NFkappaB Transcription is Necessary to Maintain Compensated Hypertrophic Growth. Rebecca K Johnston, Sundaravadivel Balasubramanian, Catalin F Baicu, Michael R Zile, Dhandapani Kuppuswamy; Medicine, Cardiology, MUSC and the Ralph H. Johnson VA Medical Center.

Hypertrophic growth is initially compensatory but eventually culminates in heart failure by a poorly understood mechanism. Identifying the molecular mechanisms activated in compensatory hypertrophy that are absent during decomposition will provide molecular targets to eventually prevent the development of heart failure. We have previously shown enhanced ubiquitination (Ub) near intercalated discs of cardiomyocytes during the early growth period of pressure overload (PO) hypertrophy. In this study, we tested the upstream signal for this Ub, whether this enhanced Ub contributes to survival signaling in early PO, and if loss of this mechanism could lead to failure. By utilizing a beta3 integrin knockout mouse for in vivo pressure overload by TAC and cultured cardiomyocytes from the beta3 KO in vitro with the integrin-activating peptide RGD, we demonstrate beta3 integrin-mediated Ub during PO hypertrophy is necessary to maintain ventricular function. Prosurvival transcription of the E3 ligase, BIFkappaBsignaling proceeds by initiation of cIAP1. When this mechanism is in place, as in the beta3 KO mice, there is an increase in cardiomyocyte death, shown by TUNEL, and decreased ventricular function during PO, measured by echocardiography. This is the first study to show how Ub is required for hypertrophy and that beta3 integrin is required for compensatory hypertrophic growth. Thus, we reveal a potential mechanism for cardiomyocyte survival necessary to preclude...
heart failure. [These studies were supported by Merit awards from the Research Service of the Department of Veterans Affairs, by Program Project Grant HL-48788 from the NIH, and by the AHA 0615468U predoctoral fellowship for Rebecca Johnston.]

094 *Soat1* is a Regulatory Target of *Hoxc13* in Both the Hair Follicle and Brain, Christopher S Potter1, Kathleen A Potter2, Nathanael D Pruett3, Micheal J Kem4, Alan R Godwin5, John P Sundberg6, Alexander Avgulewitsch7, Medicine, MUSC, *Neurosciences, MUSC, *Medicine, MUSC, *Cell Biology and Anatomy, MUSC, *Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, *The Jackson Laboratory, Bar Harbor, ME.

Abstract not available.

095 The Role of ALK1 and Endoglin Signaling in Scleroderma Fibrosis, Erin Morris1, Andreea Bujor1, Peter ten Dijke2, Maria Trojanowska1; 1Cell Biology and Anatomy, MUSC, *Neurosciences, MUSC, *Medicine, MUSC, *Cell Biology and Anatomy, MUSC, *Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, *The Jackson Laboratory, Bar Harbor, ME.

Objective: Scleroderma (SSc) is a disease of the connective tissues characterized by excessive production of extracellular matrix proteins (ECM). Transforming growth factor beta (TGF-β) is an inducer of ECM proteins in fibroblasts. Previous studies indicate that TGF-β signaling is activated in SSc via upregulation of the TGF-β type I receptor, ALK5, and pSmad1 (Pannu et al., JBC 2007 282(14)10405-10413, Arthr & Rheum 2008 58(8)2528-2537). In endothelial cells, TGF-β signals through two type I receptors and their interacting Smad proteins; ALK5 and pSmad2/3 or ALK1 and pSmad1/5/8. Expression of a type III receptor, endoglin, promotes signaling through ALK1. The goal of this study is to determine the role of endoglin and ALK1 signaling in the fibrotic phenotype of SSc fibroblasts. Methods: This study used adult SSc fibroblasts from skin biopsies and matched normal controls (NS). We measured mRNA levels of ALK5, ALK1, and endoglin using qRT-PCR. Protein expression of ALK5, ALK1, endoglin, collagen I, connective tissue growth factor (CCN2), pERK1/2, ERK1/2, pSmad1, and Smad1 was measured with western blotting. Endoglin expression was inhibited in NS and SSc fibroblasts using a siRNA adenovirus. Constitutively active ALK1 (caALK1) was overexpressed using adenovirus. Results: Data analysis showed that increased levels of ALK5 correlate with increased levels of endoglin in SSc fibroblasts. Downregulation of endoglin in NS fibroblasts led to an increase in ECM proteins. In contrast, downregulation of endoglin in SSc fibroblasts led to a decrease in ECM proteins suggesting that endoglin is a positive regulator of ECM in SSc. Consistent with this observation, overexpression of caALK1 in NS fibroblasts led to increased levels of pSmad1, activation of pERK1/2, and increased expression of collagen I and CCN2. Conclusions: Endoglin plays opposite roles in matrix gene regulation in NS and SSc fibroblasts. This data further supports the activation of ALK5/ALK1 signaling in SSc and demonstrates that endoglin is an important component of the TGF-β receptor complex. Overexpression of caALK1 in NS fibroblasts is sufficient to reproduce the main profibrotic features of SSc, including elevated ECM production. [NIH RO1 AR049459-05]

096 Retinoids Regulate TGFβ Signaling At the Level of Smad2 Phosphorylation and Nuclear Accumulation, Loretta L Hoover1, Elizabeth G Burton1, Megan L O'Neil1, Bonnie A Brooks2, Steven W Kubalak1; 1Cell Biology and Anatomy, MUSC, *Medicine, MUSC.

Indirect regulation of transforming growth factor (TGF)-β signaling by retinoids occurs on a long-term timescale, secondary to transcriptional events. Studies by our group show loss of retinoid X receptor alpha (RXRa) results in increased TGFβ2 in the midgestational heart, which may play a role in the cardiac defects seen in this model. Acute and direct interactions between retinoid and TGFβ signaling, however, are not clearly understood. Treatment of dispersed hearts and NIH3T3 cells for one-hour with TGFβ and retinoids (dual treatment) resulted in increased phosphorylated Smad2 and Smad3 when compared to treatment with TGFβ alone. Of all dual treatments, those with the RXR antagonist Bexarotene, resulted in the highest level of phosphorylated Smad2, a 7-fold increase over TGFβ2 alone. Additionally, during dual treatment phosphorylation of Smad2 occurs via the TGFβ type I receptor but not by increased activation of the receptor. As loss of RXRa results in increased levels of Smad2 phosphorylation in response to TGFβ treatment and since nuclear accumulation of phosphorylated Smad2 and Smad2/3-driven transcription are decreased during dual treatment, we propose that RXRa directly regulates the activities of Smad2. These data show retinoid signaling influences the TGFβ pathway in an acute and direct manner that has been unappreciated until now. [This work was supported by NIH Grant Number C06 RR018823 and C06 RR015455 from the Extramural Research Facilities Program of the National Center for Research Resources, NIH T32 HL07260 (LLH) and NIH/NHLBI R01 HL83116 (SWK).]

097 Sphingomyelin Synthases Regulate Production of Diacylglycerol At the Golgi and Protein Trafficking to the Cell Surface, Subathra Marimuthu1, Maristella Villani1, Yeong-Bin Im1, Young Choi1, Paola Signorelli1, Maurizio Del Poeta1, Chiara Luberto1; 1Biochemistry and Molecular Biology, MUSC, *Laboratory of Biochemistry and Molecular Biology, San Paolo University Hospital, School of Medicine.

Sphingomyelin synthase (SMS) is a class of enzymes that produces sphingomyelin by transphosphorylating serine onto ceramide. Phosphatidylcholine is believed to be the phosphocholine donor of the reaction with consequent production of diacylglycerol (DAG), an important bioactive lipid. In the present study, by modulating SMS1 and SMS2 expression, the role of these enzymes on the elusive regulation of DAG was investigated. Because we found that modulation of SMS1 or SMS2 reduced the localization of the DAG-binding protein, the fluorescently labeled conventional C1 domain enhanced in its DAG binding activity was used to probe subcellular pools of DAG in the cell. By using this approach, we found by confocal microscopy and subcellular fractionation, that modulation of SMS1 and, to a lesser extent, of SMS2 affected the formation of DAG at the Golgi apparatus. Similarly, down-regulation of SMS1 and SMS2 reduced the localization of the DAG-binding protein, protein kinase D (PKD) to the Golgi. Since PKD recruitment to the Golgi has been implicated in cellular secretion, the effect of down regulation of SMSs on transgolginetwork (TGN) to
plasmamembrane trafficking was studied. Down regulation of either SMS1 or SMS2 significantly retarded trafficking of the VSVG3-GFP reporter protein from TGN to cell surface. These results provide direct evidence that both enzymes are capable of regulating the formation of DAG in cells, that this pool of DAG is biologically active and directly implicated for the first time SMS1 and SMS2 as regulators of DAG-binding proteins in the Golgi apparatus and secretion. [This work was supported in part by the National Science Foundation/EPSCoR under grant EPS-0132573, by a Hollings Cancer Center/Medical University of South Carolina Department of Defense grant Translational Research on Cancer Control and Related Therapy (Subcontract GC-3319-05-4498CM), by NIH (Nation]

098 A Novel Signaling Pathway of Tissue Kallikrein in Promoting Keratinocyte Migration: Activation of Proteinase-Activated Receptor 1 and Epithelial Growth Factor Receptor, Lin Gao, Lee Chao, Julie Chao; Biochemistry and Molecular Biology, MUSC.

Biological functions of tissue kallikrein (TK) are mainly mediated by kinin generation and subsequent activation of the kinin B2 receptor. In this study, we investigated a potential role of TK and its signaling pathways in skin cell migration and wound healing. Herein, we show that TK promoted the migration and proliferation of cultured keratinocytes in a dose- and time-dependent manner. Inactive TK (by pretreatment with aprotinin) or kinin had no effect on cell migration. Interestingly, cell migration induced by TK was not blocked by icatibant (kinin B2 receptor antagonist) or L-NAMe (nitric oxide synthase inhibitor), indicating an event independent of kinin B2 receptor and nitric oxide formation. TK’s effect on cell migration was associated with increased phosphorylation of epidermal growth factor receptor (EGFR) and extracellular signal-regulated kinase (ERK). Cell migration, as well as EGFR and ERK phosphorylation, were blocked by inhibition of proteinase-activated receptor 1 (PAR1), protein kinase C (PKC), Src, EGFR and ERK. Moreover, TK-induced cell migration and EGFR phosphorylation were blocked by metaproteinase (MMP) inhibitor, heparin, and specific antibodies against EGFR external domain, heparin-binding EGF-like growth factor (HB-EGF) and amphiregulin (AR). Finally, local application of TK promoted skin wound healing in rats, whereas aprotinin or specific antibody to tissue kallikrein delayed healing, implicating a role of endogenous TK in wound healing. This study demonstrates a novel role of TK in skin wound healing and uncovers a new signaling pathway mediated by TK in promoting keratinocyte migration through activation of PAR1-PKC-Src-MMP pathway and HB-EGF/AR shedding-dependent EGFR transactivation. [This work is supported by National Institutes of Health grants HL-29373 and DK-066350, and C06 RR015455 from the Extramural Research Facilities Program of the National Center for Research Resources.]

099 Regulation of G-protein Signaling Pathways By AGS3 in the Neuroblastoma-Glioma Cell Hybrid NG108-15, Sukru S Oner, Joe B Blumer, Stephen M Lanier; Cell and Molecular Pharmacology and Experimental Therapeutics, MUSC.

Activator of G Protein Signaling-3 (AGS3) contains 4 G-protein regulatory (GPR) motifs each of which can serve as a docking site for Gαi-GDP free of Gβγ. AGS3 and related GPR proteins provide unexpected regulatory mechanisms for G-protein signaling systems, which are involved in diverse various cellular functions. The mechanisms by which these proteins integrate into various G-protein signaling pathways involving cell surface receptors are not fully understood. As an initial approach to address this issue, we optimized conditions for siRNA-mediated knockdown of endogenous AGS3 in the neuronal cell line NG-10815 and examined the consequences of this reduction in AGS3 on the regulation of G-protein signaling pathways regulating cAMP and ERK1/2. AGS3 protein was reduced by greater than 95% following AGS3 siRNA transfection without any change in the levels of Gαi3 or the related GPR protein GAG5/AGN. NG108-15 cells express α2-adrenergic receptors (α2-AR) coupled to G-proteins that regulate adenyl cyclase and MAP kinases. siRNA mediated knockdown of AGS3 did not alter basal cAMP or the increases in cAMP elicited by forskolin or the endogenous, Gs-coupled PGE2 receptor. α2-AR mediated increases in ERK1/2 phosphorylation were also not altered by AGS3 knockdown. Despite its clear ability to bind to Gαi proteins, these data indicate that under normal conditions with endogenous signaling components, AGS3 does not appear to influence the regulation of two typical Gi-coupled signaling pathways. These data suggest that either a additional, as yet unidentified stimuli are necessary to reveal the influence of AGS3 on G-protein coupled receptor signaling or that AGS3 and related GPR proteins function to regulate other receptor-independent signaling events that involve the “G-switch”.

100 Activation of G Protein Independent Signaling Pathways Elicits a Distinct Protein Phosphorylation Profile, Ryan T Kendall1, MiHyee Lee1, Hesham M El Shewy1, Michael G Janich2, Deirdre K K Luttrell1, Louis M Luttrell1; 1Medicine, Endocrinology, Diabetes & Medical Genetics, MUSC, 2Medicine, Nephrology, MUSC.

The octapeptide hormone angiotensin II (AngII) increases blood pressure by multiple actions in different tissues. Chronic AngII stimulation can also lead to a pathological form of cardiac hypertrophy and heart failure. These actions of AngII are mediated by G protein-coupled receptors (GPCRs). Interestingly, GPCRs are now known to exist in multiple, signal transduction-competent conformations including G protein-independent signaling pathways. Moreover, the discovery of biased agonism has revealed that these different receptor conformations can be selectively activated by extracellular ligands. For example, G protein-independent signaling functions of the angiotensin AT1a receptor, can be selectively activated by the Ang II peptide analog [Sarcosine1, Ile4, Ile8]AngII (SII). SII stimulates AT1a receptor-mediated GRK phosphorylation, β arrestin recruitment, receptor internalization, and beta arrestin-dependent ERK1/2 activation—without activating G proteins. However, the signal transduction network induced by SII and how it compares to that activated by AngII is unknown. In order to characterize this pathway, we examined the downstream targets of SII-stimulated signal transduction networks by phosphoproteomic analysis and multiplex phosphoprotein technology. SII induces both serine/threonine and tyrosine phosphorylation of the cytosolic isoform of prostaglandin E synthase, PGES3, and its interaction with beta arrestin 1. SII can also induce phosphorylation of the tumor suppressors prohibitin, I2PP2A, and p53. These studies have spurred new hypotheses about possible roles of G protein-independent pathways in the regulation of prostaglandin autocrine/paracrine endocrine function and the regulation of AT1a receptor-mediated cell cycle progression or cell fate. [This work was supported by National Institutes of Health grants NIH-HL 07260 (R.T.K.), DK55524 (L.M.L.), the South Carolina Center for Biomedical Research Excellence in Cardiovascular Disease (D.K.L.) and Department of Veterans Affairs Research Enhancement Award Program awards.]
Regulation of Activator of G Protein Signaling 3 By FERM and PDZ Domain Containing 1 (Frmpd1), Ningfei An, Joe B Blumer, Stephen M Lanier; Pharmacology, MUSC.

Abstract not available.

Effects of Null Mutation of the Gene Encoding Dysbindin-1 on Cortical Fast-Spiking Interneurons, H Trantham-Davidson1, J D Jentsch2, A Lavin3, 1Neurosciences, MUSC, 2UCLA.

Abstract not available.

Multiple Memory Systems and Extinction: Neural Inactivation of Dorsolateral Striatum Selectively Blocks Response Extinction in a Runway, Amanda Gabriele1, Mark G Packard2, 1Neurosciences, MUSC, 2Psychology, Texas A&M University.

Consistent with multiple memory systems theory, lesions of the hippocampus impair the initial acquisition of cognitive or relational memory, whereas lesions of the dorsal striatum impair the acquisition of stimulus-response habits. The new learning that underlies extinction behavior also appears to engage multiple memory systems, as neural inactivation of the hippocampus blocks latent extinction of maze runway behavior but does not affect response extinction (Gabriele & Packard, 2006). The present study examined the hypothesis that neural inactivation of the dorsolateral striatum would selectively impair response extinction in a runway. Accordingly, adult male Long-Evans rats were trained to run in a straight alley maze for food reward. Following acquisition they were placed into one of two extinction conditions. In one condition rats were allowed to run to an empty goal box (i.e. response extinction). In a second condition rats were placed into an empty goal box without making a running response (i.e. latent extinction). Prior to each daily session of extinction training, rats received intra-dorsolateral striatal infusions of either the local anesthetic bupivacaine (0.75% solution/0.5 ul), or saline. Rats receiving saline infusions displayed extinction behavior in both the response and latent conditions. In contrast, rats receiving intra-dorsolateral striatal infusions of bupivacaine extinguished normally in the latent condition, but displayed impaired response extinction. Taken together with our previous data (Gabriele & Packard, 2006), the present findings demonstrate a double dissociation of the roles of the hippocampus and dorsal striatum in runaway extinction behavior. Specifically, in a straight alley maze, the hippocampus selectively mediates latent extinction, whereas the dorsolateral striatum selectively mediates response extinction. The findings indicate that 1) The new learning that occurs during extinction can be neuroanatomically dissociated, and 2) similar to initial acquisition, the new learning that occurs during extinction can independently engage hippocampus-dependent cognitive memory and dorsal striatal-dependent habit memory. Thus, psychological and neurobiological theories of extinction behavior should employ a multiple memory systems approach that recognizes that extinction learning and memory processes are not unitary phenomena. [NSF Grant IBN-03122212]

P-Glycoprotein Inhibition and Risperidone-Induced Striatal Dopamine Release, Alejandra M Pacchioni1, Alisha Henderson1, Amanda Gabriele1, Lindsay DeVane2, Ronald E See3, 1Medicine, Neurosciences, MUSC, 2Medicine, Psychiatry and Behavioral Sciences, MUSC.

Antipsychotic drugs (APDs) are the mainstay pharmacotherapy for schizophrenia and related psychiatric disorders. While the pharmacokinetic pathways of APDs have been well defined, the role of drug transporters in the disposition and effects of APDs has not been well explored. P-glycoprotein (P-gp) has an ubiquitous expression in brain endothelial cells and plays a protective role by effluxing substrates for elimination and by limiting their accumulation in the central nervous system. Previous evidence has shown that APDs act as substrates at the P-gp transporter. Increased APD entry into the brain via blockade of the P-gp transporter may facilitate drug action on relevant receptor targets. By increasing available drug concentrations, P-gp inhibition offers a novel means of enhanced drug treatment of schizophrenia. In the current study, we utilized in vivo microdialysis to test whether P-gp is an important modulator of brain access and pharmacologic effects of the atypical APD, risperidone, on striatal dopamine (DA).
release. Male, Sprague-Dawley rats were implanted with a guide cannula aimed at the caudate-putamen. Following recovery, microdialysis probes (3 mm) were inserted and basal samples were collected at 20 min intervals for one hour. Subjects then received either 30 mg/kg of PSC833 (a selective inhibitor of P-gp) or control vehicle by oral gavage. One hour after pretreatment, rats were administered risperidone (0.01 mg/kg, s.c.). Samples were analyzed for extracellular levels of DA and DA metabolites (DOPAC and HVA) using HPLC-EC. Preliminary data indicates that risperidone alone at 0.01 mg/kg significantly increases DA release as compared to baseline or vehicle injection, with a modest increase in DA metabolite levels. Furthermore, PSC833 alone has no effect on striatal DA release. The combination of PSC833 and risperidone at the currently utilized doses does not appear to further increase DA release. Further studies will evaluate extended dose-response curves of PSC833 and risperidone. ([Supported by MH 071811])

106 Behavioral Recovery From Long-term Deleterious Methamphetamine Effects is Deficient in GDNF+/- Mice, Tara S Bender1, Emily D Denehy1, Peng Huang2, Jacqueline F McGinty1; 1Neurosciences, MUSC, 2Biostatistics, Bioinformatics, MUSC.

