UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

40th Annual Graduate Research Conference

Presented by:

GSA graduate student association
UNIVERSITY of MARYLAND

40th Annual Graduate Research Conference

presented by the Graduate Student Association

Contents:

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A Message from the President

March 15, 2018

Congratulations to the Graduate Student Association on its 40th annual Graduate Research Conference. What an incredible milestone!

This is one of the University's very best and most enduring traditions, inviting students from all schools and disciplines to share in each other's work, to learn about new avenues of discovery and research, and most importantly, to create opportunities for the kind of interprofessional, interdisciplinary collaboration that so often breeds breakthroughs.

This instinct to share is important. It's important that each of us understands how our colleagues contribute to our collective mission, and it's important that we consider our work not in isolation but in context. The search for context has ignited partnerships at all levels of this institution, and I remain convinced that we work *best* for the people of this state, this nation, and this world when we work *together*.

I hope the day proves enlightening and exciting. I hope it opens up possibilities to take your work further. I hope others might find in *your* research the spark or scaffolding they need for their own. And I hope that the act of sharing your scholarship (and why it matters) inspires in you a desire to do so more often and more publicly. Because when science and service are under attack, it's our scientists and our public servants who must lead the way forward.

That call to leadership is why you're at UMB; it's why you're at this conference. And so I thank you for your participation today—for unselfishly giving your work a new and rich life beyond you.

Sincerely,

Jay A. Perman, MD

President

Forward

Welcome to the 40th annual Graduate Research Conference (GRC) at the University of Maryland, Baltimore (UMB)! The Graduate Student Association (GSA) is proud to host this conference to allow our researchers, graduate students, professional students, and postdoctoral fellows the opportunity to present their work and discoveries. The interdisciplinary nature of our campus allows us to showcase a variety of research within one conference, including basic, nursing, social, and applied sciences.

This year, we have abstracts from students and postdoctoral fellows representative of every UMB graduate research program, which will be featured in both oral and poster presentations. As in previous years, all students presenting abstracts are eligible to win an award for outstanding presentations in their sessions. Additionally, the Geriatrics and Gerontology Education and Research Program (GGEAR) and the Center for Research on Aging (ORC) at the University of Maryland, Baltimore will be sponsoring a special award in aging research. The Office of Technology Transfer (OTT) will also present their 10th annual Graduate Translational Research Award to recognize important translational research being performed by a UMB graduate student or postdoctoral fellow. We thank the GGEAR and OTT for their continued support of GRC and the outstanding research being conducted by students and postdoctoral fellows on campus. We are proud to host our keynote speaker, Dr. Benjamin Prosser, a UMB alumnus and an Assistant Professor in the Department of Physiology at the University of Pennsylvania Perelman School of Medicine, as well as a member of the Pennsylvania Muscle Institute and Cardiovascular Institute at Penn. We are also happy to honor the graduate students who have passed their qualifying exam during the last year with the Candidacy Ceremony following the completion of the scientific program and awards of the GRC. After the Advancement to Candidacy ceremony and GRC awards, there will be a reception and social hour.

The GSA gratefully acknowledges those who helped make the GRC possible and successful. We would like to thank President Perman for his continued support of the students on our campus and their research. Special recognition is deservedly given to Dr. Erin Golembewski, Senior Associate Dean of the Graduate School, for her continued guidance and support, as well as all of the staff of the Graduate School Office. Many thanks are owed to the HS/HSL for all their help with presentation preparations and providing us with the resources necessary to perform informed research. We commend our keynote speaker, Dr. Benjamin Prosser, for his contributions to the field of science and sharing his message with our campus. We greatly appreciate the faculty members acting as judges for donating their time, expertise, and critiques. We are grateful for our amazing sponsors and supporting organizations that drive the success of our event! We thank the GSA program representatives and members for their work throughout the year, and especially for their commitment to making the GRC successful. Finally, we would like to recognize the GRC Organizing Committee for their hard work to make the GRC possible and bring together the researchers in our campus community. It is our pleasure to host you at the 40th annual Graduate Research Conference, and we hope you enjoy today's program and events!