Methamphetamine (meth) binge treatment in young adult mice has been shown to have long-term (up to 12 months) deleterious effects on behavioral activity and striatal tyrosine hydroxylase-immunoreactivity, which is exacerbated by partial GDNF gene deletion (Boger et al. 2007). In this study, a similarly treated cohort of wild type and GDNF+/- mice was evaluated at 21 months of age to determine whether these long-term deleterious effects resolve or worsen with age. Briefly, wild-type and GDNF+/- mice received four injections of saline or methamphetamine (10 mg/kg, i.p.) at 2 hr intervals at 3-3.5 months of age. At 21 months, behavioral activity was assessed by locomotor activity and accelerating rotorod performance. Densitometric analysis of tyrosine hydroxylase (TH)-immunoreactivity was conducted in the medial and lateral striatum as well as the substantia nigra. Stereological cell counts of TH staining in the substantia nigra are in progress. Although no treatment or genotype differences were observed in TH-immunoreactivity (measured by densitometry) or locomotor activity, performance on the rotorod indicated that behavioral differences were still evident at 21 months. Meth-treated wild-type mice performed significantly better than the rotorod than saline treated mice, regardless of genotype, whereas the performance of the meth-treated GDNF+/- group was significantly poorer than all other groups. These data suggest that recovery from the neurotoxic effects of meth on TH immunoreactivity in the striatum and substantia nigra is possible, but that other systems remain affected since behavioral deficits are still present 18 months after meth exposure. ([NIDA Institutional Training Grant 5T32 07288-16 and PO1 AG023630])

107 Pharmacologic Effect of 11-cis Retinal on Cone Photoreceptor in Mouse Retinal Explants Culture, Mausumi Bandyopadhyay, Baerbel Rohrer; Neurosciences, MUSC.

Certain eye diseases like Leber Congenital Amaurosis or Retinitis Pigmentosa, degeneration of photoreceptor cells lead to blindness. Lack or reduction of 11-cis retinal, chromophore for all visual pigments, has been implicated as a contributing factor to degeneration. Lack of chromophore has been shown to lead to mislocalization of cone opsins and cone outer segment membrane proteins such as cone-transducin, prior to cell death. We established retinal explant culture to determine the pharmacological relevance of 11-cis retinal on cone cells. Rpe65-rhodopsin double knockout mouse (Rpe65-/- Rho-/-) and wild type controls were used. RPE65 is required for the generation of 11-cis retinal; elimination of rhodopsin ensures that 11-cis retinal is targeted solely to cones. Retinas from postnatal day 7 were explanted and grown for 11 days in vitro; age-matched littermates were used for comparison. Spectrophotometric assays of rhodopsin, to determine the levels of 11-cis retinal in the organ cultures, revealed age-dependent increase of 11-cis retinal in wild type organ cultures, at ~10th of the levels found in vivo. In knockout retina, cone opsins were mislocalized, cone-transducin was reduced, resulting in fewer cones per retina than in wild type controls. Addition of 11-cis retinal to the culture medium improved cone opsin trafficking to outer segment (OS), increased cone-transducin expression, targeting and cell survival. Improved trafficking of cone OS proteins by exogenous 11-cis retinal resulted in width of Rpe65-/- Rho-/- cone OS was comparable to wild type control. The observations confirm and extend our in-vivo findings, demonstrating requirement of 11-cis retinal in development of functional cone photoreceptors. The retinal explants culture will be useful to study mode of action of different drugs in a more flexible manner in controlled ex vivo condition than in vivo or in vitro cell culture studies.

108 Differential Phosphorylation Of Phosphoproteins By Repeated Amphetamine Treatment In Rat Striatum Is Mediated By Different Types Of DA Receptors, Xiandang Shi, Jacqueline F McGinty; Neurosciences, MUSC.

Abstract not available.

109 Combination Therapy of Lovastatin and Rolipram Provides Neuroprotection and Promotes Neurorepair in Inflammatory Demyelination Model of Multiple Sclerosis, Manjeet K Pintaila1, Ajaib S Paintilai1, Inderjit Singh1, Robert B Skoff2, Avtar K Singh3; 1Pediatrics, MUSC, 2Wayne State University School of Medicine, Detroit MI, 3Ralph H. Johnson VA Medical Center.

Drug combination therapies for central nervous system (CNS) demyelinating diseases including multiple sclerosis (MS) are gaining momentum over monotherapy. Over the past decade, both in vitro and in vivo studies established that statins (HMG-CoA reductase inhibitors) and rolipram (phosphodiesterase-4 inhibitor; blocks the degradation of intracellular cyclic AMP) can prevent the progression of MS in affected individuals via different mechanisms of action. In this study, we evaluated the effectiveness of lovastatin (LOV) and rolipram (RLP) in combination therapy to promote neurorepair in an inflammatory CNS demyelination model of MS, experimental autoimmune encephalomyelitis (EAE). Combination treatment with suboptimal doses of these drugs in an established case of EAE (clinical disease score ≥2.0) significantly attenuated the infiltration of inflammatory cells and protected myelin sheath and axonal integrity in the CNS. It was accompanied with elevated level of cyclic AMP and activation of its associated protein kinase A. Interestingly, combination treatment with these drugs impeded neurodegeneration and promoted neurorepair in established EAE animals (clinical disease score ≥3.5) as verified by quantitative real-time polymerase chain reaction, immunohistochemistry and electron microscopic analyses. These effects of combination therapy were minimal and/or absent with either drug alone in these settings. Together, these data suggest that combination therapy with LOV and RLP has the potential to provide neuroprotection and promote neurorepair in MS, and may have uses in other related CNS
110 Role of CXC Chemokine Ligand 13 in Squamous Cell Carcinoma Associated Osteolysis in Athymic Mice, Yuvaraj Sambandam1, Subramaniya NM Pandravuda1, Liu Xang2, James S Norris3, Srinivasan Shanmugarajan1, William L Ries1, Steave V London3, Reddy V Sakamuri2, Charles P. Darby Children’s Research Institute, 1Microbiology & Immunology, MUSC, 2Wake Forest Baptist University Medical Center, Winston-Salem, NC, 3Biostatistics, Bioinformatics, and Epidemiology, MUSC.

Head and neck squamous cell carcinoma is the most common malignant neoplasm estimated to be more than 40,000 cases per year in the US. These malignant tumors are known to have a potent activity of local bone invasion; however the molecular mechanisms of SCC associated osteolysis are unknown. In this study, we identified high level expression of chemokine ligand, CXCL13 and RANK ligand (RANKL) in squamous cell carcinoma (SCC) derived cell lines. SCC 14a cell conditioned media (20%) induced osteoclast differentiation which was inhibited by addition of OPG in human peripheral blood derived monocyte cultures indicating that SCC cells produce soluble RANKL. In addition, recombinant CXCL13 (10 ng/ml) significantly enhanced RANKL stimulated osteoclast differentiation in these cultures. Trans-well migration assay further identified that CXCL13 induces (7-fold) chemotaxis of peripheral blood monocytes in vitro which was inhibited by addition of anti-CXCR5 receptor antibody. Zymogram analysis of conditioned media obtained from RAW 264.7 macrophage cells stimulated with CXCL13 for 48 hr demonstrated a significant increase (4.0-fold) in the level of MMP-9 expression. Real-time PCR analysis of total RNA isolated from human bone marrow derived stromal cells stimulated with CXCL13 for 48 hr showed a significant increase (4-fold) in RANKL mRNA expression. Interestingly, CXCL13 treatment to SCC 14a cells induced CXCR5 receptor and MMP-9 expression suggesting an autocrine regulatory function in SCC cells. To further examine the molecular mechanisms associated with SCC tumor cell invasion and osteolysis of bone, we established an in vivo model for SCC by subcutaneous injection of SCC 14a cells (7x106 cells in PBS) onto the surface of calvaria in NCr-nu/nu athymic mice, which developed tumors in 4-5 weeks. Immunohistochemical analysis confirmed CXCL13 and MMP-9 expression in the tumor cells and invasion of bone/osteolysis in vivo. Histochemical staining further demonstrated a significant increase in the numbers of multinucleated TRAP positive osteoclasts at the tumor bone interface. Thus, our data implicate a functional role for CXCL13 in SCC tumor cells invasion/osteolysis of bone and may be a potential therapeutic target to prevent osteolysis associated with SCC in vivo.

111 Predictors of Response to Anti-TNF-α Therapies in Two University-Based Populations with Rheumatoid Arthritis, Rodney S Daniel1, Rae Bourne2, Annie N Simpson3, Kenneth S O’Rourke4, Marcy B Bolster1, 1Rheumatology and Immunology, MUSC, 2Wake Forest Baptist University Medical Center, Winston-Salem, NC, 3Biostatistics, Bioinformatics, and Epidemiology, MUSC.

The objective of this study was to determine clinical predictors of anti-tumor necrosis factor alpha (anti-TNF-α) therapy in rheumatoid arthritis. Medical records of patients with rheumatoid arthritis were reviewed for demographics, disease characteristics, and laboratory findings. Adult subjects without other autoimmune diseases except secondary Sjogren syndrome were included. Subjects were assigned to a group based on response to anti-TNF-α therapy: Responder, Switcher, or Failure. A predictive model was created using logistic regression. Of the 1313 records reviewed, 110 were Responders, 48 Switchers, and 21 Failures. The model included ESR > 50 mm/hr, methotrexate (MTX) use, an ESR-MTX interaction term, and thyroid dysfunction or osteoporosis. Patients taking MTX with an ESR > 50 mm/hr had an increased likelihood of anti-TNF-α therapy failure [OR 23.6 (P= 0.0144)]. Patients prescribed adalimumab first had the lowest likelihood of switching therapy [OR 0.293(0.117, 0.734) P=0.0088], while etanercept had the greatest likelihood of switching [OR 2.51(1.129, 5.580) P=0.0240] regardless of MTX dose. Patients on MTX < 15mg weekly were 2.8 fold more likely to switch to a second anti-TNF-α therapy (P=0.0194), than patients on MTX > 15mg weekly at baseline. In conclusion, methotrexate dose should be titrated to at least 15 mg weekly and attempts should be made to lower ESR prior to anti-TNF-α therapy to minimize the likelihood of anti-TNF-α discontinuation. Patients prescribed adalimumab first had the lowest likelihood of switching therapy, while etanercept had the greatest likelihood of switching regardless of MTX dose.

112 Role of HuR in Bcl-2 MRNA Stability in Human HL60 Leukemia Cells, Sivakumar Ramalingam, Daniella Ishimaru, Baby G Tholanikunnel, Daniel J Fernandez, Eleanor K Spencer; Biochemistry and Molecular Biology, MUSC.

Abstract not available.

113 DHHC20: A Potential Novel Target For the Development of Anticancer Therapeutics, Jeremiah M Draper, Charles D Smith; Pharmaceutical and Biomedical Sciences, MUSC.

Abstract not available.

114 Murine Hematopoietic Stem Cells But Not Progenitor Cells Are Highly Susceptible Towards Radiation Exposure and Are Less Proficient in the DSB Repair, Senthil Kumar Pazhanisamy, Yong Wan, Daohong Zhou; Pathology and Laboratory Medicine, MUSC.

Abstract not available.

115 An Analysis of Ceramide Levels in Neuroblastoma Tumor Tissues, Heather Escoto, Jacqueline M Kraveka; Pediatrics, Division of Pediatric Hematology Oncology, MUSC.

Abstract not available.

116 FGF-2 Stimulates RANK Ligand Expression in Paget's Disease of Bone, Kumaran Sundaram1, Joseph Senn2, Sudhahar D Rao3, Srinivasan Shanmugarajan4, Sakamuri V Reddy2, 1 medicine, MUSC, 2Bristol Myers Squibb Pharmaceuticals, Syracuse, NY, 3Henry Ford Hospital, Detroit, MI, 4Pediatrics, Endocrinology, MUSC, 5Pediatrics, MUSC.

RANK ligand (RANKL), a critical osteoclastogenic factor expressed in marrow stromal/preosteoblast cells is upregulated in Paget’s disease of bone (PD). We previously demonstrated that heat shock factor-2 (HSF-2) is a downstream target of fibroblast growth factor-2 (FGF-2) signaling to induce RANKL expression in bone marrow stromal/preosteoblast cells. In this study, we identified a 2.5-fold increase in serum FGF-2 levels in...
patients (n=8) with PD compared to normal subjects (n=10). We showed that HSF-2 co-immunoprecipitates with heat shock protein-27 (HSP-27) and that FGF-2 stimulation significantly increased phospho-HSP-27 levels in marrow stromal cells. Confocal microscopy demonstrated HSF-2 co-localization with HSP-27 in unstimulated cells. Recent evidence indicates suppressors of cytokine signaling (SOCS) interact with and modulate FGF signaling. We therefore hypothesized that FGF-2 modulates SOCS levels to enhance RANKL expression in PD. Interestingly, real-time PCR analysis demonstrated a significant increase in the levels of SOCS-1 (3.4-fold) and SOCS-3 (3.5-fold) mRNA expression in pagetic bone marrow mononuclear cells. Also, FGF-2 stimulation enhanced SOCS-1 and SOCS-3 mRNA expression 5.3 and 4.8-fold in stromal/preosteoblast cells respectively. We next examined if SOCS plays a role in FGF-2 signaling to modulate RANKL expression in PD. Co-expression of SOCS-1/3 with hRANKL gene promoter-luciferase reporter plasmid in bone marrow stromal cells demonstrated a 3.0-fold increase in promoter activity without FGF-2 stimulation. Since signal transducers and activators of transcription (STAT) molecules are implicated in growth factor signaling and SOCS expression, we further examined participation of STAT in FGF signaling to enhance RANKL expression in marrow stromal/preosteoblast cells. FGF-2 stimulation significantly increased the levels of p-STAT-1/3 in these cells. Western blot analysis demonstrated that siRNA suppression of STAT-1/3 decreased (3.2-fold) RANKL expression in FGF-2 stimulated cells. Also, FGF-2 stimulated hRANKL gene promoter activity was significantly decreased by siRNA suppression of STAT-1/3. These results suggest STAT-1/3 are downstream effectors of FGF-2 signaling and that elevated levels of FGF-2 stimulates RANKL expression in PD.

117 Endogenous Tissue Kallikrein Ameliorates Chronic Renal Injury By Inhibiting Oxidative Stress and Activating Matrix Degradation Pathways, Yuying Liu, Makoto Hagiwara, Yang Zhirong, Lee Chao, Julie Chao; Biochemistry and Molecular Biology, MUSC.

Abstract not available.

118 Increasing Virus Entry and Infection in Macrophages By MicroRNA Encoded By an Oncogenic Herpesvirus, Qin Zhiqiang, Parsons Chris; Medicine, MUSC.

MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression through post-transcriptional modification or degradation of target mRNA. Recently, 12 virally-encoded miRNA have been identified within the genome of the Kaposi’s sarcoma-associated herpesvirus (KSHV), the most common cause of cancers associated with HIV infection and organ transplantation. These KSHV-miRNAs are expressed in infected cells within KSHV-associated tumors, but their precise functions have not been characterized. Macrophages provide an important reservoir for KSHV within the tumor microenvironment. We sought to determine whether KSHV miRNAs play a role in virus entry and subsequent latent infection in macrophages. In this study, a BALBc-derived mouse macrophage cell line, RAW 264.7, was transiently transfected using a pcDNA3.1-miRNA construct encoding 10 of the 12 KSHV-miRNAs, then incubated with purified KSHV. Immunofluorescence assay (IFA) and RT-PCR indicated that miRNAs transfectedants greatly increase virus entry and expression of several major latent viral proteins compared with control transfecants. Furthermore, KSHV miRNAs upregulate transcript expression of several known cellular receptors for virus entry, including xCT, DC-SIGN and β-integrin, and increase reactive nitrogen species (RNS) release within culture supernatants as quantified with a standard Greiss reaction technique. Interestingly, elevation of RNS has been reported to facilitate KSHV entry and infection of endothelial cells. Based on these data, we tested strategies to reduce KSHV entry and infection in macrophages, including the use of specific miRNA inhibitors and an iNOS inhibitor, L-NMMA. IFA and RT-PCR confirmed that both of these approaches inhibit virus entry and suppress latent viral protein expression with no discernable toxicity. Future investigations will focus on: 1. Determining mechanisms for KSHV miRNA targeting and regulation of cellular receptors; 2. The use of an animal model to ascertain whether L-NMMA reduces KSHV infection and dissemination in vivo. [This work was supported by the Medical University of South Carolina Department of Medicine, and the NIH (NCI).]

119 Modulating Complement Activation Inhibits Radiotherapy Induced Apoptotic Cells Clearance on Breast Cancer, Quan Fang, Jennifer Schepp, Fei Qiao, Stephen Tomlinson; Microbiology and Immunology, MUSC.

Abstract not available.

120 C3 Deficiency Minimized Inflammation Against Dextran Sulfate Sodium-Induced Colitis, Jennifer Schepp-Berglind, Stephen Tomlinson; Microbiology and Immunology, MUSC.

The complement system has been implicated as playing a role in the tissue injury associated with inflammatory bowel disease (IBD). It has been reported that C3b deposition can be detected on luminal epithelial cells in lesions of IBD. However, the mechanism and the consequence of activation is unknown. In order to begin evaluating how the complement system may contribute to gut inflammation and its potential role in IBD pathogenesis, we compared the severity of dextran sulfate sodium-induced colitis in C3-deficient and control mice (C57BL6). 5 Days after consuming 5% dextran sulfate sodium in their drinking water, the control mice suffered greater weight loss, uniformly bloody diarrhea as compared with the minor changes in the C3 deficient mice. The control mice also developed shortened colons and had larger spleens. Histological examination of the distal colons showed a massive increase in neutrophils and mononuclear cell infiltration as well as greater epithelial cell destruction in the control mice compared to minimal damage to the C3 deficient mice. We have shown that the injury induced by DSS absorption is minimized in the distal colin of C3 deficient mice, which raises the possibility that regulating complement activation may help protect against IBD inflammation and pathogenesis. Future studies are underway to determine how the complement activation pathways are involved in pathogenesis and to evaluate the therapeutic potential of different complement inhibitory proteins. [Salary Support by Rheumatology Training Grant: T32 AR050958-04.]

121 Role of Cilia in Tooth Development, Evgeni Efimenko, Darwin P Bell, Courtney J Haycraft; MUSC Medicine.

In mammals cilia are nearly ubiquitous organelles that project from the surfaces of different cell types. Cilia have been implicated directly in many processes such as the generation of left-right asymmetry, maintenance of the renal epithelium, or respiratory function. Defects in cilia structure or function lead to a wide range of developmental problems and diseases (ciliopathies). Cilia have previously been identified on the
odontoblasts of developing tooth. Mice with partial loss of cilia function have defects in the patterning of the teeth. Finally, patients with some ciliopathies demonstrate teeth abnormalities, suggesting a role for cilia during tooth development. The goals of this study are to establish the spatio-temporal distribution of cilia on odontogenic cells in mice and to investigate their function in tooth formation using a conditional allele of the cilia gene Ift88 and an inducible Cre recombinase. This approach will allow us to disrupt cilia at both the initiation and morphogenesis stages of tooth development. Sensory cilia transduce a multitude of sensory stimuli, including chemical concentrations of growth factors, hormones and developmental morphogens. Consider that we will analyze the change in expression of signal transduction molecules important for tooth development in cilia mutants, including Ptc1, Gli1, Barx1, Msr2, Msr1, Sprouty4, Lef1, Ectodin, Edar, Dspp, Wnt10a and Runx2. Recently, using antibodies against IFT88 protein and acetylated alpha-tubulin we have demonstrated that odontogenic cells are less ciliated at early stages of tooth development and more ciliated at the stage of differentiation/secretion. These data will provide important information for further interpretation of the results obtained from conditional Ift88 mutants.

122 Oxidized LDL-Immune Complexes Trigger Enhanced Production of Collagen 4 By Human Mesangial Cells, Souzan A Abdel-Razek1, Charlyne Chassereau2, Hasnae El ouardihi3, Gabriel Virella4, Maria Lopes-virella1;
1Medicine/Endocrinology, MUSC, Ralph H. Johnson VA Medical Center, 2Ralph H. Johnson VA Medical Center, 3MUSC/Pharmacology, 4MUSC/Physiology.

Abstract not available.

123 Disparity Between Two Automated Immunochemiluminescent Intact Parathyroid Hormone (iPTH) Assays, David Holloman, Laurel Willis, Robin Schreiber, Joyce Foster, Christine Papadea, Yusheng Zhu; Pathology and Laboratory Medicine, MUSC.

Background: Intact PTH (iPTH) is an 84-amino acid hormone. The transferability of results among these assays is hindered by various factors. For example, different fragments of iPTH antigen in the sample, non-commutable matrices of assays, and non-standardized calibrators may be confounding variables. We report the disparity between two automated immunochemiluminescent iPTH assays on the ADVIA Centaur® and the Immulite® 1000 analyzers and our efforts to understand the possible cause(s) for the observed differences. Methods: Sixty-six freshly collected patient specimens including 46 plasma samples (14, EDTA; 32, heparin) and 20 sera were assayed for iPTH comparison on the both platforms simultaneously. Two freshly prepared levels of calibrators for each assay were also included as samples. The Immulite Turbo is a 15-minute assay intended for use only in the intraoperative settings for rapid assessment of the surgical resection of hyperfunctioning parathyroid tissue. The Centaur is a 22-minute assay with a biotinylated polyclonal goat anti-human PTH (39-84 region) capture antibody and a polyclonal goat anti-human PTH (1-34) tracer antibody. Both assays use the same tracer antibody, but the Turbo capture antibody is goat anti-human PTH (44-84). Results: For all samples combined, 43 (65%) of Centaur results were lower and 23 (35%) were higher than Turbo results. Of the samples where Centaur results were lower, 33 (77%) were below 72 pg/mL, the upper limit of Centaur reference interval, while of the samples where Centaur results were higher, 20 (87%) were higher than 72 pg/mL. Conclusions: iPTH results measured by Centaur and Turbo assays are not interchangeable. Centaur result is lower if iPTH < 77.0 pg/mL, while it is higher if iPTH > 77.0 pg/mL. The disparity between these assays is most likely due to the differences in calibrations, but other factors may co-exist. Our results indicate a critical need for vendors to standardize iPTH assays.

124 Heterophilic Antibody Interference Causing False-Positive Rapid Human Immunodeficiency Virus Antibody Testing, Deborah V Spencer, Frederick S Nolte, Yusheng Zhu; Pathology and Laboratory Medicine, MUSC.

Background: Naturally occurring human heterophilic antibodies can bind to a variety of substances, including antibodies and antigens, and cause interference in many immunoassays. Heterophilic antibody interference in two-site sandwich immunoassays employing two antibodies is well-documented; however, the interference in rapid immunochromatographic HIV antibody screening assays using two recombinant HIV antigens has not been reported. We report the first known case of a false-positive human immunodeficiency virus-1 (HIV-1) antibody test caused by heterophilic antibody interference in a solid phase rapid immunochromatographic assay. Methods: The Uni-Gold Recombigen HIV immunoassay (Trinity Biotech) was used to test the patient’s serum for anti-HIV-1 antibodies. The sample was also tested using Abbot HIBAB HIV-1/HIV-2 EIA, Western Blot for HIV antibodies, and Roche COBAS AMPLICOR HIV-1 Test for HIV-1 RNA. The sample was treated with Heterophilic blocking tube (HBT) and Non-specific antibody blocking tube (NABT) (Scantibodies Laboratory) and was retested using the Uni-Gold Recombigen HIV immunoassay. Results: The initial result of HIV-1 antibody determined by the Uni-Gold Recombigen HIV immunoassay was weakly positive as compared to the control line and the positive control, and the results were reproducible. The confirmatory testing was negative determined by Abbot HIBAB HIV-1/HIV-2 EIA and Western Blot for HIV antibodies and PCR for HIV RNA. The Uni-Gold Recombigen HIV immunoassay gave a negative result in the sample treated with HBT, but remained weakly positive after treatment with NABT. Conclusions: The initial result determined by the Uni-Gold Recombigen HIV immunoassay was false-positive caused by interfering heterophilic antibodies in the sample. Since this type of rapid HIV screening test has been widely used in clinical laboratories and point-of-care settings, laboratorians and clinicians should be aware of the possibility of false-positive results caused by heterophilic antibodies. One should always consider the presence of heterophilic antibody if HIV test results are ambiguous.

125 The F Box Protein of Skp1-Cdc53/Cullin F Box (SCP) E3 Ubiquitin-Ligase Complex, Dia2 Promotes Genome Stability By Negative Regulation of Ty-1 Retro-Transposition in Yeast, Narendra K Bairwa, Deepak Bastia; Biochemistry, MUSC.

The maintenance of replication fork integrity during DNA synthesis phase of cell cycle is essential for the genome stability and faithful segregation of genetic material from parent to daughter cells. It was previously suggested that Dia2 protein, an F box protein of Skp1-Cdc53/cullin F box (SCP) E3 ubiquitin-ligase complex, is enriched in nucleolus and is essential for stable passage of the replication fork through damaged DNA and natural replication fork pause sites thereby contributing towards faithful duplication of genetic material. The cells having deletion of dia2 exhibits increased GCR (gross chromosomal rearrangement) and ERC (extra-chromosomal r-DNA circle) formation. Here we describe the novel role of Dia2 protein in
regulation of Ty1–retro-element transposition thereby promoting genome stability. We observed that in the absence of the dia2 protein there was more than 25 fold enhancement of Ty1 element transposition over WT and this was attributed to increase in the total Ty1 cDNA and its multi-merization. We also observed shortening of telomeres and sensitivity towards hydroxyurea, a genotoxic agent in dia2 deletion mutant. Our results explain the role of Dia2 in promoting genome stability by suppressing transposition of Ty1 element.

126 Role of Beta3 Integrin - BMX Signaling for STAT3 Activation During Compensatory and Decompensatory Cardiac Hypertrophy. Geetha Suryakumar, Rebecca K Johnston, Michael Zile, Sundaravadi Balasubramanian, Dhandapani Kuppuswamy, Medicine, Cardiology, MUSC.

Abstract not available.

128 Characterization of PABA/NO Treated HL-60 Cells. Arcia D Binder1, Danyelle Townsend2, Steven Hutchens3, Yefim Manevich1; 1Voorhees College, Division of Arts & Science, Denmark, SC, 2Pharmacy, Pharmaceutical Sciences, MUSC, 3Cell Biology and Anatomy, MUSC.

Abstract not available.

129 Secretion of Acid Sphingomyelinase By Human Monocytic Cells Exposed to Oxidized LDL and Oxidized LDL Immune Complexes. Christabelle M Piansay1, Russell W Jenkins2, Kent J Smith3, Yusuf A Hannun4, Samar M Hammad3; 1Clemson University, 2MUSC, 3Pharmacology, Pharmaceutical Sciences, MUSC, 4Pediatrics, MUSC.

Low-density lipoproteins (LDL) are the major carriers of cholesterol in humans. LDL can become potentially damaging when modified to form oxidized LDL particles (oxLDL). In circumstances such as diabetes, chronic inflammation, obesity, and aging, the generation of modified LDL is enhanced. The body may react to oxLDL by producing antibodies forming immune complexes (oxLDL-IC). It has been determined that oxLDL-IC activates macrophages and prolongs cell survival in comparison to oxLDL alone. Therefore, signaling pathways and potential targets for the regulation of inflammatory responses induced by oxLDL-IC are the focus of our studies. Sphingolipids have been shown to act as signaling molecules influencing functional events such as cell survival and inflammation. Ceramide, a class of sphingolipid involved in the pro-apoptotic pathway, is generated through hydrolyzing sphingomyelin through the “sphingomyelin cycle” by the enzyme acid sphingomyelinase (A-SMase). A single protein precursor gives rise to two distinct A-SMases via alternative protein trafficking, lysosomal and secretory A-SMase. In this study, we examined if the activity of secretory and lysosomal A-SMase is regulated by lipoproteins, and whether oxLDL-IC and oxLDL regulate A-SMase differently. We measured the activity of secreted A-SMase using radio-labeled sphingomyelin substrate. All forms of LDL (native LDL, oxLDL, and oxLDL-IC) inhibit the activity/secretion of secretory A-SMase at 5 hr; however, lysosomal A-SMase is acutely induced at 30 min. Thus, it is concluded that low-density lipoproteins modulate SMase activity; however, the effect of oxLDL on A-SMase does not differ from oxLDL-IC. Future studies will include the use of a genetic mouse model of A-SMase deficiency to determine the role of A-SMase in oxLDL-induced ceramide. [the National Heart, Lung and Blood Institute of NIH (grant #R25HL092611)]

130 Regulation of NFAT Transcription Factor Gene Expression By Mutant P62 in the Osteoclasts of Patients with Paget’s Disease of Bone. Danielle D Mumford1, Sakamuri Reddy2; 1South Carolina Governor’s School for Science and Mathematics, Hartsville, SC, 2Pediatrics, MUSC.

Abstract not available.

131 Targeting Hyaluronan-CD44 Interaction in MPNSTs. Paul A Bomar1, Thomas J Knackstedt2, Jennie Gilg3, Lauren B Tøller4, Bryan P Toole5, Mark G Slomiany6, Bernard Maria6; 1Pediatrics - SURP, MUSC - Clemson, 2Medicine, MUSC, 3Pediatrics - Hematology / Oncology, MUSC, 4Pediatrics, MUSC, 5Cell Biology and Anatomy, MUSC.

Neurofibromatosis (NF) is the most common neurocutaneous disorder, affecting 1:4000 Americans. NF causes an array of clinical manifestations, most notably tumors such as gliomas, neurofibromas, plexiform neurofibromas, and malignant peripheral nerve sheath tumors (MPNSTs). Though surgical resection and chemotherapy are mainstays of MPNST treatment, five-year survival rates remain poor. As growing evidence implicates multi-drug resistance in the failure of chemotherapy, numerous studies have identified molecules that correlate with metastatic behavior and chemoresistance. Among them is hyaluronan (HA), a large (>10,000,000 Dalton) glycosaminoglycan instructing malignant behaviors through binding to various cell surface receptors, including CD44. Enriched in a variety of tumors, including MPNSTs, and often predictive of malignancy, our lab has demonstrated that disruption of endogenous CD44-HA interactions suppresses multi-drug resistance. Furthermore, CD44 has been shown to complex at the plasma membrane with ATP-Binding Cassette (ABC) multi-drug transporters. Short HA oligomers (o-HA) (=2,500 Dalton), competitively disrupt HA-CD44 interactions and trigger the internalization of the CD44-ABC transporter complexes. Consequently, the overarching goal is to obtain preclinical data on the efficacy of o-HA in NF-related tumors, with particular emphasis on MPNSTs. We hypothesize that o-HA triggers internalization of CD44-ABC family drug transporter complexes in MPNST cells, thereby decreasing drug efflux and resistance to chemotherapy drugs. Corollary to this, we believe that HA-CD44 interactions promote malignant behaviors of NF1-related tumors. Studies are ongoing, employing subcutaneous MPNST xenografts in nude mice, to determine 1) whether systemic delivery of o-HA is comparable to intratumoral injection, 2) whether tumor growth is affected by o-HA alone, and 3) whether sub-optimal doses of both chemotherapy (Doxorubicin 1mg/kg) and o-HA (10ug) combined have an additive/synergistic effect. Thus, by evaluating HA antagonism to drug resistance, we will have a strong scientific rationale for proposing a pilot human clinical trial of o-HA in patients with MPNSTs. [Summer Undergraduate Research Program]

132 Prostate Derived ETS Factor RepressesSlug Expression in Breast Cancer Cells. M R Lauer1, V J Findlay2, D P Turner3, D K Watson4; 1University of North Texas, Denton, TX, 2Pathology and Laboratory Medicine, MUSC.

ETS is a family of conserved transcription factors that regulate genes involved with cell proliferation, apoptosis, differentiation, lymphoid cell development, tissue remodeling, angiogenesis, and invasiveness. Prostate Derived ETS Factor (PDEF) is an ETS family member whose expression is restricted to tissues of high epithelial cell content. PDEF is a presumptive tumor suppressor found to inhibit migration and invasion when
expressed in invasive breast cancer cell lines. PDEF has been shown to negatively regulate mRNA expression of SLUG a transcriptional repressor that promotes EMT (epithelial mesenchymal transition) and is associated with the increase in migration and invasion of invasive breast cancer cells. Based upon these observations, we hypothesize that PDEF decreases migration in part by binding to and repressing transcription from the SLUG promoter. To test this model, HEK 293 cells were transfected with a SLUG promoter construct and PDEF. Using a Luciferase Assay we found a decrease in SLUG promoter activity with increasing concentrations of PDEF. In the invasive breast cancer cell line MDA MB 231, re-expression of PDEF was shown to decrease SLUG mRNA and protein expression, and the functional effects of this were examined by migration. We observed a decrease in migration in MDA MB 231 cells when PDEF was re-expressed in these cells. Furthermore, we showed that this phenotype could be reversed by exogenous expression of SLUG under the control of the CMV promoter, which is not responsive to PDEF. Our collective data support the model that PDEF-mediated repression of migration is mediated in part through the repression of the SLUG promoter.

133 The Effects of Prostate Derived ETS Factor (PDEF) in Mammary Gland Development of Black 6 Strain Mice, Christine T Hang1, Victoria J Findlay2, Dennis K Watson2; 1South Carolina Governor's School for Science and Mathematics, Hartsville, SC, 2Pathology and Laboratory Medicine, MUSC.

The prostate derived-ETS factor (PDEF) is part of the E twenty-six specific (ETS) family of transcription factors, which regulates cell proliferation, apoptosis, differentiation, and invasion. The PDEF protein was first identified in prostate tissue and expressed in epithelial tissues such as prostate, breast, colon, and bladder. The loss of the expression of the protein is found to correlate with the defined tissue's invasive characteristics. Currently, the role of PDEF in normal developmental processes is not well understood. Understanding the normal developmental processes can help to determine the relationship between PDEF and cancer. The aim of this study was (1) to identify the role of PDEF in mammary gland morphology and (2) determine the role of PDEF in mammary gland cell proliferation. This was determined using both knockout mice and wild type Black Strain 6 mice. The role of PDEF was tested using immunohistochemistry, which involved a specific antibody (monoclonal antibody Ki67) binding to a specific antigen (Ki67 protein). Morphology and proliferation patterns were observed in the wildtype and knockout genotypes in several stages (8 week, lactation day 7, and involution day 7) of the mammary gland cycle. Research indicated dramatic morphological changes in the 8 week and lactation day 7 stages. The wildtype’s fat cells were smaller and more abundant than the knockout type in the 8 week stage, and the wildtype’s lobular alveoli were larger in the lactation day 7 stage. The involution stage had a similar morphology between the two genotypes. Similar proliferation patterns were seen for all three stages of mammary development: the wildtype had more proliferating cells than the knockout genotype. [Thank-you to Dr. Dennis K. Watson (mentor) and Dr. Victoria J. Findlay (postdoc) for a wonderful research experience. It was truly an academically rewarding endeavor. Also, my thanks goes to Dr. Perry V. Halushka and Ms. Debra A. Shoemaker for giving me the opportunity to conduct research at the M]

134 The Effects of Different Antioxidants on MMP-1 Expression By U937 Macrophages, Sana A Ail1, Yan Huang2; 1Columbia College, Columbia, SC, 2Medicine, Endocrinology, MUSC.

It has been well established that periodontal disease is one of the complications of diabetes. Diabetic patients with poor glucose control are more susceptible to gum diseases and therefore, lose more teeth than non-diabetic patients and diabetic patients with good glucose control. Matrix metalloproteinase (MMP)-1 is known to play a crucial role in periodontal disease by degrading collagen and other matrix proteins in the periodontal tissue. Our recent study has shown that N-acetylcysteine (NAC), an antioxidant, inhibited lipopolysaccharide (LPS)-stimulated MMP-1 expression by human U937 macrophages. In this study, we determined if other antioxidants such as quercetin, cocoa extract, vitamin C, vitamin E, alpha-lipoic acid, and epigallocatechin gallate (EGCG) also inhibit MMP-1 expression by U937 macrophages. We treated U937 macrophages with LPS in the presence or absence of the antioxidants for 24 h. After the treatment, MMP-1 released by U937 cells into medium was quantified using enzyme-linked immunosorbent assay (ELISA) and cellular MMP-1 mRNA was quantified using real-time polymerase chain reaction (PCR). Results showed that NAC, quercetin and cocoa extract significantly inhibited LPS-stimulated MMP-1 secretion and lipoic acid increased expression. Surprisingly, vitamin C and alpha LPS-stimulated MMP-1 expression while EGCG and vitamin E had no effect. In conclusion, this study shows that different antioxidants have markedly different effects on MMP-1 mRNA expression, suggesting that the inhibition of MMP-1 expression by NAC, quercetin and cocoa extract may be independent of their antioxidant action. [R25HL092611-National Heart, Lung and Blood Institute of NIH]

135 The Role of ADAMTS-9 in Cardiac Development and Maintenance, Danielle N Geeting1, Ebony Alston2, Amo Wessels3, Suneel Apte3, Christine B Kern; 1Biology, College of Charleston, 2Medicine, MUSC, 3Cell Biology and Anatomy, MUSC, 4Biomedical Engineering, Cleveland Clinic.

Abstract not available.

136 Renal Dysfunction in Cardiac Surgery: Identifying Potential Risk Factors, Jennifer L. Barnum, Joseph J. Sistino; College of Health Professions, Clinical Services, Cardiovascular Perfusion, MUSC.

Abstract not available.

137 In Vitro Modeling and Study of Respiration-dependent Subdiaphragmatic Flow Reversal in the Fontan Circulation, Margaret A Zawaski1, Amanda Hutchenson1, Tiffany Camp2, Tim Conover3, Richard Figliola4, T-Y Hsia3; 1Clemson University, 2Biology, College of Charleston, 3Medicine, MUSC, 4Cell Biology and Anatomy, MUSC, 5Biomedical Engineering, Cleveland Clinic.

Abstract not available.

138 Comparison of Visual Responses and Receptive Fields in Biological and Artificial Retina, Grace M Dion1, Prakash Kara2; 1Clemson University, 2Neurosciences, MUSC.

Abstract not available.
139 Study on Renal Cell Carcinoma with Thrombosis Involvement of the Inferior Vena Cava, Ashok K Ramachandra, Justin Ellet, Ken Chavin; 1Medicine, MUSC, 2Microbiology and Immunology, MUSC, 3Medicine, Surgery, MUSC.

Abstract not available.

140 The Synthesis of a Hedgehog Pathway Inhibitor, GANT-61, Michael S Humeniuk, John Oats, Alexander Krupenko, George Cooper; 1Medicine, Cardiology, MUSC, 2Pharmacology and Experimental Therapeutics, MUSC, 3Biochemistry and Molecular Biology, MUSC, 4Medicine, Cardiology, MUSC and Ralph H. Johnson VA Medical Center.

The Hedgehog (Hh) signaling pathway is used in many animals to determine limb development, organogenesis, and other types of patterning during the growth of an embryo. Recent studies have shown that the Hh pathway, thought to be mostly dormant in adults, is turned back on in the heart during pressure overload cardiac hypertrophy. The ability to inhibit the pathway at various stages in the signaling process would be helpful for further study of the hypertrophic growth process. Workers have shown that GANT-61 and GANT-58 inhibit GlI1, one of the terminal transcription factors in the Hh pathway, with the former inhibitor being more potent than the latter. Since there is neither commercially available GANT-61 or GANT-58, nor a published synthesis for their preparation, we have devised a synthesis for GANT-61. Usage of this molecule in animal models of human disease will 1) provide a means for determining the role of the Hh signaling pathway in pathological hypertrophy and 2) provide a means for determining whether blocking this pathway in vivo prevents the progression from compensated cardiac hypertrophy to decompensated cardiac failure. [Gazes Cardiac Research Institute Development Fund, Training Grant T35DK007431]

141 Extracellular Biomarkers in Hypertensive Heart Disease; Unique Gender and Ethnicity Profiles, Adonteng A. Kwakye, Sheila Thompson, Catherine McClure, Teresa Brinsa, Robert Stroud, John Mulchay, Michael G. Zile, Francis G. Spinale; 1Medicine, MUSC, 2Medicine, Cardiology, MUSC, 3Medicine, Surgery, MUSC, 4Medicine, Surgery, MUSC, 5Medicine, Surgery, MUSC, 6Medicine, Surgery, MUSC, 7Medicine, Surgery, MUSC, 8Ralph H. Johnson VA Medical Center.

Background—Patients with uncontrolled or poorly managed hypertension can exhibit changes in their myocardial extracellular matrix (ECM), specifically collagen homeostasis. This may possibly lead to Left Ventricular Hypertrophy (LVH). These changes can also be reflected in the balance between the ECM proteases—matrix metalloproteinases (MMPs) and the tissue inhibitors of matrix metalloproteinases (TIMPs). Furthermore, changes in these metalloproteinases have a significant role in the structural, functional, and clinical outcomes of hypertensive heart disease. Additionally, hypertension affects various populations differently. However, a MMP and TIMP profile has yet to be clearly established in regards to gender and ethnicity. Methods—LV Mass, plasma MMP-2, 3, 7, 8, and 9, TIMP 1, 2, and 4 values, and Doppler echocardiography were acquired from 150 subjects who were carefully screened and enrolled in the study after providing informed consent. These subjects were further bifurcated into a (1) reference control group, with no evidence of hypertension (2) Hypertensive subject group. Subjects with hypertension were further grouped into those with the absence or presence of LVH. Lastly, subjects who were found to have hypertension and LVH were stratified based on gender (male or female) and ethnicity (black or white). Results—Compared with reference control, patients with hypertension had significant changes in MMP/TIMP values. Subjects with hypertension and hypertrophy exhibited a differential profile when compared to hypertensive patients with no hypertrophy. Males and females, when compared also showed significant changes in MMP/TIMP values as well as blacks versus white subjects. Conclusion—There is a unique MMP/TIMP profile that exists in Hypertension and a gender and ethnicity sub-profile may exist. This study suggests that there are specific plasma profiles of biomarkers, specifically the MMPs and TIMPs, in the myocardial matrix that may play a role in the clinical manifestations of hypertensive heart disease.