<u>GSA Executive Board</u>
Courtney Chandler – President
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Alyssa Grogan, Julia Thayer, Courtney Chandler, Devin Snyder, Linda Senbanjo, Christine Carney, Jackline Lasola, Ramon Martinez and Janelle Hauserman

Student Award Winners

The Graduate Student Association would like to congratulate the students who have won our awards during the 2017-2018 academic year. The Graduate Student Research Award provides funding to those students who need extra resources to complete their studies. The Travel Award supports students so they may attend seminars and conferences in their fields.

Research Award

Molly Hritzo
Hong Yang

Travel Award

Kyeongmo Kim, Third Quarter 2017
Hyeshin Park, Third Quarter 2017
Sarah Jackson, Third Quarter 2017
Sally Hageman, Third Quarter 2017
Joonyup Lee, Third Quarter 2017
Yanfeng Xu, Third Quarter 2017

Elizabeth Woytowicz, Fourth Quarter 2017
Eric Kong, Fourth Quarter 2017
Husam Albarmawi, Fourth Quarter 2017
Kaila Noland, Fourth Quarter 2017
Rahul Khairnar, Fourth Quarter 2017
Susannah Shissler, Fourth Quarter 2017

Sarah Holmes, First Quarter 2017
Eryn Dixon, First Quarter 2017
Katy VanEgmond, First Quarter 2017
Lori Stewart, First Quarter 2017

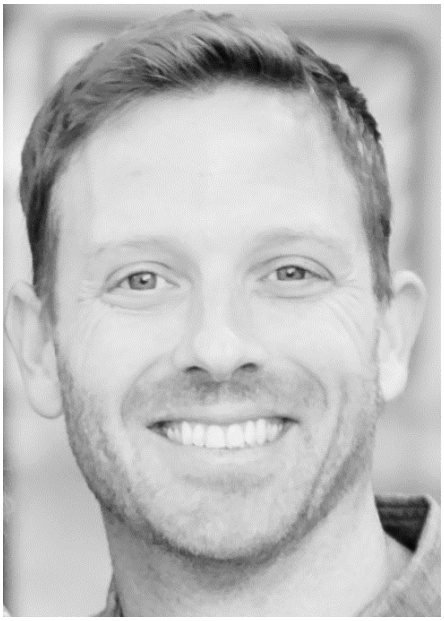
Wan-Wan Liao, Second Quarter 2017
Sarah Holmes, Second Quarter 2017
Chieh-ling Yang, Second Quarter 2017

Abstract Booklet Image
Gurmannat Kalra

Keynote Speaker Biography

Dr. Benjamin Prosser

GPILS Alumnus of the Year, 2017
Assistant Professor of Physiology, University of Pennsylvania, Perelman School of Medicine



Keynote Speaker Dr. Benjamin Prosser is an alumnus from the Program in Molecular Medicine and winner of the GPILS' 2017 Alumnus of the Year at the University of Maryland, Baltimore. Dr. Prosser is an Assistant Professor in the Department of Physiology at the University of Pennsylvania Perelman School of Medicine, as well as a member of the Pennsylvania Muscle Institute and Cardiovascular Institute at Penn. The Prosser Lab is interested in the mechanobiology of the heart - how the heart cell generates force, and how external forces feed back to regulate myocyte form and function. We combine super-resolution microscopy with advanced approaches to manipulate stress and strain to understand the interplay between the mechanical environment and the patho/physiology of the heart cell. The GSA and student body of UMB would like to welcome Dr. Prosser home to campus and express our thanks for his willingness to share his story at our conference.

40th Annual Graduate Research Conference

Schedule of Events

SMC Campus Center
March 15th, 2018

8:00-9:00 am	**Breakfast & Registration**	**Second Floor**
9:00-10:30 am	**Oral Presentations**	
	Session A	**Elm Ballroom A**
	Session B	**Elm Ballroom B**
10:30-10:45 am	**Coffee Break**	
10:45 am-11:45 am	**Poster Presentations**	**Room 349**
	Session C	
	Session D	
	Session E	
11:45 am-1:00 pm	**Lunch**	**Elm Ballroom**
	Dr. Benjamin Prosser	
1:00-2:00 pm	**Poster Presentations**	**Room 349**
	Session F	
	Session G	
	Session H	
2:00-2:15 pm	**Coffee Break**	
2:15-3:45 pm	**Oral Presentations**	
	Session I	**Elm Ballroom A**
	Session J	**Elm Ballroom B**
4:00-5:00 pm	**Candidacy Ceremony and GRC Awards**	**Elm Ballroom A**
5:00-7:00 pm	**Reception & Social Hour**	**Second Floor**