142 Myocardial Matrix Metalloproteinase Signatures with Atrial Fibrillation, Effect of Aldosterone Blockade, Charles C Peyton, Robert E Stroud, Martha R Stroud, Michael R Gold, David Gregg, Francis G Spinale, Rupak Mukherjee; 1Medicine, MUSC, 2Division of Cardiothoracic Surgery and Adult Cardiology, MUSC.

Atrial fibrillation (AF) produces changes in atrial structure, specifically in the composition of the extracellular matrix (ECM). Matrix metalloproteinases (MMPs) regulate ECM structure and composition and have been implicated in influencing AF-associated ECM remodeling. AF often occurs in the presence of concomitant structural heart disease, such as heart failure (HF), which is also associated with MMP profile changes. Aldosterone levels increase with HF with and without concomitant AF and increased aldosterone levels is associated with a myocardial fibrotic response as well as changes in MMP levels. Aldosterone receptor blockade (ALDOBLK) may reduce myocardial fibrosis. Whether alterations in atrial MMP abundance are differentially regulated by AF and the use of ALDOBLK remains unclear. Right (RA) and left atrial (LA) myocardial samples were collected from 100 explanted hearts with end-stage HF. AF was documented in 42 patients, of which 21 received pre-transplant ALDOBLK. Age, gender, and ejection fraction were similar between AF and non-AF groups. LA size and use of coumadin and amiodarone was higher in the AF group. Myocardial levels of MMP-1, -2, -3, -8, and -9 were quantitatively determined. Results showed specific MMP pattern changes in the presence of AF, and further chamber-specific changes in MMP abundance with ALDOBLK. For example, RA and LA MMP-3 was significantly elevated with AF when compared to HF alone (p<0.05), and RA MMP-3 was further elevated in AF patients who received ALDOBLK treatment (p<0.05). The results of this study provide a better framework for understanding the biochemical underpinnings for changes in myocardial ECM structure in the presence of AF with HF and the impact of ALDOBLK on the pathogenesis of AF with HF.

143 Differential Matrix Metalloproteinase and Endogenous Inhibitor Expression in Ascending Thoracic Aortic Aneurysms Associated with Bicuspid Aortic Valve Subtypes, Stewart M Benton, Jeffrey A Jones, Robert E Stroud, Francis G Spinale, John S Ikonomidis; College of Medicine, MUSC.

Ascending thoracic aortic aneurysms are associated with the presence of a bicuspid aortic valve (BAV). BAVs are categorized depending on the cusp fusion pattern, which in turn may indicate propensity towards aneurysm formation. Matrix metalloproteinases (MMPs) and their endogenous inhibitors (TIMPs) are integral in the formation of ascending thoracic aortic aneurysms. This preliminary study tested the hypothesis that...
differences in MMP and TIMP expression will also differ between the three subtypes of BAV. 28 ascending thoracic aortic aneurysm specimens from patients with a BAV of known cusp fusion morphology were analyzed for MMP and TIMP abundance via immunoblotting. The results were expressed as a percentage change from a reference control group comprised of normal aortic samples (n=26) and logged in an online tissue database. This data was obtained and analyzed for differential MMP and TIMP abundance in the aneurysm sample. MMP-2 increased in right coronary and left coronary (RL) cusp fusions by 37% +/-15%, while MMP-9 decreased in the RL by 49% +/-8% and in the right coronary and non-coronary (RN) cusp fusions by 64% +/-13% (p<0.05). MMP-14 decreased in RL subtype by 64%, +/-6% while MMP-14 in the RN subtype differed significantly from that in the RL configuration (p<0.05). TIMP 2 decreased in the RL subtype by 21% +/-9%. TIMP 2 abundance in the RN subtype was significantly different that that seen in the RL subtype (p<0.05). This unique study represents differential MMP and TIMP abundance in aneurysm samples according to BAV subtype. Data regarding the specific proteolytic signatures within these aneurysm subtypes may lead to advances in screening, diagnosis, prognostication and therapeutic decision making in this potentially devastating disease.

**144 Differential Proteolytic Profiles in Pediatric Cardiomyopathies.** Nidhi Kumar¹, Robert Stroud², Jeremy Ringewald³, Nadia Roessler³, Francis Spinales², Tain-Yen Hsia²; ¹Medicine, MUSC, ²Surgery, MUSC, ³Pediatric Cardiology, MUSC, ⁴College of Medicine, Claude Bernard University, Lyon, France.

Objective: Both dilated (DCM) and hypertrophic (HCM) cardiomyopathies lead to abnormal structural and functional changes in the myocardium. DCM exhibits ventricular dilatation and systolic dysfunction; HCM produces ventricular thickening and diastolic dysfunction. A structural underpinning of both cardiomyopathies is extracellular matrix changes, which are determined by a balance between matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs). This study tests the hypothesis that different plasma MMP/TIMP profiles occur in pediatric DCM and HCM patients when compared with normal age-matched subjects. Methods/Results: Plasma samples obtained from 1 cc of blood were analyzed in 7 pediatric patients with DCM (age: 8.0±7.2 years), 6 with HCM (age: 3.7±4.8 years), and 26 age-, sex-matched control subjects. Informed consent was obtained from all patients and subjects. Using the Multiplex Suspension Array assay, plasma levels were quantified for the following MMP classes: gelatinases (MMP-2, -9), collagenases (MMP-8), matrixins (MMP-3, -7), and TIMP-1, -2, and -4. Compared to controls and HCM groups, plasma MMP-7, TIMP-1, and TIMP-4 concentrations were elevated in pediatric DCM patients. Discussion: Pediatric DCM patients exhibit a robust increase in MMP-7, which possesses proteolytic activity against all components of the extracellular matrix. Along with increased TIMP-1 and -4 levels, these distinct differences in determinants of myocardial matrix structure and function likely contribute to the different phenotype between pediatric DCM and HCM. This unique signature obtained from the Multiplex Suspension Array assay may potentially be useful as a screening, diagnostic, and prognostic tool. [The Summer Health Professional Program (College of Graduate Studies, MUSC)]

**145 TGF Beta Signaling in Embryonic Left-Right Axis Development.** Megan Lee¹, Ann Ramsdell¹, Jayne Bernanke²; ¹Medicine, MUSC, ²Cell Biology and Anatomy, MUSC.

TGF betas are signaling molecules known to be important to the normal development of the left-right body plan in vertebrates. Previous studies in mouse, chick, frog, and zebrafish have indicated that dysfunction of the TGF beta signaling system leads to left-right axis defects and the development of heterotaxy. Heterotaxy is a failure of establishment of proper left-right asymmetry in the body plan during development. In humans, heterotaxy has an incidence of 1 in 8,000 to 25,000 individuals and is often associated with mutations in components of the TGF beta signaling pathway. When defects in left-right axis patterning occur, they are very frequently associated with congenital heart defects; ninety percent of people born with heterotaxy will have some form of congenital heart defect. While previous studies have focused on TGF beta signaling at stages after the start of heart looping, we have focused on TGF betas’ actions beginning at gastrulation, well before the appearance of the heart fields. Through our experiments on Xenopus laevis with SB505124, a TGF beta receptor antagonist, we have shown that TGF beta signaling is necessary for the development of the left-right axis continuously from gastrulation (stages 10-12) through heart field development (stages 20-26). No change in left-right axis development was seen in embryos treated at stages 27-30 or later in development, indicating that, by the time heart tube development has begun, the left-right body axis is fully and irreversibly established. Using an ALK4 dexamethasone-inducible "rescue receptor", we were able to demonstrate that TGF beta signaling specifically through the ALK4 receptor is necessary for left-right axis establishment at the previously mentioned time points. [Dr. Ann Ramsdell, Jayne Bernanke, Argraves Lab, Diana Ho and Malcolm Whitman, Summer Health Professionals Research Program]

**146 Heterotaxy & Heart Field Development.** David L Bowen¹, Ann Ramsdell¹, Jayne Bernanke²; ¹Medicine, MUSC, ²Cell Biology and Anatomy, MUSC.

Abstract not available.

**147 Novel Peptides Promote Cardiac Fibroblast Adhesion.** Michael J Hinton¹, Russell A Norris²; ¹Medicine, MUSC, ²Cell Biology and Anatomy, MUSC.

**ABSTRACT** It has become increasingly clear that cardiac development is not complete during intrauterine life. Rapid enlargement and adaptive (or physiological) remodeling in humans occurs during the first three weeks of the postnatal period to bridge embryonic/fetal development with the fully defined/mature mammalian heart. This postnatal response is necessary to comply with the increased systolic pressures of the growing neonate. The forced adaptation of the myocardial wall is accomplished largely in part through the increase in the cardiac fibroblast population and their localized secretion of critical stabilizing matrix proteins such as collagen I. Collectively, this remodeling event results in an increase in ventricular wall thickness and stiffness (i.e. tensile strength). In the mouse, the adaptive response peaks during the first two weeks post-natally as the mature cardiac phenotype is fully established by 30 days. However, cardiac remodeling can be rekindled during adult life in response to changes in the environment (e.g. pressure overload or ischemic injury). Unlike neonatal remodeling, adult remodeling can progressively evolve
The development of the cardiac outflow tract involves the transformation of a common outlet which is surrounded by a transient myocardial sleeve into separate mature outlets referred to as the aorta and pulmonary trunk. The mature vessels are surrounded by arterial tissue instead of the original myocardial tissue. The mature semilunar valves originate from the endocardial cushion swellings of the common outlet and are comprised of extra cardiac cells originating from the neural crest. The extracellular matrix of the outflow tract and the substrates contained within, such as the versican variants have been shown to be critical for the development of the outflow tract. Recent published work from this laboratory also demonstrated that cleavage products generated by matrix metalloproteinases such as ADAMTS-9 may have distinct activities from the intact substrates. As a result of this we hypothesize that ADAMTS-9 deficiency will alter extra-cardiac cell migration and outflow tract remodeling resulting in cardiac outflow tract malformations. After the histological examination at various stages of both wild-type hearts, which contained both copies of the ADAMTS-9 gene, and of heterozygous hearts, which contained only one copy of the ADAMTS-9 several phenotypic changes where noted in the region of the semilunar valves and within the aorta. Semi-lunar valves from the ADAMTS-9 heterozygotes contained mal-patterned valves with a disorganized matrix and appeared thicker than the wild type littersmates. Due to these findings we conclude that deficiencies in ADAMTS-9 and therefore possibly a decrease in cleavage of versican or other extracellular matrix substrates significantly impacts the development and maintenance of the cardiac outflow tract. [Summer Health Professionals Research Program]
that an increase in membrane associated transporter proteins may underlie the increase in renal solute reabsorption induced by exposure to low salinity.

151 Signal Transduction Pathways Involved in the Development of Interstitial Kidney Fibrosis. Nicole Swavey1, Rick Visconti2, Wayne Fitzgibbon3, Sema Sivritas4, Pal Gooz5, Monika Gooz5, 1Medicine, MUSC, 2Medicine, Cell Biology and Anatomy, MUSC, 3Medicine, Nephrology, MUSC, 4Medicine, Rheumatology, MUSC, 5Medicine, Nephrology, MUSC and Ralph H. Johnson VA Medical Center.

Renal fibrosis is a prevalent complication of many conditions including diabetes, hypertension, and obstructive renal disease. This fibrotic pathology can be mirrored using the chronic unilateral ureteral obstruction (UUO) model, which is characterized by inflammatory response, progressive accumulation of extracellular matrix molecules in the interstitial space of the kidney, and apoptosis of tubular epithelial cells. Some specific proteins, such as tumor necrosis factor alpha (TNFalpha) and caspases 3 and 8, have been implicated in MMP/mg tissue) to MMP concentrations in adjacent normal tissue. Analysis of the combined tumor groups showed increased MMP abundance compared to normal tissue (MMP-1: tumor: 19.4±5.1, normal: 0.4±0.1; MMP-2: tumor: 103.8±18.3, normal: 39.2±5.0; MMP-3: tumor: 7.7±2.4, normal: 0.4±0.1; MMP-8: tumor: 189.5±41.3, normal: 61.0±8.9; MMP-9: tumor: 150.2±16.6, normal: 163.7±18.4; MMP-12: tumor: 16.1±3.4, normal: 0.2±0.1; MMP-13: tumor: 2.6±1.0, normal: 0.0±0.0). Analysis of SCC tumor groups versus AC tumor groups revealed a distinct MMP profile for each histological subtype (MMP-1: SCC: 30.8±9.3, AC: 6.8±2.1; MMP-2: SCC: 128.2±30.1, AC: 52.1±8.1; MMP-3: SCC: 13.9±4.3, AC: 0.9±0.2; MMP-8: SCC: 396.0±83.5, AC: 31.2±8.6; MMP-9: SCC: 209.9±19.5, AC: 65.1±16.2; MMP-12: SCC: 24.7±5.7, AC: 4.9±1.2; MMP-13: SCC: 3.4±1.9, AC: 1.4±0.4). All MMP values are listed in picograms of MMP per milligrams of tissue. (* p<0.05) Conclusions: The results of this unique study demonstrated that MMP abundance and profiles for NSCLC are increased in tumor tissue over normal, and that there are disparate MMP concentration profiles for SCC versus AC. Continued understanding of the biochemical basis for lung cancer invasion and metastasis could be helpful in developing histology-specific screening tools, imaging modalities, and adjuvant therapy protocols for patients with stage I and II nonsmall cell lung cancer. [American Association for Thoracic Surgery]

153 Systemic Treatment of Therapy-Resistant Malignant Peripheral Nerve Sheath Tumors with Hyauronan Oligomers. Thomas J Knackstedt1, Paul Bomar2, Lauren Tollervey1, Bernard L Maria3, Mark G Slomiany1, Bryan P Toole4; 1College of Medicine, MUSC, 2Clemson University, 3Pediatrics, MUSC, 4Cell Biology and Anatomy, MUSC.

Neurofibromatosis is one of the most common neurocutaneous disorders in America. Individuals present with a wide range of symptoms including café au lait spots, Lisch nodules, and various cutaneous and plexiform neurofibromas. Plexiform neurofibromas may develop into aggressive malignant peripheral nerve sheath tumors (MPNST) with a poor prognosis and few treatment options. Previous research has observed elevated concentrations of hyaluronan in MPNSTs. Hyaluronan (HA) is a large, complex glycosaminoglycan with extensive structural and signaling functions. HA has been shown to be involved in the malignant progression of these tumors via its interactions with membrane bound CD44. These interactions promote antiapoptotic signaling and multi-drug resistance through increased expression of MRP2, BCRP, and p-glycoprotein. Consequently, it has been hypothesized that oligomers of hyaluronan (o-HA) will downregulate the activity of RTKs and ATP binding cassettes while triggering the internalization of CD44 drug transporter complexes, therefore counteracting the effects of systemic hyaluronan. The primary focus of my research, as part of the Summer Health Professions Research Program, was to investigate the effects of systemic o-HA treatments on the progression of MPNSTs in nude athymic mice. Previous research has shown that intratumoral o-HA injections reduce MPNST tumor growth. Consequently, we hypothesized that the o-HA will cause a reduction in xenograft tumor growth and increase sensitivity to chemotherapeutic agents. Varying concentrations of o-HA oligomer were systemically injected into different treatment groups and a decrease in tumor size was noted with concentrations as low as 100µl. The effect of hyaluronan oligomers and the establishment of a clinical threshold dose may then be combined with other chemotherapeutic agents for a more promising clinical method of treating highly resistant cancers and pilot human clinical trials. [This research was funded by the Summer Health Professionals Research Program, MUSC]

152 Matrix Metalloproteinases and Non-Small Cell Lung Cancer. Sonam A Shah1, John S Ikonomidis2, Robert E Stroud3, Eileen I Chang3, Francis G Spinal4, Carolyn E Reed2; 1Medicine, MUSC, 2Medicine, Surgery, MUSC, 3Surgery, MUSC.

Rationale: Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths. There is a limited ability to detect the probability of recurrence following removal of stage I and II lung tumors. Matrix metalloproteinases (MMPs) are an endogenous proteinase system shown to facilitate cancer invasion and metastasis. The purpose of this study was to evaluate MMP expression in the two most common histologies of NSCLC, squamous cell (SCC) and adenocarcinoma (AC) relative to normal lung tissue. Methods: A comprehensive MMP multiplex plate analysis was run on homogenates of 23 SCC and 22 AC surgically resected tumor specimens and compared (pg of MMP/mg tissue) to MMP concentrations in adjacent normal tissue. Results: Analysis of the combined tumor groups showed
154 Bone Fracture Healing in Adult Mice: The Role of Periostin, Kathryn F Glenn1, Russell A Norris2, Kyle P Kokko3, Michael J Kern2, 1Medicine, MUSC, 2Cell Biology and Anatomy, MUSC, 3Orthopaedic Surgery, MUSC.

Abstract not available.

155 Expanding the Female Neurologic Phenotype of Duplicated Xp Syndrome, Anna C Edens1, Kenton R Holden2, Barbara DuPont3, 1Medicine, MUSC, 2Neurology, MUSC, 3Greenwood Genetic Center.

Purpose: To present a 14-year-old Hispanic female with intractable epilepsy, dysmorphic facial features, short stature, obesity, and neurodevelopmental delays with mental retardation who was found to have duplication of Xp and several gene deletions. The extent of the impact of duplication Xp on neurologic phenotypes has not been well described. We aim to further expand the neurologic phenotype of this syndrome.

Methods: Peripheral blood was recovered to perform high resolution cytogenetic analysis, methylation studies of the X chromosome, and OGT X array microarray to detect copy number gains and losses. A brain MRI, EEG, and CT scan were obtained in Honduras. Results: Cytogenetic analysis revealed a karyotype of 46,X,dup(X)(p22.3p11.2), which is consistent with an inverted duplication involving the short arm of chromosome X. The patient has a highly skewed x-inactivation pattern (94:6), and X array studies further describe copy gains of Xp11.2p22.33 and losses of Xp22.33 (including the SHOX gene), Xq21.31 (including the PCDH11X and TGFbeta2X genes), and Xq28 (including the SPRY3 gene). Brain MRI revealed thickening of the cerebral cortex in the right temporal lobe and left medial temporal lobe which are suggestive of cortical dysplasia. EEG was abnormal and brain CT results were within normal limits. Conclusion: Duplication Xp has been rarely reviewed in the literature to help expand the duplication Xp neurologic phenotype. [Greenwood Genetic Center - Cytogenetic and Molecular Laboratories]}

156 Thermal Activation of Polymer Microfluidic Valves, Elizabeth A Gordon1, Jian Liu2, Daniel R Knapp3, 1Medicine, MUSC, 2Pharmacology, MUSC Proteomics Center.

A thermally-activated microfluidic valve was designed for use in a manifold valve chip as a component of a system for separation of peptides during proteome analysis. This valve serves to divert collected fractions from a first dimension strong cation exchange (SCX) separation to a series of reverse phase high performance liquid chromatography (RP-HPLC) columns for a second dimension separation. The second effluent will then be diverted to a mass spectrometer for final analysis. The valve in a cyclic olefin copolymer (COC) microchip was made from a thermally activated polymer, poly(N-isopropylacrylamide), or PNIPAAm, and could be opened and closed using a light beam. [This work was funded by the Summer Health Professions Research Grant of MUSC, and by the NHLBI Proteomics Initiative N01-HV28181.]

157 Oral Health in the Lowcountry Gullah Population, Zachary Evans, Michele Ravenel; Dental Medicine, MUSC.

Abstract not available.

158 The Role of Msh5 in Immune Deficiency in Systemic Lupus Erythematosus, Alexander T Page1, Gary S Gilkeson2, Hideharu Sekine2, 1Medicine, MUSC, 2Rheumatology and Immunology, MUSC.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that is strongly associated with selective IgA deficiency. Defects in the antibody class switch recombination (CSR) pathway have been theorized to be one contributing factor in both disorders. Recently, the Msh5 gene has been implicated in the CSR mechanism, while mutations in Msh5 have been linked to an increased prevalence of both SLE and IgAD. We hypothesize that Msh5 polymorphisms have a causative role in the pathogenesis of SLE and IgAD. Sera samples from the SLEIGH database at MUSC had IgA and IgG concentrations quantified from SLE patients and unafflicted controls. Samples with the twenty highest and lowest IgA concentrations were analyzed for five previously described SNPs in the Msh5 gene. The C580G SNP occurred at an increased frequency in the low IgA SLE group compared to the high group, possibly indicating its involvement in the CSR pathway. [MUSC SHP Research Program]

159 Gamma-interferon-inducible-Lysosomal-Thiol Reductase Regulates Acidic Proteases and Costimulatory Molecules in Melanoma Cells, Duncan L Norton1, Dan Zhao2, William J McCrary2, Peter Komlosi3, Azizul Haque2, 1Microbiology and Immunology, Hollings Cancer Center, MUSC, 2Microbiology and Immunology, Hollings Cancer Center, Darby Children’s Research Institute, MUSC, 3Darby Children’s Research Institute, MUSC.

HLA class II-restricted antigen (Ag) processing and presentation are important for the activation of CD4+ T cells, which provide help for sustained killing of malignant tumors by cytotoxic CD8+ T cells. The majority of melanoma cells express HLA class II proteins, thus they could be prime targets for CD4+ T cells. We have previously shown that human melanoma cells lack an enzyme, gamma-interferon-inducible-lysosomal-thiol reductase (GILT), which perturbs CD4+ T cell recognition of these tumors. Here we show that the introduction of GILT upregulates Ag processing, epitope generation and costimulatory molecules such as CD80/CD86 within melanoma cells. Western blot analysis showed that GILT expression in two different melanoma cells, J3 and 1359-mel, did not alter HLA class II protein levels, but elevated HLA-DM molecules and active forms of cysteinyl and aspartyl cathepsins. Transfection of J3 cells with GILT cDNA significantly increased cell surface costimulatory molecules (CD80/CD86) as demonstrated by confocal microscopy. GILT expression also enhanced cathepsin S activity, IgG processing and CD4+ T cell recognition of melanoma cells as determined by biochemical and functional Ag presentation assays. These data suggest that elevation of HLA-DM, cathepsin protein expression and activity as well as costimulatory molecules by GILT, may contribute to enhanced immune recognition of melanoma cells via the HLA class II pathway. [NIH, Leukemia and Lymphoma Society, and Hollings Cancer Center]
Sarcoidosis is multisystemic inflammatory disease of obscure etiology, with a disproportionate burden in the United States among blacks. The contribution of race to prognosis is controversial, and requires examination of a broad unselected population in order to minimize referral biases. This study examines racial differences in sarcoidosis-related mortality in the United States, using the complete death certificate-based Multiple Cause Mortality files from 1991-1998 (ICD-9 coding) and 1999-2005 (ICD-10 coding). Over 1991-1998, sarcoidosis-attributed mortality was 12.4 per million among non-Hispanic blacks and 1.0 per million among non-Hispanic whites; from 1999-2005 these rates averaged 14 per million and 1.4 per million, respectively. Non-Hispanic black persons with a sarcoidosis-related death were more likely than non-Hispanic whites to die with sarcoidosis as the underlying cause in both time periods examined (65.1% vs 50.4%, p<0.0001 and 66.1 vs 49.2%, p<0.0001), and they died a median of 12-18 years earlier than their white counterparts. Black persons with sarcoidosis had nearly double the proportion of pulmonary circulation disorders contributing to death (15% compared to 8.3%, p<0.01), while age-stratified proportions with chronic pulmonary disease were similar by race. The ratios of black:white sarcoidosis-related mortality were 9.4:1 and 7.4:1 from 1991-1998 and 1999-2005, respectively. Racial differences in mortality appear to reflect an intrinsically different disease course with a more proximally fatal outcome, though racial differences in mortality ratios are less than previously published estimates and may be decreasing. Identifying the cause of the apparent differences will require further investigation of genetic influences, as well as more thorough disease surveillance. [This research was conducted through The CDC Experience, a one-year fellowship in applied epidemiology at the CDC funded by Pfizer Public Health Group through the CDC Foundation.]

RPE65 is a protein located in the retinal pigment epithelium that is essential for generating 11-cis retinal, the ligand of the photoreceptor visual pigment. Knocking out the RPE65 gene results in a progressive loss of photoreceptors. Cone opsins is the pigment within cones involved in cellular maturation as well as the initiating events for light perception. The long-term degenerative process is caused by activation of the transcription cascade by unliganded opsin. However, the most devastating effect is the loss of cones, which are responsible for acute day vision in humans. Acute cone loss is due to mistransferring of unliganded opsin within the cell. This closely resembles alterations seen in Type 2 Leber’s Congenital Amaurosis (LCA2), caused by RPE65 gene mutations. Absence of a normal visual cycle leads to early onset cone degeneration in young LCA2 patients. RPE65-/- mice serve as an acceptable model for opsin studies and the effects of an impaired visual cycle on retina since their visual function is impaired. Potential therapies for LCA2 should ideally be administered during infancy to prevent cone degeneration. Genetic therapy has recently been shown to have potential for treating congenital eye diseases. However, there are important shortcomings: (1) Infants may be more susceptible to complications associated with recombinant viral vectors, thus use in this patient population is significantly limited. (2) The majority of cone degeneration in LCA2 patients occurs early in life; therefore the inability to administer genetic therapy early on diminishes its value as a stand-alone method of treatment for LCA2. Gel-based sustained delivery systems have been shown in vitro to deliver compounds to the retina. This holds great promise for developing safe and alternative therapies to preserve cones in young LCA2 patients until they grow to tolerate more invasive treatments. Furthermore, gel-based sustained delivery systems allow for novel approaches to investigate the underlying mechanisms of cone pathophysiology. This study was undertaken to compare the efficacy of an in vivo gel-based system for delivering 9-cis retinal to RPE65-/- mice cones in a subdermal manner as compared to intraperitoneal injection. Using this novel system, we further investigated the early pattern of cone degeneration with regards to regional short and mid-wave cone opsin expression in the retina and protein mislocalization within cones.
Multiple Sclerosis (MS) is characterized by inflammatory demyelination and neurodegeneration, the latter of which is abstractly modeled in its animal model, experimental autoimmune encephalomyelitis (EAE). Optic neuritis (ON), inflammation of the optic nerve, is strongly associated with MS, and is the first sign in the diagnosis of 15-20% of MS cases. Decreased visual evoked potential (VEP) and electroretinogram (ERG) readings in patients indicate degeneration of the optic nerve and retinal damage, respectively, with oligodendrogial death, myelin and axonal damage, and retinal ganglion cell (RGC) death. These events lead to transient vision loss and other signs of visual impairment. Findings of increased activity and expression of calpain, a Ca2+ -activated protease, in the optic nerves of EAE animals implies a role for calpain in the pathogenic events of ON. Furthermore, calpain modulates many signaling proteins involved in apoptosis. In this in vivo study, we characterized the neuroprotective efficacy of calpain inhibitors calpeptin and SNJ1945 in acute and chronic-progressive disease models, respectively. Lewis rats were immunized with MBP (myelin basic protein) followed by pertussis toxin (0 and 48hrs). Animals were treated twice daily (b.i.d.) by intraperitoneal injection of calpeptin on days 1-9 post-EAE induction, then sacrificed on day 10 for tissue analysis. C57BL6 mice were immunized with MOG35-55 (myelin oligodendrocyte glycoprotein) followed by pertussis toxin (0 and 48hrs) and monitored daily for clinical symptoms of paralysis. The mice received b.i.d. oral dosing of the calpain inhibitor SNJ1945 from days 7-21 post-EAE induction. Retinal tissue was analyzed to determine the effect of calpain inhibition on calpain expression, cell death, and glial cell reactivity when administered prior to the onset of clinical symptoms vs. vehicle treated controls. Preliminary Western blotting results in the acute model indicate that treatment with 50µg/kg, 100µg/kg, or 250 µg/kg doses of calpeptin reduced the levels of 80kD and 76kD (active) calpain. Similarly, all three doses decreased retinal levels of 32kD and 20kD (active) caspase-3 relative to vehicle treated EAE animals (N<2). Preliminary results in the chronic-progressive model demonstrate that treatment with 50 mg/kg of SNJ1945 delays the onset of clinical symptoms relative to EAE-vehicle treated mice (N=3). The higher dose (200mg/kg) did not alleviate symptoms in terms of latency to onset or severity. Biochemical, molecular and immunohistochemical parameters of interest in the retina and optic nerves of these animals are currently being analyzed.

Acid Ceramidase Up-Regulation in Prostate Cancer Cells Confers Resistance to Radiation: A Potential Radio-Sensitizer, Joseph C Cheng, Ayman EM Mahdy, Jun Li, Saeed ElOjeimy, S. Tucker Morrison, William D Meacham, Xiang S Liu, James S Norris; Microbiology and Immunology, MUSC.

Radiation resistance in a subset of prostate tumors remains a challenge to prostate cancer radiotherapy. The current study on the effects of ionizing radiation on prostate cancer cells reveals that radiation programs an unpredicted resistance mechanism by up-regulating acid ceramidase (AC). Irradiated cells demonstrated limited changes of ceramide levels while elevating levels of sphingosine and sphingosine-1-phosphate. By genetically down-regulating AC with siRNA, we observed radio-sensitization of cells using clonogenic and cytotoxicity assays. Conversely, AC over-expression further decreased sensitivity to radiation. We also observed that radiation-induced AC up-regulation was sufficient to create cross-resistance to chemotherapy as demonstrated by decreased sensitivity to Taxol and C6 ceramide compared to controls. Lower levels of caspase 3/7 activity were detected in cells pretreated with radiation, also indicating increased resistance. Finally, utilization of the small molecule AC inhibitor, LCL385, sensitized PPC-1 cells to radiation and significantly decreased tumor xenograft growth. These data suggest a new mechanism of cancer cell resistance to radiation, through up-regulation of AC that is, in part, mediated by application of the therapy itself. An improved understanding of radiation therapy and the application of combination therapy achieved in this study offer new opportunities for the modulation of radiation effects in the treatment of cancer. [This work was supported by NIH/NCI PO1 CA97132, Division of Laboratory Animal Research, NIH, C06 RR015455 and the MUSC Lipidomics Core, NIH, C06 RR018823.]

Metacaspase Expression and Activity in Karenia brevis Cultures: Preliminary Insight Into Cellular Mechanisms Regulating Bloom Termination, Jillian G Lynch, Frances M Van Dolah; MCBP/MBES, MUSC, NOAA Center for Coastal and Environmental Health and Biomolecular Research.

Karenia brevis, a toxic dinoflagellate, is responsible for near annual harmful algal blooms (HABs) off the west coast of Florida. These blooms cause extensive ecological and economic losses due to massive fish kills, marine mammal mortalities, and human illness caused by neurotoxic shellfish poisoning and respiratory irritation. The development of successful management strategies for K. brevis blooms is contingent upon understanding the molecular mechanisms that govern bloom initiation, propagation, and termination. Molecular mechanisms regulating K. brevis bloom demise, in particular, have remained largely uninvestigated, although recent studies have discovered programmed cell death (PCD) pathways in several other bloom-forming phytoplankton species. We have identified in K. brevis putative metacaspases, known central mediators of PCD in plants, fungi, and protists, containing a well-conserved caspase catalytic diad domain. Western blot analysis of K. brevis protein extracts collected over a growth curve revealed immunohybridization of multiple proteins to a polyclonal antibody raised against a recombinant Emiliania huxleyi metacaspase protein, which changed in prominence as cultures aged. Growth-stage specific caspase-specific activity was examined by measuring specific cleavage of fluorogenic canonical caspase tetrapeptide substrates. Preliminary results from these studies indicate an increase in caspase-specific activity in stationary phase cultures when compared to early and mid-logarithmic cultures. Identification of putative metacaspases from our EST libraries, cross reactivity with an E. huxleyi metacaspase polyclonal antibody, as well as caspase-specific activities in aging cultures provide preliminary evidence that Karenia brevis contains PCD machinery and may utilize an apoptosis-like pathway during cell death. Further characterization of the involvement of metacaspases in cell death may lead to the identification of molecular biomarkers for bloom termination. [Funding provided by NOAA National Ocean Service’s Center for Coastal Environmental Health and Biomolecular Research and the College of Graduate Studies, MUSC.]
166 Identification and Characterization of Senescence-Associated MicroRNAs in Human Fibroblasts, Melissa N Morris, Yong Wang, Jessica A Cloy, Joshua Kellner, Daohong Zhou; Pathology and Laboratory Medicine, MUSC.

Cellular senescence is a state of permanent growth arrest thought to contribute to the decline of tissue structure and function, resulting in organismal aging. The process by which cellular senescence is regulated remains unknown. MicroRNAs (miRNAs), small approximately 22 nucleotide non-coding RNA molecules, have been implicated in an array of biological processes, including the development and lifespan of Caenorhabditis elegans; however little insight has been uncovered as how miRNAs regulate aging and cellular senescence. Using microarray analysis, we profiled the expression of miRNAs in proliferating, quiescent, and senescent WI-38 human diploid fibroblasts. Our studies revealed that 62, 36, and 28 miRNAs are differentially expressed in ionizing radiation (IR)- and busulfan treatment (BU)-induced prematurely and replicatively senescent cells, respectively (p<0.01). Among these miRNAs identified, there were eight miRNAs expressed in both stress-induced (by IR or BU) and replicatively senescent cells, indicating that they are senescence associated miRNAs (SA-miRNAs) (>2.0 fold). Four of these SA-miRNAs were up-regulated (miR-152, miR-410, miR-431, and miR-493) and four were down-regulated (miR-15a, miR-20a, mir-25, and miR-155). The differential expression of the eight SA-miRNAs (excluding miR-431 due to assay unavailability) was confirmed by real-time RT-PCR by having at least a two-fold change in expression level to be considered significant. A time course study revealed significant changes in the expression of the SA-microRNAs at 3 days post IR and continued at this level until day 14 when the cells were deemed senescent. In contrast, the expression of miR-34a, a known down-stream target of p53 and an important mediator of DNA damage response, peaked at 3 days after IR and then subsided to an insignificant level by day 7 (<2.0 fold), indicating the SA-miRNAs may play a role in inducing and maintaining cellular senescence.

167 Caveolin-1 Regulates Normal and Scleroderma Monocytes Functions and Transformation Into Fibrocyte, Mathieu L Richard1, Elena V Tourkina2, Richard M Silver2, Stanley Hoffman2, 1MCBP, MUSC, 2Medicine, Rheumatology, MUSC.

Scleroderma lung disease and other form of lung fibrosis are very debilitating diseases with poor prognosis and virtually no treatment options. Recent studies have demonstrated that monocytes are the progenitors of fibrocytes, a circulating population of collagen-positive, fibroblast-like cells that participate in wound repair and fibrosis. We have previously shown that caveolin-1 expression is diminished in the bleomycin-induced murine model of lung fibrosis, and upregulating caveolin-1 activity with the caveolin-1 scaffolding domain (CSD) peptide attenuated the severity of inflammation and fibrosis. The aim of this study is to investigate caveolin-1-regulated signaling and function in normal and scleroderma monocytes and the role of caveolin in the activation of monocytes into fibrocytes. Our results demonstrate that less caveolin-1 is present in peripheral blood monocytes and neutrophils isolated from scleroderma patients than in these cells isolated from healthy volunteers (on average, caveolin-1 levels were only 41 ± 5 % as high in scleroderma monocytes. The expression/activity of several signaling molecules (MAP kinases family members) regulated by caveolin-1 is also altered. Our data indicate that the percentage of scleroderma monocytes that differentiate into fibrocytes in vitro is enhanced two-fold compared to normal monocytes and that CSD-peptide treatment inhibits the transformation of normal and scleroderma monocytes to fibrocytes. In addition, in murine bleomycin-induced lung fibrosis, CSD treatment decreased the number of fibrocytes recruited to the lungs as well as the severity of the fibrotic response. Taken together, these observations suggest that the low level of caveolin-1 present in scleroderma patient monocytes plays an important role in the progression of systemic inflammation and fibrosis, and that the CSD-peptide can provide remarkable protection against inflammation and fibrosis by reversing the abnormal regulation of signaling that results from the underexpression of caveolin-1. Thus, the CSD-peptide may represent an important novel therapeutic agent for the treatment of scleroderma. [Div. of Rheumatology and Immunology, Dept. of medicine, MUSC R01-HL-73718 K01-AR-054143]

168 Connexin 43 Gap Junction Dynamics in the Diabetic Heart, Joseph Palatinus, Robert Gourdie; Cell Biology and Anatomy, MUSC.

Abstract not available.

169 Exploring Protein Functional Similarities By Their Relationships in Three Dimensional Conceptual Space, Brian A Muller, Adam J Richards, Xinghua Lu; Biostatistics, Bioinformatics, and Epidemiology, MUSC.

The Gene Ontology is the most commonly used controlled vocabulary for annotating proteins. Biological concepts are represented by terms in the ontology and are organized as a graph. In this graph, each node corresponds to a term and each edge denotes the parent-child semantic relationship between a pair of terms. The Gene Ontology database also contains protein annotations which further create links between proteins and their functional annotations. When viewed as a whole, the Gene Ontology represents the contemporary knowledge about proteins and their functional relationships. The entire graph produced from the Gene Ontology is quite large; viewing the entire structure is rather overwhelming. For those biologists studying a specific lists of proteins and their associated terms there are distinct problems encountered when attempting to visualize even a subset of the whole graph. The goal of this research is to provide a software program that facilitates the visualization of user defined relevant portions of the Gene Ontology graph. A subgraph is automatically created based on a researchers list of proteins of interest, and that subgraph is then displayed in a threedimensional full interactive interface. The researcher can then easily see the spacial relationships of their research concepts as well as other related biological terms. [This research is partially supported by the following NIH grants: R01LM009153-01A1, T15LM07438, and 2P20RR017677. BAM is currently supported by a stipend from the College of Graduate Studies.]

170 Temporal and Gender Trends in Concordance of Urine Drug Screens and Self-Reported Use in Cocaine Treatment Studies, Megan S Schuler1, William V Lechner2, Rickey E Carter1, Robert Malcolm2, 1Biostatistics, Bioinformatics, and Epidemiology, MUSC, 2Psychiatry, Center for Drug and Alcohol Programs, MUSC.

Our aim was to describe temporal trends in concordance, sensitivity, and specificity and to explore demographic trends in concordance in two outpatient treatment studies for cocaine dependence. Concordance in this context is defined as the
agreement between a subject’s self-reported cocaine use and urine drug screen results. We collected 2229 urine drug screens and corresponding self-use reports from 129 individuals. To model concordance, sensitivity, and specificity as a function of time, we used a general linear model framework and the generalized estimating equations (GEE) approach to account for repeated measures. Also, we tested for demographic effects on concordance among subjects who achieved 100% concordance and subjects who achieved 70% concordance, a recently proposed reliability threshold for substance abuse trials. We found that both sensitivity and concordance decreased over time in a significant manner, yet specificity remained relatively constant. Overall concordance was quite high at 88%. Among all subjects, concordance varied significantly by gender, with females achieving significantly higher concordance than males (96% vs. 86%). Similarly, we observed that females were almost twice as likely to achieve 100% concordance as males (42% of females, 22% of males). Finally, 80% of subjects achieved the proposed 0.70 concordance, and we did not observe any differences among demographic groups with regards to the 0.70 concordance threshold. Overall, temporal effects on concordance may erode the validity of relying on self-use reports as the primary outcome measure in substance abuse trials. Similarly, our observed gender effect is evidence that females, who constitute only a small percentage of subjects, may consistently achieve higher concordance than males. In general, differential patterns in concordance over the course of a study may lead to incorrect conclusions about true treatment effect. Thus, a composite outcome measure, combining the strengths of both self-reports and urine screens, holds great promise, yet the proposed 70% reliability threshold for such a composite score requires more validation. [This research was supported by grants # R01 DA019903 and # R01 DA016368 from the National Institute on Drug Abuse.]

171 Inhomogeneous Solute Diffusion in Temporomandibular Joint Discs, Changcheng Shi1, Christopher Bowers4, Lixia Zhang3, Hai Yao3; 1Clemson-MUSC Bioengineering Program, Clemson University, 2Dental Medicine, MUSC, 3Clemson-MUSC Bioengineering Program, Clemson University, College of Dental Medicine, MUSC.

Abstract not available.

172 Insights Into the Formation and Function of Membrane Vesicles From the Bacterium Burkholderia Vietnamiensis PR1301, Benjamin A Neely1, Venetia D Lyles2, Noelle T Garvin3, Gary L Mills3, Paul M Bertsch1, Pamela J Morris1; 1Marine Biomedicine and Environmental Sciences Center, MUSC, 2Neurosciences and Neuroscience Institute, MUSC; Ralph H. Johnson VA Medical Center.