Session Assignments

Session A – Oral Session, 9:00-10:30 am, Elm Ballroom A
(#1 Yanfeng Xu), (#2 Alayna Blazakis), (#3 Maya Hanna), (#4 Caroline Harmon-Darrow), (#5 Priyanka Gaitonde) (#6 Shamir Kalaria)

Session B - Oral Session, 9:00-10:30 am, Elm Ballroom B
(#7 Erin McClure), (#8 Amber Mueller), (#9 Amy Defnet), (#10 Jackline Joy Lasola), (#11 Courtney Chandler), (#12 Maria Ibrahim)

Session C – Poster Session, 10:45-11:45 am, Room 349
(#13 Timileyin Adediran), (#14 Shamir Kalaria), (#15 Ozell Sanders), (#16 Jennifer Linehan), (#17 Aparna Vadlamani), (#18 Bansri Desai), (#19 Kaia Amoah), (#20 Emily Stucke)

Session D – Poster Session, 10:45-11:45 am, Room 349
(#21 Chad Johnson), (#22 Edith Hernandez), (#23 Ebehiremen Ayewoh), (#24 Stephanie Catalano), (#25 Jason Alipio), (#26 Heather Neu), (#27 Julia Thayer), (#28 Camilo Vanegas), (#29 Joel Brandis)

Session E – Poster Session, 10:45-11:45 am, Room 349
(#30 Melissa Metry), (#31 Kayla Rayford), (#32 Angela Lee), (#33 Allison Gerber), (#34 Nicholas Palmateer), (#35 Courtney Matson), (#36 Cecilia Najera), (#37 Luke Brewster), (#38 In Seo La), (#39 Ivie Conlon)

Session F – Poster Session, 1:00-2:00 pm, Room 349
(#40 Hamzah Alghzawi), (#41 Sharmila Das), (#42 HyoJin Son), (#43 Wan-wen Liao), (#44 Gurmannat Kalra), (#45 Laura Gessler), (#46 Brian Johnson), (#47 Chieh-ling Yang), (#48 Nandini Raghuraman), (#49 Hannah Oseghale and Esther Kimani)

Session G – Poster Session, 1:00-2:00 pm, Room 349
(#50 Rahul Khairnar), (#51 Alecia Dent), (#52 Hilary Bright), (#53 Kimberly Wilson), (#54 Brandon Drennen), (#55 Bishal Tandukar), (#56 Jordan Pritts), (#57 Tyree Wilson), (#58 Kiwon Ok), (#59 Jake Dow), (#60 Alyssa Grogan)

Session H – Poster Session, 1:00-2:00 pm, Room 349
(#61 Daniel Garman), (#62 Ramon Martinez III), (#63 Garrick Centola), (#64 Elizabeth Robinson), (#65 Paige Zambrana), (#66 Megan Moorer), (#67 Mc Millan Ching), (#68 Vikas Saxena), (#69 Nisha Pawar), (#70 Devin Snyder)

Session I – Oral Session, 2:15-3:45 pm, Elm Ballroom A
(#71 Rahul Khairnar), (#72 Raqeeb Jamil), (#73 Michael Kessler), (#74 Anthony Herrera), (#75 Nimasha Fernando and Yolanda Peprah)

Session J – Oral Session, 2:15-3:45 pm, Elm Ballroom B
(#76 Kimberly Filcek), (#77 Patrick Bailey), (#78 Manasa Srikanth), (#79 Amanda Labuza), (#80 Ashley Mitchell), (#81 Aksinija Kogan)

Abstracts

1. PREDICTORS OF NON-U.S. BORN MOTHERS' PARENTING STRESS ACROSS EARLY CHILDHOOD IN FRAGILE FAMILIES: A LONGITUDINAL ANALYSIS

Yanfeng Xu

Xu, Y., Wang, X., Ahn, H., and Harrington, D.