Burkholderia vietnamiensis is the third most frequently isolated member of the Burkholderia cepacia complex in cystic fibrosis patients. Additionally, strains of B. vietnamiensis such as PR1301 (PR1) have been studied for bioremediation applications due to their ability to degrade organic contaminants. Our laboratory has examined Zn resistance in PR1 and has found that membrane vesicles (MVs) may be playing a role in pH-dependent Zn resistance and that MV production is influenced by pH. Bacterial MVs are extracellular formations derived from the outer-membrane of Gram-negative bacteria, and their roles include transport of virulence factors, protein and DNA exchange, cell-cell communication, and biofilm formation. MVs are also involved in host-pathogen interactions (e.g., they have been shown to promote gastritis by Helicobacter pylori). To date, MVs produced by Burkholderia spp. have not been studied, and limited proteomic analysis exists for MVs in general. We have purified MVs produced by PR1 at pH 5 and 7 and characterized them using phospholipid fatty acid (PLFA) profiling and shotgun-proteomics. PLFA analysis found MVs produced at both pH had increased 16:1w7c and decreased 17:0cycl levels relative to the cellular fraction, suggesting changes in membrane fluidity may play a role in MV formation. Shotgun-proteomics identified 406 proteins in at least 2 replicates within each condition, and 245 were shared with 120 and 41 being unique to pH 5 and 7 respectively. The majority of identified transporters, porins and lipoproteins were found at both pH, though MVs from pH 5 contained more cytoplasmic proteins. This indicates that although MVs from different pH may have differences in function, broadly they share the same core functions. Overall, these results will help develop a better understanding not only about the formation and function of MVs, but also what drives changes in MV function as it relates to host-pathogen and metal-microbe interactions.

173 The Impact of Methylmercury on Transcriptomic Patterns of the Vitamin D3 Pathway in Dolphin Skin, Blake C Ellis1, Mark S Kindy2, Sebastiano Gattoni-Celli3; 1Marine Biomedicine and Environmental Sciences Center, MUSC, 2Neurosciences and Neuroscience Institute, MUSC; Ralph H. Johnson VA Med, 3Radiation Oncology, MUSC; Ralph H. Johnson VA Medical Center.

The Atlantic bottlenose dolphin has attracted attention as a potential sentinel for human health and because of the evident impact of the environment on its health. Greater knowledge of how the dolphin responds to environmental stress is needed, but such studies are limited by its status as a protected species. As a consequence, we have established cell cultures derived from skin of the Atlantic bottlenose dolphin as in vitro tools for measuring effects of environmental stressors at the molecular level. Specifically, we are investigating in these cells the presence of the vitamin D3 pathway and its potential role as a protective mechanism between the dolphin and its environment. Vitamin D is of interest due to its acknowledged chemopreventative and immunomodulatory properties within terrestrial animals; however, nothing is known about its physiological function in marine mammals. The bioactive and hormonal metabolite of vitamin D3, 1,25-dihydroxyvitamin D3 (1,25D3), interacts with the vitamin D receptor (VDR), a potent regulator of gene transcription. We have previously detected within dolphin skin cells a 1,25D3-induced upregulation of VDR levels and expression of specific genes, as identified by cDNA microarray analysis; these are similar patterns as those established in humans. One stressor relevant to the dolphin’s environment is methylmercury which tends to bioaccumulate up to extremely high levels within tissues of many marine mammals. While few studies have addressed the biological ramifications of mercury for marine mammals, methylmercury has been implicated as an immunotoxin, neurotoxin, and carcinogen in humans. We show in dolphin cells that sublethal concentrations of methylmercury compromise 1,25D3’s ability to upregulate VDR and to transactivate specific target genes and a vitamin D-sensitive promoter. Such findings may help elucidate the roles of vitamin D and methylmercury on innate immunity in dolphin skin and potentially in human skin as well, considering similarities in the vitamin D pathway between the two species.
The dinoflagellate, Karenia brevis, is responsible for harmful algal blooms in the Gulf of Mexico that cause extensive marine mortalities and human illness on a nearly annual basis. The molecular mechanisms controlling the cell cycle in this dinoflagellate are important because bloom development occurs through vegetative cell division. The dinoflagellate nucleus is characterized by novel adaptations, including massive genomes with permanently condensed chromatin, a lack of nucleosomes to aid in chromatin packaging, a permanently intact nuclear envelope with an extranuclear mitotic spindle that interacts with chromosomes via cytoplasmic channels. Microarray and qPCR studies have demonstrated that, unlike typical eukaryotes, dinoflagellate cell cycle genes are not regulated at the transcriptional level, including replication fork proteins that are typically activated by the E2F transcription factor at the restriction point, which regulates entry into S-phase (Van Dolah et al., 2007). Post-transcriptional control of these genes is further suggested by the presence of a trans-spliced leader sequence on their transcripts. In the current project, we are therefore investigating whether the expression of replication fork proteins in the dinoflagellate is regulated at the translational or post-translational level. To this end, peptide antibodies were developed for three K. brevis replication fork proteins: proliferating cell nuclear antigen (PCNA), replication factor C (RFC), and replication protein A (RPA). Immunolocalization with anti-K. brevis PCNA showed that PCNA protein is present only in cells actively traversing the cell cycle. However, PCNA is present in the nucleus well before S-phase is apparent by flow cytometry, suggesting that the restriction point occurs earlier than anticipated. We are currently investigating the expression of RFC and RPA. Together, their expression patterns will be used to define the restriction point in K. brevis, which will enable us to investigate precisely how S-phase entry is regulated in the absence of transcriptional activation of S-phase genes. [National Ocean Service Medical University of South Carolina]

Transplantation of neural progenitor cells derived from human embryonic stem cells (hESC) provides a potential therapy for the treatment of ischemic stroke. However, poor cell survival after transplantation into the host environment has dampened therapeutic benefits and possible application of the cell therapy. The present investigation tested a preconditioning strategy to enhance hESC tolerance, thereby improving graft survival and the therapeutic potential of hESC therapy. UC06 hESCs were subjected to a six week neural induction protocol, followed by terminal differentiation for up to 30 days. This protocol produces a neural precursor population which matures into the three neural lineages, exhibiting extensive neuritic and axonal projections, as well as action potential generation and synapse formation. To induce a cytoprotective phenotype, hESC-derived neurospheres were briefly cultured at 0.1% oxygen tension for 12 hrs then plated for terminal differentiation at 21% oxygen. Immunocytochemistry and patch clamp recordings demonstrated that sub-lethal hypoxic preconditioning enhanced neurogenesis and neuronal maturation. Western blot analysis revealed a two-fold upregulation of the oxygen dependent transcription factors HIF-1α and HIF-2α after 12 hours hypoxic culture. Analysis of HIF targets and other proteins revealed a biphasic protein response during hypoxia and subsequent reoxygenation, including upregulation of EPO, VEGF and GLUT-1, increased Akt1/2 activation and changes in the expression of Bcl-2 family members. This cytoprotective phenotype resulted in a 50% reduction in both total and neural precursor cell death following either hydrogen peroxide insult or oxygen-glucose deprivation. Enhanced cellular protection was observed for at least five days after the initial hypoxic stimulus and corresponded to upregulation of neuroprotective proteins. We are currently examining the mechanisms underlying the observed cellular protection and assessing hESC survival after transplantation to a rat cerebral ischemia model. These results suggest hypoxic preconditioning could be used to improve the effectiveness of human neural precursor transplantation therapies. [NIH 1T32ES012878-02 NIH NS045810 NIH NS045155]

Relapse to drug-seeking in both animals and human addicts is often driven by environmental cues that have become associated with the reinforcing effects of the drug over time. Because the hippocampus is central to the formation and retrieval of contextual associations, it may contribute to increased proclivity to relapse triggered by re-exposure to the context in which a drug was previously taken. In this study, the response of activity-regulated genes within subregions of the dorsal hippocampus was investigated after 22 h or 15 d of abstinence from cocaine. Rats self-administered i.v. cocaine or received yoked-saline infusions in daily 2 h sessions for 10 days. During prolonged abstinence, rats were exposed to an alternate environment distinctly different from the self-administration chamber on abstinence days 8-14 for 2 h/day. On the test day, rats were re-exposed to one of the following environments for 1h: (1) the self-administration chamber with access to drug-associated levers, (2) the self-administration chamber with no access to the levers, or (3) the non-drug-associated alternate environment. Following 15 d of abstinence, zif/268, arc and bdnf mRNA levels were significantly increased in dorsal hippocampal CA1 and CA3 pyramidal cells of rats re-exposed to the environment previously associated with cocaine administration. Interestingly, this was also true for arc mRNA expression in CA1 apical dendrites. Twenty-two h after self-administration, arc and bdnf, but not zif/268 mRNA, was significantly increased in CA1 pyramidal cells of rats with a history of cocaine. In CA3 pyramidal cells, arc expression was increased in cocaine-treated animals regardless of lever availability, while zif/268 mRNA was only significant in animals that had access to the levers. These data support the critical role of the hippocampus in cocaine-seeking elicited by the self-administration context apart from the operant performance of lever pressing, and processing situationally remote versus recent/familiar contextual information may differentially activate hippocampal subregions. [Supported by P50 DA15369 and F32 DA023768 (TLS)]
The formation of the outer layer of cells in the heart, the epicardium, is critical for normal cardiac development. Abnormalities in the epicardium lead to cardiac defects as shown in the retinoic X receptor α knockout mouse (RXRa/-), a model of congenital heart disease that exhibits defects in the epicardium and other regions of the heart. The RXRa/- epicardium is slower to form and, once formed, is detached from the myocardium. We speculate that disturbances in cell adhesion to the subepicardial extracellular matrix (ECM) or neighboring myocardial cells will result in epicardial detachment. Osmotic Stress Effects on MAPKs-dependent Phosphorylation of SPF45 and Regulation of Fas Alternative Splicing, Adnan M Al-Ayoubi, Hui Zheng, Tao Bai, Scott T Eblen; Cell and Molecular Pharmacology, MUSC.

Possible Role for VCAM-1 in Aberrant Epicardium Development in the RXRa/- Model of Congenital Heart Disease, M. Elizabeth G Burton, Loretta L Hoover, Laura E Brichler, Steven W Kubalak; Cell Biology and Anatomy, Bennett, Peter A Lee, Michael G Janech, Giacomo R Environmental Science, 4Marine Biomedicine and MUSC, 2College of Charleston.

178 MAPKs-dependent Phosphorylation of SPF45 and Regulation of Fas Alternative Splicing, Adnan M Al-Ayoubi, Hui Zheng, Tao Bai, Scott T Eblen; Cell and Molecular Pharmacology, MUSC.

Abstract not available.


Sea-ice is one of earth’s major biomes and diatom dominated sea-ice algal communities are the foundation of this unique, highly productive polar foodweb. Ice-diatoms contain large concentrations of the biogenic compound dimethylsulfoniopropionate (DMSP), which plays significant roles in global carbon and sulfur biogeochemical cycles as well as serving several possible cellular physiological functions. Production of this compound is modulated by and can modulate the earth’s climate. Since polar ecosystems regulate global climate via atmospheric and oceanic convection systems and they are highly sensitive to climate change, it is imperative to advance knowledge of physio-biological parameters controlling production of DMSP. Ice-diatoms encounter extreme salinity gradients during seasonal environmental cycles of sea-ice. During ice formation sea-salts are concentrated into brine channels that reach salinities beyond 200ppt and during spring ice melt it is not uncommon for transient freshwater melt ponds to form, this equates to osmolality shifts on the order of two magnitudes. DMSP is believed to be part of the unique physiology of ice-diatoms that enable them to tolerate such extreme osmotic fluctuations. It is a swit-on and compatible solute and therefore intracellular concentrations are expected to change in response to changes in external salinities. The current experiment investigates intracellular and extracellular DMSP levels in the polar sea-ice diatom Fragilariopsis cylindrus in response to shifts in media salinity. Log phase cultures initially grown at 35ppt were manipulated over a 24 hour period to achieve final salinities of 10ppt, 20ppt, 35ppt, 50ppt, and 70ppt. Cell counts, chlorophyll a (chl a), photosynthetic efficiency (Fv/Fm), and total and dissolved DMSP were quantified at various time points during the three week experiment. Results confirmed the hypothesis that intracellular DMSP increases in response to increasing external salinities, and decreases in response to decreasing external salinities coinciding with increases in extracellular (dissolved) DMSP.

180 Nucleic Acid Adducts of Brevetoxins, Tod Leighfield, John Ramsdell; MUSC, MCBP, MBES, NOAA National Ocean Service.

Brevetoxins are potent secondary metabolites produced during harmful algal blooms by the dinoflagellate Karenia brevis. Brevetoxins have been implicated in the morbidity and mortality of diverse organisms, from invertebrates to humans. Metabolic activation after exposure may result in the formation of reactive brevetoxin intermediates which can create conditions favorable for binding to nucleic acids. This study aims to characterize the adduction of brevetoxins with nucleotides, and to determine their role and significance in the induction of epigenetic modifications. Further studies will investigate the role of these unique metabolites as tools for biomonitoring.

181 An Evaluation of Logic Forest for Identification of Disease Biomarkers. Bethany J Wolf, Elizabeth G Hill, Elizabeth H Slate; Biostatistics, Bioinformatics, and Epidemiology, MUSC.

Introduction: Adequate screening tools allowing physicians to diagnose diseases such as cancer, CDH, and stroke in asymptomatic individuals or to identify individuals at elevated risk of developing disease have potential to greatly reduce overall disease related mortality. Research focused on identification of biomarkers for use in disease risk assessment, screening, prognosis, and treatment has yielded relatively few highly effective individual biomarkers. Multiple studies cite the need for a noninvasive test that would be both sensitive and specific for a particular disease. A diagnostic test based on multiple biomarkers may lead to enhanced sensitivity and specificity. For example, the presence of absence of a particular cancer, a binary outcome, may be associated with expression of three genes, binary predictors, of which at least two must be expressed for cancer to occur. Statistical methodologies that can model complex biologic interactions and that are easily interpretable allow for the translation of biomarker research into diagnostic tools. Logic regression, a relatively new multivariable regression method that predicts binary outcomes using logical
combinations of binary predictors, has the capability to model the complex interactions in biologic systems in easily interpretable models. However, the performance of logic regression degrades in data with a noisy response or in data containing a latent variable. Methods: We implement an extension of current logic regression methodology to an ensemble of logic trees, which we call logic forest. We conduct a simulation study to compare the ability of logic regression and logic forest to identify interactions among variables that are predictive of disease status. Results: Our findings indicate that Logic Forest is superior to logic regression for identifying important predictors, particularly in data with a noisy response or a latent variable. Conclusions: logic forest provides a new statistical tool capable of identifying predictors and predictor interactions associated with disease. [NIH/NIDCR "Statistical Methods for Head and Neck Cancer Proteomics" (K25DE016863) NIH/NIGMS "Biostatistics Training for Basic Biomedical Research" (T32GM074934)]

182 Selection Bias Adjustment of Growth Estimates for South Carolina Bottlenose Dolphins (Tursiops truncatus), Mary Tress1, Wayne McFee2, Elizabeth Slate1, Biostatistics, Bioinformatics, and Epidemiology, MUSC, National Ocean Service, CCEHBR.

Stranded bottlenose dolphins (Tursiops truncatus) off the coast of South Carolina provide data essential for population health assessment. A total of 91 animals stranded along South Carolina’s coast from 1993 to 2007 were necropsied. Of the 87 animals measured for total length only 52 were brought back to the laboratory for total weight measurements. It is more feasible to transport smaller animals to the laboratory setting for weight measurements than larger animals, introducing a selection bias in the sampling method and corresponding dataset. Regression and propensity score multiple imputation methods are utilized to account for missing data. Fitted Gompertz growth curves with adjustment for missing data are compared to those derived from the observed data without adjustment to assess the overall magnitude of selection bias. The fitted growth curves are also compared to those obtained for a sample of dolphins stranded in the Gulf of Mexico. The findings suggest that investigators should account for the selection bias inherent in sampling stranded dolphins. [NIH/NIGMS1T32GM074934-01]}

183 The Association Between Skin Characteristics and Sun-protection Behaviors, Lee Wheless1, Rhoda Alan2, Sandra Clipp3, Judith Hoffman-Bolton4, Timothy J Jorgensen5, Nanette Liegeios2, Paul J Strickland3, Anthoy J Alberg6, Lee Wheless1, Rhoda Alan2, Sandra Clipp3, Judith Hoffman-Bolton4, Timothy J Jorgensen5, Nanette Liegeios2, Paul J Strickland3, Anthoy J Alberg6; 1Microbiology and Immunology, MUSC, 2Pathology and Laboratory Medicine, MUSC, 3Dental Medicine, Stomatology, Microbiology and Immunology, MUSC.

BACKGROUND: The first complement component (C1) of the classical pathway is activated primarily through C1q globular heads that bind to immune complexes, but C1 is also activated in the absence of antibodies. C-reactive protein (CRP), an acute phase protein that, when bound to bacteria and apoptotic cells, activates C1. Furthermore, apoptotic and necrotic cells expose and liberate substances capable of directly activating C1, such as cardiolipin. If not adequately controlled, C1 activation could lead to the inadvertent deposition of covalently-bound C4b, and if the cascade continues, C3b and the membrane attack complex (MAC). Deposited C4b and C3b are opsonins that assist phagocytosis; and the MAC may lead to cell membrane damage, including inadvertent damage to healthy bystander host cells. Furthermore, C3a and C5a, fluid phase components formed as a result of complement activation, are inflammatory mediators. Interestingly, deficiencies in C1 and CRP have been linked to autoimmunity, possibly due to the inability to clear apoptotic cells. HYPOTHESIS: Since C1q globular heads must bind to activating substances in order to activate the proenzymes in macromolecular C1, we propose that a single chain antibody variable fragment against the globular heads will specifically inhibit C1 activation. RESULTS: A single chain antibody variable fragment against the globular heads of C1 (QuScFv) was engineered, expressed and isolated via transfected CHO-s cells in serum free media. QuScFv blocked C1q binding and C1-mediated C4 deposition on immobilized human IgG and on immobilized CRP. NuScFv also blocked C4 deposition on cells sensitized with HulG, on apoptotic cells, and on apoptotic cells sensitized with CRP. CONCLUSION: The specific interaction of C1 by QuScFv not only allows for dissecting the role of C1 in various experimental conditions but also reveals a potential therapeutic role in limiting complement mediated inflammation and host tissue damage. [This research was supported by NIH, National Institute of Allergy and Infectious Diseases AI069957, and the MUSC College of Dental Medicine.]

184 Specific Inhibition of the Classical Complement Pathway with an Engineered Single Chain Antibody Variable Fragment, Marcus R Duvall1, Hee Young Hwang2, Robert J Boackle3, Microbiology and Immunology, MUSC, 4Pathology and Laboratory Medicine, MUSC, 5Dental Medicine, Stomatology, Microbiology and Immunology, MUSC.

Background: Behaviors such as sunscreen use and use of skin-protective clothing can help prevent skin cancer, but little is known about how these sun protection behaviors vary by phenotypic risk factors for skin cancer. Objective: We carried out a cross-sectional study (n = 6898) nested within a community-based prospective cohort in Washington County, MD. We measured the associations between skin cancer risk characteristics (skin type, complexion, freckling, and eye color) and personal sun protection behaviors (sunscreen and sun-protective clothing use). Results: The prevalence of regular use of sunscreen was 23%, and the prevalence of regular use of sun-protective clothing was 21%. There were consistent trends indicating those at highest risk of skin cancer were most likely to engage in sun protection behaviors. For example, compared to those who tan without burning, those who develop blistering sunburns were more likely to use sunscreen (OR 6.55, 95% CI 3.08 - 13.92 men, OR 4.87, 95% CI 3.34 – 7.09 women) and sun-protective clothing (OR 2.90, 95% CI 1.73 - 4.85 men, OR 4.29, 95% CI 2.81 – 6.55 women). Those with fair skin were more likely than those with medium or dark brown complexion to use sunscreen or sun-protective clothing. Other factors significantly associated with sun protection behaviors were lifestyle-related factors such as lower body mass index and never smoking. Conclusion: The overall prevalence of sun protection behaviors was low. Our results indicate individuals with the highest skin cancer susceptibility are most likely to use sunscreen and sun-protective clothing, and may also be most receptive to skin cancer prevention educational interventions. [Supported by NIH/NCI grant R01CA105069 (Alberg) and by grant number T32RR023258 from the National Center For Research Resources (Whelless). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or th]
Characterization of Alveolar Epithelial Cells Cultured in a Hollow Fiber Model System, Christina L Grek1, Xuejun Wen2, Demetri D Spyropoulos3, John E Baat4, MBP, Pediatrics, MUSC, 2Clemson-MUSC Bioengineering Program, 3Pathology and Laboratory Medicine, MUSC, 4Pediatrics, MUSC.

A challenge presented in studies focusing on the in vitro characterization of alveolar epithelial cells is that such techniques lack airflow, air-liquid interface and the dynamic stretching characteristics of native lung tissue. These features are critical for normal phenotypic gene expression and cellular function in vivo. Our laboratory has established a novel selectively semi-permeable hollow fiber membrane-based model system that more accurately mimics the microenvironment of the alveolar epithelium. Alveolar epithelial cells were seeded within the hollow fibers and introduced to slow, constant air flow (5% CO2, 21% O2). Using immunocytochemistry, electron microscopy, and protein analyses we have shown that alveolar type-II cells grown within the hollow microfibers maintain the phenotypic and genotypic characteristics consistent with those of in vivo primary alveolar epithelial type II cells. Specifically, murine lung epithelial cells grew to complete confluence and maintained a cuboidal morphology, formed tight junctions, secreted surfactant proteins A and B, and produced the surfactant C proprotein. Electron micrographs indicated numerous lamellar bodies, the presence of apical microvilli, and confirmed surfactant secretion. These features are often entirely lacking or rapidly lost in alveolar epithelial cells that are cultured in current in vitro systems. Our data suggests that the microfiber environment represents optimal conditions that may more closely mimic what is seen in vivo in the alveolar microenvironment than cells grown in standard cell culture models. The implementation of our novel model system may prove optimal for future experiments involving studies of specific gene and protein expression involving alveolar epithelial cells and their response to various stressors. [Funding provided by the National Heart Lung and Blood Institute (NHLBI)]

Phosphatase Regulation of Cellular Motility in the Tumor Microenvironment, Jarrett E Walsh1, M. Rita I Young2; 1Microbiology and Immunology, MUSC, 2Research Service, Ralph H. Johnson VA Medical Center, Otolaryngology and Medicine, MUSC.

An increasing number of anti-tumor therapies have focused on angiogenesis pathways. Targeting various aspects of angiogenesis has been shown to disrupt tumor growth and reduce tumor progression and recurrence. Our studies show that treatment of microvascular endothelial cells with TGF-beta leads to alterations in the activity of protein phosphatases PP-1 and PP-2A with a simultaneous increase in motility. While previous work has focused on the inactivation of PP-2A, we are currently investigating the increased activity of PP-1 that occurs simultaneously. We hypothesize that TGF-beta activates endothelial cell PP-1, increasing cellular migration potential by modifying focal adhesion stability. Specifically, our studies have shown that phosphorylation of paxillin, a focal adhesion adapter protein, is critically dependent on PP-1 for stability at sites of focal adhesion. Since paxillin phosphorylation has been shown to induce both focal adhesion stability and turnover, investigating site-specific phosphatase activity on paxillin is important to understanding the process of cell motility. While PP-1 is known to dephosphorylate paxillin binding partners, our recent data suggests that PP-1 directly dephosphorylates paxillin. Furthermore, PP-1 inhibition limits TGF-beta induced endothelial migration. Understanding the phosphatase regulation of paxillin and other associated focal adhesion proteins may provide new targets for limiting cellular motility, angiogenesis and metastasis. [NIH CA97813(MRIY) and NIH CA85266(MRIY)]

The Dorsal Mesenchymal Protrusion (DMP), a Second Heart Field Derivative, Plays an Important Role in AV Septal Development, Brian Snarr, Jessica O’neal, Mastan Chintalapudi, Elaine Wirrig1, Aimee Phelps, Thomas Trusk, Steve Kubalak, Andy Wessels; Cell Biology and Anatomy, MUSC.

In the embryonic heart, mesodermal cells from the second heart field (SHF) contribute to the myocardium of the right ventricle and outflow tract. Expression of the LIM homeodomain transcription factor Islet-1 (Isl1), has been used to characterize these SHF cardiac progenitor cells. While a domain of Isl1 expression is also found in the venous pole of the developing heart, the contribution of the SHF to the cardiac venous pole is poorly understood. We show that, in the venous pole, Isl1 is strongly expressed in a discrete, non-endocardially derived, mesenchymal structure, known as the dorsal mesenchymal protrusion (DMP), which has been shown to play a significant role in atrioventricular septation. Furthermore, we demonstrate that the mesenchyme of the DMP eventually becomes muscularized as a result of a mesenchymal-to-myocardial differentiation, during which the DMP mesenchymal cells, which are characterized by a Isl1+/Nkx2.5− expression profile, transition into cardiomyocytes with a Isl1−/Nkx2.5+ signature. Finally, we show that abnormal development of this SHF-derived structure is a characteristic feature in a number of mouse models of atrioventricular septal defects. These results identify a novel role for the SHF at the cardiac venous pole and provide a new insight into the etiology of congenital heart disease.

Inhibition of Cx43/ZO-1 Interaction Improves Gap Junction Intercellular Communication and Reduces Connexon Hemichannel Activity, J Matthew Rhet, Jane Jourdan, Michael O’Quinn, Robert G Gourdie, Cell Biology and Anatomy, MUSC, 2Medicine, Cell Biology and Anatomy, MUSC.

Intercellular communication is important in many processes including wound healing, metastasis, and conduction in the heart. Direct cytoplasmic communication between cells is achieved by an aggregate of membrane channels called the gap junction (GJ). Individual intercellular channels comprising GJs are formed from hexameric oligomers called connexons or hemichannels; one connexon each contributed by the plasma membranes of adjacent cells. It has been shown that the carboxyl(C)-terminus of the main subunit of cardiac connexons, Connexin 43 (Cx43), is bound by the PDZ-2 domain of zonula occludins-1 (ZO-1). Previous work in our lab has shown that disruption of this interaction by a peptide based on the C-terminus of Cx43 - termed Alpha-Connexin-C-terminal peptide-1 (ACT-1) – results in larger GJs. We hypothesize that ZO-1 binding of Cx43 limits the rate at which connexons enter GJ aggregates. The focus here is to examine the functional implications of this hypothesis: a) GJs will be larger in ACT-1 treated cells, and therefore GJ intercellular communication (GJIC) should be enhanced by disruption of Cx43/ZO-1 interaction and b) larger GJs will be recruited from membrane connexon pools, with concomitant decreases in hemichannel activity. GJIC was assayed by the scrape-loading method; application of ACT-1 to Hela cells expressing Cx43 showed a
robust increase in communication. Connexon function was assayed by live imaging of ethidium bromide uptake in Cx43-expressing Hela cells. We found, as expected, that coupled cells - but not non-contacting, uncoupled cells - treated with ACT-1 displayed reduced hemichannel activity. Contemporaneous to this study, work in our lab also indicated that treatment of cryoinfarcted hearts with ACT-1 reduces the propensity for arrhythmia. In this light, the work reported here implies potential roles for connexon transitions between hemichannels and GJ aggregates in the pathology and treatment of heart failure. [South Carolina Space Grant Consortium]

189 A Peptide Containing the Carboxy-Terminal Domain of Connexin43 Reduces Arrhythmias and Improves Cardiac Function After Myocardial Injury, Michael P O’Quinn, Brett S Harris, Kenneth W Hewett, Robert G Gourdie; Cell Biology and Anatomy, MUSC.

Abstract not available.

190 Neutralizing Antibody Treatment Against Interferon-alpha in SCID Mice with HIV Encephalitis, Andrew R Sas1, Heather A Bimonte-Nelson2, William R Tyror3, 1Microbiology and Immunology, MUSC, 2Arizona State University, 3Neurosciences, MUSC.

The pathogenesis of HIV associated dementia (HAD) is incompletely understood. Since highly active antiretroviral therapy is only partially effective, new treatments are needed based on delineation of HAD pathogenesis. It is hypothesized that HIV infected cells produce putative neurotoxins that damage neurons. Interferon Alpha (IFNα) is a pleomorphic cytokine produced by nucleated cells in response to viral infection. Treatment with IFNα in patients has side effects including cognitive impairment resembling subcortical dementia, which is the hallmark of HAD. It has been shown that IFNα is increased in the cerebrospinal fluid of HIV dementia patients compared to HIV patients without dementia symptoms. We hypothesized that the inhibition of IFNα in the central nervous system (CNS) would ameliorate the cognitive dysfunction function and pathological abnormalities seen in SCID mice with HIV encephalitis. In addition, we have previously shown a correlation between IFNα in the CNS and cognitive performance in this model with higher levels of IFNα correlating with increased cognitive deficits during testing. In this study, HIV mice treated with intraperitoneal (i.p) injections of IFNα neutralizing antibodies demonstrated significantly improved cognitive function (p<0.05) as determined in the water radial arm maze compared to HIV mice that received either isotype matched control antibody treatment or a saline injection. Pathological analysis showed presence of IFNα neutralizing antibodies in the brain. Anti-IFNα antibody treated HIV mice exhibited decreased microgliosis (p<0.05) compared to HIV mice with control antibody or saline injections. Also, anti-IFNα antibody treated mice showed improvements in loss of dendritic arborization surrounding HIV infected cells compared to other HIV infected mice. The data in the HIVE mouse model indicates that blocking IFNα improves cognition and improves some pathological markers of HIVE suggesting it could be a therapeutic target for HAD patients. [NIH F31 NS054592-01A2 MUSC Institute of Neuroscience Grant NIH C06 RR015455 VA Merit Award #0007]

191 Capturing and Mapping the Distribution of Phosphorylated AQP0 in the Ocular Lens, Danielle B Gutierrez1, Rosalie K Crouch2, Kevin L Schey3, 1Cell and Molecular Pharmacology and Experimental Therapeutics, MUSC, 2Ophthalmology, MUSC, 3Department of Biochemistry, Vanderbilt University.

Purpose: To determine the distribution of phosphorylated AQP0 throughout the ocular lens in spatially resolved regions of lens fiber cell differentiation and aging. Rationale: Aquaporin 0 (AQP0) is a water channel in lens fiber cells that is critical to the maintenance of lens transparency. AQP0 water permeability is altered by Ca2+ in a calmodulin (CaM) dependent manner. AQP0 phosphorylation reduces CaM binding to AQP0, suggesting that phosphorylation may regulate the water permeability of AQP0 through Ca2+-CaM. AQP0 is phosphorylated at S235, S229 and S231; however, their distribution throughout the lens has not been carefully examined. We hypothesize that AQP0 water permeability is differentially regulated via phosphorylation during fiber cell differentiation and aging. Our objective is to map the distribution of phosphorylated forms of AQP0 across lens regions. Methods: A laser capture microdissection (LCM)-proteomics method has been developed to measure AQP0 phosphopeptides from dissected lens regions. Bovine lens sections were fixed and dehydrated. Tissue from cortical and core regions was captured on polymeric films with an Arcturus XT (Molecular Devices). Captured tissue was washed to enrich for membrane proteins, then digested with trypsin. A phosphopeptide enrichment method was developed and applied to the captured, membrane-enriched peptides. The samples were analyzed by LC-MS/MS. Results: Phosphopeptide enrichment was accomplished by immobilized metal affinity chromatography (IMAC), using manually dissected human lens samples. Phosphopeptides detected from the inner cortical fibers included: AQP0 229-238 singly phosphorylated at S235 and doubly phosphorylated at S231 and S235, and AQP0 227-233 singly phosphorylated. When the enrichment procedure was applied to LCM captured bovine lens core tissue, AQP0 229-238, phosphorylated at S235 was detected. Conclusions: These results support that LCM-proteomics method developed can be used to map AQP0 phosphopeptides throughout the lens with high spatial resolution. Future studies will use an internal standard to quantitate phosphorylation of AQP0 at S235. [NIH EY-13462. Medical University of South Carolina Mass Spectrometry Facility Vision Core Grant, NIH R24 EY14793.]

192 Inflammatory Gene Expression in an Alveolar Macrophage Cell Line Following Exposure to Brevetoxin-2, Kelli M Sas1, James C Ryan2, Frances M Van Dolah2, John E Baatz2, 1Marine Biomedicine and Environmental Sciences Center, MUSC, 2NOAA, Center for Coastal and Environmental Health and Biomolecular Research, 3Pediatrics, Marine Biomedicine and Environmental Sciences Center, MUSC.

Brevetoxins are potent marine algal toxins produced by Karenia brevis, the organism responsible for Florida red tides. Brevetoxin exposure through ingestion or inhalation has been associated with a variety of adverse effects including human illnesses, marine mammal and seabird mortalities, and massive fish kills. Pathological reports from manatee mass mortality events have documented the presence of lung inflammation and edema, and have identified that brevetoxins accumulate within macrophages and lymphocytes. We have recently shown in a mouse alveolar macrophage cell line that brevetoxin-2 exposure results in increased proinflammatory cytokine secretion and increased phagocytosis of latex beads. In this study, we utilized
a mouse whole-genome microarray and qPCR to test the hypothesis that in vitro brevetroxin-2 exposure results in the upregulation of genes involved in the inflammatory process. Results of the microarray indicated that a low percentage of genes were significantly altered and no genes encoding proinflammatory cytokines were differentially expressed. However, expressionst changes were identified for genes involved in other aspects of an immune response, including genes encoding for cellular migration and adhesion as well as antigen processing and presentation. Taken together, the results indicate that brevetroxin-2 alters the immune response in the MH-S alveolar macrophage cell line. Further research, such as histological examination including cellular infiltration, will be necessary to further define the lung’s response to brevetroxin-2.

193 Role of Cag L in H. Pylori-induced H,K-ATPase Alpha Subunit Gene Repression, Arindam Saha¹, Adam J Smolka², Monika Gooz³; ¹MCBP, MUSC, ²Medicine, MCBP, MUSC.

Introduction/Rationale: Helicobacter pylori represses H,K-ATPase alpha subunit (HKalpha) gene transcription, causing hypochlorhydria and gastritis. Disintegrin and metalloproteases (ADAMs) are a family of cell surface enzymes, generating inflammatory mediators like TNFalpha and EGF. Inactive ADAMs are bound to integrin molecules and ADAM17 is activated by dissociating from β1 integrin. H. pylori structurally binds to integrin molecules and ADAM17 is critical in excitable tissues such as heart and brain, but the mechanisms that govern GJ remodeling remain poorly defined. Previously we showed that fusion of GFP to the C-terminus of Cx43 leads to the formation of aberrantly large GJs. Cx43 GJs are resistant to Triton detergent extraction, yet Cx43-GFP GJs are largely Triton-soluble. Interestingly, Triton-insoluble Cx43-GFP localizes predominately to plaque edges—the site of GJ growth—suggesting that GJ edges are stabilized by cytoskeletal interactions that influence GJ size. Fluorescence labeling revealed minimal interaction of actin filaments with Triton-insoluble Cx43-GFP. In contrast, plaques composed of native Cx43 were extensively colocalized with actin polymer. However, Cx43-GFP plaques appear to acquire more microtubule contacts than native Cx43 GJs. Live cell imaging showed GJs containing a mix of Cx43-GFP and native Cx43 are more dynamic than plaques comprised solely of Cx43-GFP. Inhibition of either actin polymerization or Cx43 interaction with the actin binding protein ZO-1 suppressed the dynamics of mixed Cx43 GJs. These results suggest that Cx43 C-terminal elements, including the PDZ binding domain, determine cytoskeletal interactions at GJ edges, with ZO-1-mediated actin connections promoting active GJ remodeling, whereas microtubule contacts confer GJ stability and growth. [Supported by NIH grants HL07260, K12GM081265, HL56728, HL082802.]

195 Microtubules and Actin Differentially Influence Remodeling of Connexin43 Gap Junctions, Andrew W Hunter, Robert G Gourdie; Cell Biology and Anatomy, MUSC.

Regulation of Cx43 gap junction (GJ) size and organization is critical in excitable tissues such as heart and brain, but the mechanisms that govern GJ remodeling remain poorly defined. Previously we showed that fusion of GFP to the C-terminus of Cx43 leads to the formation of aberrantly large GJs. Cx43 GJs are resistant to Triton detergent extraction, yet Cx43-GFP GJs are largely Triton-soluble. Interestingly, Triton-insoluble Cx43-GFP localizes predominately to plaque edges—the site of GJ growth—suggesting that GJ edges are stabilized by cytoskeletal interactions that influence GJ size. Fluorescence labeling revealed minimal interaction of actin filaments with Triton-insoluble Cx43-GFP. In contrast, plaques composed of native Cx43 were extensively colocalized with actin polymer. However, Cx43-GFP plaques appear to acquire more microtubule contacts than native Cx43 GJs. Live cell imaging showed GJs containing a mix of Cx43-GFP and native Cx43 are more dynamic than plaques comprised solely of Cx43-GFP. Inhibition of either actin polymerization or Cx43 interaction with the actin binding protein ZO-1 suppressed the dynamics of mixed Cx43 GJs. These results suggest that Cx43 C-terminal elements, including the PDZ binding domain, determine cytoskeletal interactions at GJ edges, with ZO-1-mediated actin connections promoting active GJ remodeling, whereas microtubule contacts confer GJ stability and growth. [Supported by NIH grants HL07260, K12GM081265, HL56728, HL082802.]

196 Activation of a Distant Replication Origin By Long Range Contact with a Replication Enhancer, Mukesh Saxena, Deepak Bastia; Biochemistry, MUSC.

Activation of a replication origin at a distance by contact with the primary binding site of the initiator protein located thousands of base pairs away in a chromosome is a topic of considerable general interest. The replication origins α and β of plasmid R6K are activated by DNA looping to the distantly located γ enhancer that contains the primary binding sites for the plasmid-encode τ initiator protein. Here we report genetic and biochemical analyses of the α origin and the γ enhancer in order to test 2 alternative hypotheses. The enhancer γ merely delivers the initiator protein τ by DNA looping to α by cooperativity at a distance. Alternatively, the mechanism is more intricate and involves formation of a preinitiation complex involving DnaA and τ at γ before it can activate α. We discovered that certain mutations that alter the physical proximity between α and τ binding
site and a DnaA binding site on γ inactivate initiation from γ without abolishing its ability to bind to τ and promote contacts with a physically separated α site in vitro. However, such mutations abolished the ability of the γ enhancer to activate α at a distance. We show further that a sequence element located upstream of the α iteron controls the copy number of the α replicon. A G-site (primase binding site) and its relative spacing from the π-binding α iteron were critical for initiation at α. A deletion of an upstream DnaA binding site in γ that is dispensable for initiation at γ inactivated α. These studies further illuminate the process of replication initiation at a distance by α−γ DNA looping.

197 Ceramide Generated By Acid Sphingomyelinase And Ceramide Synthase 5 Is Involved In Hypoxia/Reoxygenation-Induced Bax Redistribution To Mitochondria, Junfei Jin1, Qi Hou1, Thomas D. Mullen1, Youssef H. Zeidan1, Jacek Bielawski1, Jacqueline M. Kraveka4, Alicja Bielawska2, Yi-Te Hsu1; 1Biochemistry and Molecular Biology, MUSC, 2Pharmacology, Peking Union Medical College, 3Medicine, MUSC, 4Pediatrics, MUSC.

Apoptosis, also known as programmed cell death, is a physiological process required for the development and cellular homeostasis of multicellular organisms. Dysregulation of apoptosis is related to diseases such as cancer, cardiac and cerebral ischemia, neurodegenerative and autoimmune disorders, and viral infections. The pro-apoptotic protein Bax is a member of the Bcl-2 family that plays an important role in apoptosis regulation. It is primarily a soluble protein in healthy cells and its translocation from the cytoplasm to mitochondria constitutes a key step in apoptosis induction. The molecular regulations involved in Bax redistribution to mitochondria, however, are not known. In our study, we found that treatment of NT-2 neuronal precursor cells to hypoxia/reoxygenation (H/R) induced Bax translocation to mitochondria. We also found that this treatment led to the upregulation of ceramide, a sphingolipid that functions as an important second messenger in apoptosis signaling. Using a number of molecular and biochemical analyses, we have shown that this elevation in the ceramide level was primarily due to the actions of acid sphingomyelinase and ceramide synthase LASS 5. Down-regulation of either acid sphingomyelinase or LASS 5 would attenuate ceramide accumulation and H/R-induced Bax translocation to mitochondria. Overall, we have demonstrated that ceramide upregulation following H/R serves as an important signaling step to Bax activation to promote cell death. [NIH grants NS40932 (to Y.-T.H.) and CA97132 (to Y.A.H.).]

198 Mechanistic Insights Into Reb1-Ter3 Complex Mediated Replication Termination in Schizosaccharomyces Pombe, Subhrajit Biswas, Deepak Bastia; Biochemistry and Molecular Biology, MUSC.

Replication fork can be arrested at random sites on chromosomes due to DNA damage caused by intrinsic or extrinsic factors or due to depletion of dNTP pool. Such arrest induces checkpoint pathways until the DNA damage is repaired and fork progression resumed. There is also programmed fork arrest mediated by binding of replication terminator proteins to natural replication termini, called Ter sites. The transcription and replication terminator protein Reb1 of S. pombe binds to Ter2 and Ter3 sequences in the non-transcribed spacers of rDNA to cause polar replication fork arrest. Reb1 is a dimeric protein and the N-terminal dimerization domain of the protein was dispensable for replication termination. Unlike its mammalian counterpart Ttf1, Reb1 did not need an accessory protein to bind to Ter3. The two myb/SANT domains and an adjacent, N-terminal 154 amino acid long segment (called myb-associated domain) were both necessary and sufficient for optimal DNA binding in vitro and fork arrest in vivo. We have also determined the contact points of the protein with the sugar phosphate backbone and the bases of Ter3 that are critical for replication fork arrest. Investigations with prokaryotes have suggested two models of polar fork arrest mechanism. Model I postulates that terminator protein-Ter interaction is both necessary and sufficient whereas a second model requires, in addition, specific interaction between the termination complex and the replisome. Implicit in model I is the notion that the protein DNA complex should function in a foreign cell milieu as long as the protein were correctly expressed, properly folded and had access to the Ter site in the nucleus. In contrast, the second model suggests that fork arrest might not occur if the foreign replisome failed to provide the necessary protein-protein interactions with the termination complex. Here, we present evidence that supports the second model.

199 Assessing the Composition and Structure of Bacterial Communities Associated with the Upper Respiratory Tract of the Atlantic Bottlenose Dolphin, Tursiops Truncatus, Wesley R Johnson, Manolito Torralba, Karen E Nelson, Gregory D Bossart, Patricia A Fair, Pamela J Morris; 1Marine Biomedicine and Environmental Sciences, MUSC, 2J. Craig Venter Institute, 3Harbor Branch Oceanographic Institute, 4Center for Coastal Environmental Health and Biomolecular Research, 5Cell Biology and Anatomy, Marine Biomedicine and Environmental Sciences, MUSC.

In light of increased interest in the human microbiome, there is concomitant interest in the roles of microorganisms as pathogens and symbionts in the health of all mammals, as well as their co-evolution with their host. However, the structure and ecology of microbial communities associated with mammalian hosts remain largely unexplored. Most of our understanding of microbe/mammal interactions is based on the study of pathogens with much of the data coming from impaired or deceased animals. An understanding of the “normal” flora associated with healthy Atlantic bottlenose dolphins (Tursiops truncatus) is an important first step in understanding interactions between cetacean hosts and their microorganisms. In this work, we investigated the bacterial communities associated with the upper respiratory tracts (URTs) of dolphins from the Southeastern coast of the U.S. to assess their diversity and structure. Bacterial clone libraries of 16S rRNA genes were generated from URT fluids of four healthy male dolphins sampled in 2005 as part of the Health and Risk Assessment (HERA) bottlenose dolphin project. Sequence analysis revealed that communities were dominated by two phyla, Bacteroidetes (35.9%) and Proteobacteria (54.9%). While diversity was low at the phylum level, there were numerous, closely-related sequences at the species/strain level that accounted for most of the diversity within the library. Comparisons to 16S databases showed the majority of sequences to be most closely related to Cardiobacterium sp., Suttonella ornithicola, Tenacibaculum spp., or Psychrobacter spp. yet the homologies were sufficiently low to suggest that these sequences represent novel genera and species. Additionally, these sequences showed high intra-specific diversity, suggesting these are stable, symbiotic communities that have co-evolved with their hosts rather than collections of opportunists derived from the environment. These findings are in agreement with results from the human microbiome which demonstrated similar patterns in general taxonomy and community structure.
200 The Effect of Aquaporin-0 C-Terminal Phosphorylation on Plasma Membrane Surface Expression In HEK-293 Cells, Eric R Buck1, Kevin L Schey2, Rosalie K Crouch1; 1Pharmacology, MUSC, 2Biochemistry, Vanderbilt, Ophthalmology, MUSC.

Aquaporin-0 (AQP0) has been found to be the most abundant gene expression (PRL-GE) occurs in pulses in single cultures. Interestingly, the Bmal1 RNA pulse preceded the PRL expression by 4-8 h, a temporal relationship that would be consistent with a BMAL1 action on the PRL promoter. In our next experiments, ChIPs was conducted to determine whether or not an in vivo association occurred between these circadian factors and the PRL promoter. Using standard conditions, we found that a 170 bp segment of DNA including the E-box 133 region was amplified when DNA was immunoprecipitated with antibodies directed against the circadian elements mentioned above. When taken together, our findings of a temporal association of Bmal1, Per1, Per3 as well as Cry1 with PRL expression during an oscillatory event indicates strongly that these factors play a role in PRL-GE pulse activity. In fact, such an interaction between specific circadian elements and the PRL promoter, may not only define the mechanism underlying pulse PRL-GE activity, but also may demonstrate the manner in which the circadian system can control a peripheral output gene such as prolactin. An understanding of the process(es) linking circadian genes and other systemic elements is critical for the treatment of diverse disease states such as cardiovascular disorders, diabetes, and cancer progression in which circadian timing is disrupted. [Supported by R01 DK073270 to FRB.]

202 Differential Effect of Wall Tension on Matrix Metalloproteinase Promoter Activation in the Thoracic Aorta, Jean Marie Ruddy, Jeffrey A Jones, Rupak Mukherjee, Francis G Spinale, John S Ignomidi; Surgery, MUSC and Ralph H. Johnson VA Medical Center.

Abstract not available.

203 Inhibition Of Histone Deacetylase Activity Represses Matrix Metalloproteinase-9 Induction And Preserves Cardiac Function Post Myocardial Infarction, Santhosh K Mani1, Christine B Kern1, William T Rivers2, Rebecca A Pylter2, Francis G Spinale2, Rupak Mukherjee2, Donald Menick2; 1Medicine, Cardiology, MUSC, 2Surgery, MUSC.

Myocardial remodeling, which occurs following myocardial infarction (MI), can manifest in LV dilation. Post-MI, increased expression of matrix metalloproteinases (MMPs), such as MMP-9, is associated with deleterious effects on extracellular matrix remodeling (ECM). Histone deacetylases (HDACs) are a class of enzymes that can greatly affect the transcriptional regulation of genes during pathological conditions. This study tested the hypothesis that suppression of HDACs would repress the MMP-9 induction following MI and lead to more favorable ECM remodeling, thereby preventing LV dilation post-MI. To study this, MI was induced in transgenic mice with the MMP-9 promoter sequences fused to the Beta-galactosidase (Beta-gal) gene. Twelve hours prior to MI, mice were administered the HDAC inhibitor trichostatin A (TSA, 2 mg/kg/day) or vehicle. TSA (n=28) or vehicle treatment (n=23) continued until hearts were harvested 7 days post-MI. The post-MI change in LV end-diastolic volume (echo) was lower in the TSA treated mice (49±9 %) than in mice administered vehicle (69±12%). Beta-gal staining of the post-MI LV was lower in the TSA mice compared to vehicle. Immunohistological staining and zymographic levels of MMP-9 were lower with TSA than in vehicle. This decrease in MMP-9 protein abundance with TSA was complemented by an increase in fibrillar collagen and periostin compared to vehicle. In conclusion, suppression of HDAC activity by TSA reduced MMP-9 expression and affects ECM and LV remodeling following MI. TSA treatment, through inhibition of the histone deacetylases, may provide a novel therapeutic means to attenuate adverse LV remodeling post-MI.
204 Fibroblasts of Hematopoietic Origin Contribute to Embryonic Heart Valve Development. Zoltan Hajdu1, Richard P Visconti2, Medicine, Cell Biology and Anatomy, MUSC, 2Dental Medicine, Cell Biology and Anatomy, MUSC.

The embryonic heart valves develop at discrete regions of the developing heart as an expanded, hyaluronan-rich basement membrane that is subsequently cellularized to form the endocardial cushions. These rudimentary valves are remodeled during in utero development into mature valve leaflets. A number of embryonic sources of the cells that populate the endocardial cushions have been identified. Regarding the atrioventricular valves, the endocardium delivers the first cells through endothelial-to-mesenchymal transition, a process through which endocardial cells leave the endocardial epithelium and adopt a mesenchymal phenotype as they migrate into the ECM of the cushions. Later, cells from the proepicardial organ and the dorsal mesenchymal protrusion also contribute to the endocardial cushion development. Recently, using a murine model, we have demonstrated that circulating cells derived from bone marrow hematopoietic stem cells differentiate into fibroblasts in the adult valves. The goal of this study was to investigate whether cells of hematopoietic origin contribute to the cushion mesenchyme during embryonic valve development. To accomplish this, we used avian embryos to generate quail/chick chimeras and perform immunohistochemistry (IHC). Using IHC, we found CD45+ (common leucocyte antigen) cells in the developing cushions from day 4 (HH stage 23-24) onward throughout embryonic development. Using anti-BrdU double immunofluorescence, we showed CD45+ cell proliferation. We also used antibodies to pro-collagen type I, Hsp47, and α-smooth muscle actin to demonstrate the fibroblastic phenotype of CD45+ cells. By transplanting 3-day (HH stage 20) quail aorta (the earliest intraembryonic hematopoietic area) into 3-day chicken embryos and using the QH1 (quail hematopoetic marker) antibody, we found similar expression patterns to CD45 in the developing valves, providing further evidence of the hematopoietic origin of these cells. We conclude that cells of hematopoietic origin are continuously recruited into the developing endocardial cushions/valves where they differentiate into fibroblasts starting from the early stages of valvulogenesis.

207 Targeting Sphingolipid Metabolism to Control Gene Expression By an Oncogenic Herpesvirus. Sarumathi Mohan1, Chris Parsons2, Medicine, Infectious Diseases, MUSC, 2Medicine, Infectious Diseases, Microbiology and Immunology, MUSC.

Kaposi’s sarcoma (KS) represents the most common tumor associated with HIV infection and organ transplantation. The gamma-herpesvirus, Kaposi’s sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus-8), is etiologically associated with KS. Conventional chemotherapy, the current treatment approach for KSHV-associated cancers, carries additional toxicity and failure rates for HIV-infected patients and, therefore, there is an urgent need for more effective and less toxic approaches. Metabolism of sphingolipids, including ceramides, incurs the activation of a number of signaling pathways important for KSHV infection of target cells and, ultimately, viral oncogene expression. Whether targeting sphingolipid metabolism disrupts KSHV gene expression during initial infection is unknown. We sought to determine whether inhibition of sphingosine kinase (SK), an important intermediate in ceramide-induced signaling, disrupted KSHV gene expression during initial infection of HeLa cells. Using RT-PCR, we found that mRNA levels for two latent KSHV encoded genes, v-cyclin and v-FLIP, decreased during infection with SK inhibition, whereas levels of two other lytic mRNA, encoding vGPCR and RTA, increased. In addition, a decrease in the expression of the KSHV latency-associated nuclear antigen (LANA) during infection was verified by an immunofluorescence assay. These results suggested that SK inhibition altered the viral replication cycle to favor lytic gene expression during initial infection, which typically results in cell death. Using flow cytometry, we verified that SK inhibition did increase cell death during infection based on annexin-FITC/7AAD staining. KSHV v-FLIP activates the classical and alternative NF-κB pathways by interacting with different components of the IkB kinase (IKK) complex and, therefore, SK inhibition may cause premature cell death through a decrease in v-FLIP expression and NF-κB activation. We are currently investigating v-FLIP interactions with the IKK complex and the levels of NF-kB in endothelial cells and KSHV-infected B cells during treatment with SK inhibitors. Overall, these data support the possibility of using SK inhibition
to target KSHV-infected tumor cells through the alteration of the viral life cycle.

208 Characterization of the Dihydroceramide Desaturase Enzyme and the Effects of Fenretidine on Enzyme Activity In-Vitro, Mehrdad Rahmaniyan1, Yusuf A Hannun2, L M Obeid3, Jacqueline M Kraveka4; 1Pediatrics, Division of Pediatric Hematology Oncology, MUSC, 2Biochemistry and Molecular Biology, MUSC, 3Biochemistry and Molecular Biology, Medicine, MUSC, Ralph H. Johnson VA Medical Center, 4Pediatrics, Division of Pediatric Hematology Oncology.

Abstract not available.

209 Low Prevalence of Osteoporosis in Children with Sickle Cell Anemia Receiving Chronic Red Blood Cell Transfusion, Elizabeth T Walsh1, Yaw Appiagyei-Dankah1, Ramasubramanian Kalpathi1; 1Pediatric Endocrinology, MUSC, 2Pediatric Hematology and Oncology, MUSC.

Introduction: Bone mineralization is significantly compromised in children with sickle cell anemia (SCA) due to marrow hyperplasia from chronic hemolysis. Few studies have shown high rates of reduced bone mineral density in children and adolescents with SCA. However the true prevalence of osteoporosis in children with SCA undergoing chronic PRBC transfusions have not been investigated. These patients receive monthly PRBC transfusions for abnormal transcranial ultrasound or history of sickle cell crisis, acute chest syndrome etc), available markers of bone mineralization. The purpose of this study was to determine the prevalence of osteoporosis in children with SCA receiving chronic PRBC transfusions.

Methods: Electronic medical records of children with SCA receiving chronic PRBC transfusions were reviewed. These patients receive monthly PRBC transfusions for abnormal transcranial ultrasound or history of stroke. We reviewed the demographic data, auxology data, sickle cell phenotype, clinical markers of severe SCA (e.g. pain crisis, acute chest syndrome etc), available markers of bone metabolism, and bone density by use of DEXA scan z-scores for both femoral neck and total lumbar spine. Results: Twenty-eight patients were included ranging from 10-21 years (mean 15.2 years) with an even gender distribution (16 males; 12 females). Median DEXA z-score of femoral neck was -0.76; median DEXA z-score of total lumbar spine was -0.09. Osteoporosis (DEXA z-score <-2.0) was not found in any femoral neck studies and five (17%) total lumbar spine studies. Osteopenia (DEXA z-score -1 to -2) was found in nine (32%) femoral neck studies and six (21%) total lumbar spine studies. All patients had low Vitamin D (range <6 to 25ng/mL; normal range 25-80ng/mL). Discussion: Our data suggest that children with SCA undergoing chronic monthly PRBC transfusions have a decreased rate of osteoporosis than found in previous pediatric studies. This may indicate an additional benefit of chronic transfusion therapy. This study generates the theory that different chronic therapies (PRBC transfusions) of sickle cell anemia may affect bone health differently.

210 Regulation of Fli1 Expression By Ets Factors in Lymphocytes, John L Svenson, Katherine Chike-Harris, May Amria, Tamara K Nowling; Medicine, Rheumatology, MUSC.

Lupus is a systemic autoimmune disease characterized by increased expression of several inflammatory and transcription factor genes. Mounting evidence indicates that the expression level of the transcription factor gene Fli1 has a significant impact on the pathogenesis of lupus. Previously, we identified several cis-regulatory elements that are required for optimal promoter activity in lymphocytes. However, precisely how Fli1 expression in non-autoimmune or lupus prone lymphocytes is controlled is not completely understood. To gain a better understanding of how Fli1 expression is controlled in lymphocytes, we analyzed binding to and activation of the Fli1 promoter by trans-acting factors through identified cis-regulatory elements. We demonstrate that the Fli1 promoter can be activated by various Ets transcription factors including Ets1, Ets2, Fli1 and Elf1 and that GATA1 and GATA3 can stimulate the Fli1 promoter synergistically in conjunction with Ets1, Ets2, Fli1 and/or Elf1. In vitro binding studies identified binding of transcription factors Elf1, Tel and Fli1 to three Ets binding sites in the Fli1 promoter in both primary B and T cells from non-autoimmune mice. In vivo binding assays in primary T cells from BALB/c mice demonstrate that Ets1 and Ets2 bind the endogenous Fli1 promoter and to a lesser extent Fli1 and Elf1. Together these results demonstrate for the first time mechanisms involved in regulating Fli1 transcription in lymphocytes. Future studies are aimed at determining whether Fli1 transcription is differentially regulated in lymphocytes from lupus prone mice. [This work was supported by NIH grants DK072306 and AR053376.]

211 Silencing of Abcd1 and Abcd2 Genes Sensitizes Astrocytes for Inflammation: Implication for X-Adrenoleukodystrophy, Jaspreet Singh, Mushfiquddin Khan, Inderjit Singh; Medicine, Pediatrics, MUSC.

X-linked adrenoleukodystrophy (X-ALD) is a metabolic disorder arising from a mutation/deletion in the ABCD1 gene, leading to a defect in peroxisomal ALD protein (ALDP) which inhibits the oxidation of very long chain fatty acids (VLCFA). Thus, these VLCFA accumulate. In a cerebral form of ALD (cALD), VLCFA accumulation induces neuro-inflammation that leads to loss of oligodendrocytes and myelin, which ultimately shortens the lifespan. To establish a relationship between the metabolic disease and inflammatory disease induction, we document that siRNA-mediated silencing of Abcd1 (ALDP) and Abcd2 (ALD related protein, ALDRP) genes in mice primary astrocyte cultures resulted in accumulation of VLCFA and induction of an inflammatory response characteristic of human cALD. Correction of the metabolic defect using monoenoic fatty acids in Abcd1/Abcd2-silenced cultured astrocytes decreased iNOS and inflammatory cytokine expression, suggesting a link between VLCFA accumulation and inflammation. The inflammatory response was found to be mediated by transcription factors NF-κB, AP-1, and C/EBP in Abcd1/Abcd2-silenced mouse primary astrocytes. Although mechanisms of VLCFA-mediated induction of the inflammatory response have been investigated here in vitro, the in vivo mediators remain elusive. Our data represent the first study to suggest a direct link between the accumulation of VLCFA and the induction of inflammatory mediators. [This study was supported in part by grants from the National Institutes of Health: NS-22576, NS-34741, NS-37766, NS-40810, C06 RR018823, and C06 RR015455.]

212 Chronic Ethanol-Induced Homeostatic Plasticity in the Hippocampus Involves Opposing Changes in SK2 Channels and NMDA Receptors, Patrick J Mulholland1, Howard C Becker2, John J Woodward3, Judson Chandler4; 1Medicine, Neurosciences, MUSC, 2Medicine, Psychiatry, MUSC.

Small-conductance, calcium-activated K+ (SK) channels are central to the function of neurons where they regulate intrinsic excitability and synaptic plasticity. Recent studies have established a link between NMDA receptor activity and modulation of SK2 channels, and evidence suggests that
synaptic NMDA receptors and SK2 channels form a regulatory calcium-mediated feedback loop. We have previously demonstrated that chronic ethanol produces a homeostatic targeting of NMDA receptors to synaptic, but not extrasynaptic sites. Here, we sought to characterize changes in the expression, function, and localization of SK2 channels following chronic ethanol exposure and during acute ethanol withdrawal (EWD) hyperexcitability. Alterations in SK2 channels were assessed by immunoblot, electrophysiological and behavioral analyses using established in vivo and in vitro models of chronic ethanol exposure and withdrawal. In contrast to the upregulation of synaptic NMDA receptors, chronic ethanol exposure induced a reduction in the expression of SK2 channels. Similarly, a marked reduction in the amplitude of apamin-sensitive tail currents was observed in slices treated chronically with ethanol. Activating SK2 channels with the positive modulator 1-EBIO markedly attenuated EWD hyperexcitability in vitro and reduced the severity of handling-induced convulsions in ethanol-treated C3H/He mice. These data suggest that decreases in SK2 channels and increases in synaptic NMDA receptors represent a common homeostatic adaptive response to prolonged reductions in NMDA receptor activity during ethanol exposure. We further suggest this represents a functional uncoupling of the SK channel-NMDA receptor calcium-dependent feedback loop in synapses that may contribute to tolerance development and to hyperexcitability during EWD. These data on SK2 channels provide evidence for a novel therapeutic target for the control of EWD hyperexcitability and possibly relapse. [Supported by NIAAA Grants: AA010983 (LJC), AA016450 (PJM)]

213 Orexin Neurons That Project to the Ventral Tegmental Area Are Activated By Morphine Preference During Protracted Forced Abstinence, Kimberlei A Richardson, Paul T Knackstedt, Gary Aston-Jones; Neurosciences, MUSC.

Abstract not available.
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