Session A; Oral Presentation; Ballroom A

The transition into motherhood is a life stressor, and it can be more stressful for non-U.S. born mothers because of the intersections among migration, limited financial capabilities, and less social and family support to take care of children (Dreby, 2015; Falicov, 2007; Paris, 2008). This study examined the predictors of non-U.S. born mothers' parenting stress across early childhood using data from the Fragile Families and Child Well-Being Study. Results of the longitudinal multilevel analysis indicated that support from extended family and friends; mothers' involvement, depression, age, and education; children's temperaments; and Asian race were significant predictors of maternal parenting stress over time. However, fathers' involvement did not significantly decrease maternal parenting stress. Implications for research and practice are discussed.

2. IMPLEMENTATION OF AN OUTPATIENT FALLS EVALUATION AND PREVENTION PROGRAM FOR INDEPENDENT OLDER ADULTS

Alayna Blazakis

Blazakis, A. M.

Session A; Oral Presentation; Ballroom A

Falling represents one of the most significant causes of injury and mortality in older adults over the age of 65. A quality improvement falls intervention program was developed within an older adult residential community with a high incidence of falls. The program's purpose was to ensure all patients in this population who suffered a fall were evaluated by primary care within the facility, and prevention measures for future falls were achieved. A falls algorithm was developed based on these guidelines which lead staff through steps of the evaluation and prevention measures based on the residents' risk. Both STEADI and AGS/BGS guidelines recommend assigning a falls risk based on patient assessment, and then performing interventions tailored to the patient to prevent future falls. Basic interventions included strength and balance training and vitamin D supplementation.

The anticipated primary outcome of the project was an increase in provider involvement in post-fall assessment and treatment practices, measured by rate of implementation of the steps of the falls program. Twenty falls were counted during the 8-week implementation phase. 90% of these residents had follow up by the staff nurse; 35% subsequently visited a nurse practitioner in the clinic with 100% of all visits utilizing the Falls Evaluation Form. Interestingly, 60% of all falling residents began physical therapy programs and 20% were evaluated by occupational therapy. These results indicate that residents who fall were sometimes bypassing primary care. There may be room to improve interdisciplinary communication between the primary care and rehabilitation staff.

3. EXAMINING DISEASE-SPECIFIC HEALTHCARE UTILIZATION AMONG

INDIVIDUALS WITH DEMENTIA PRIOR TO DIAGNOSIS

Maya Hanna

Hanna M.L., Albrecht J.S., Kim D., and Perfetto E.M.

Session A; Oral Presentation; Ballroom A

Background: Health care utilization (HCU) is higher among individuals diagnosed with Alzheimer's disease and related dementias (ADRD), even years prior to diagnosis. However, few studies have described comorbidities or services associated with higher HCU. Objectives: characterize all-cause and disease-specific HCU three years prior to a diagnosis of ADRD, and compare HCU in individuals diagnosed with ADRD versus matched controls. Methods: Using de-identified data from the OptumLabsTM Data Warehouse, we identified individuals at first, new ADRD diagnosis from 2011 to 2014 (n=36,838). Cases were matched 1:4 to controls. ADRD was defined using ICD-9 codes and prescription fills for anti-dementia medications. Individuals required a 36-month look back to confirm index diagnosis and capture HCU. Generalized estimating equations were used to test the association between HCU and case status, controlling for year and matching variables. Results: All cause, 36-month HCU prior to ADRD diagnosis was significantly higher among cases (rate ratio (RR) 1.48; 95% confidence interval (CI) 1.46, 1.50). HCU among cases was higher in long-term care settings (RR 5.13; 95% CI 4.87, 5.41) followed by inpatient care settings (RR 2.0; 95% CI 1.95, 2.03). Increased disease-specific HCU among cases was observed for Parkinson's disease (RR 9.0; 95% CI 7.89, 10.37), psychiatric disease (RR 4.56; 95% CI 4.30, 4.85), and chronic liver disease (RR 3.89; 95% CI 3.43, 4.41). Conclusions: HCU is significantly elevated among individuals with ADRD prior to diagnosis. HCU by comorbid condition may be equally, if not more informative than health care setting alone in understanding early indicators of ADRD.

4. COMMUNITY-BASED MEDIATION EVALUATION: A MEASUREMENT STUDY USING EFA AND CFA

Caroline Harmon-Darrow

Harmon-Darrow, C. L.

Session A; Oral Presentation; Ballroom A

Continued growth of mediation and other conflict resolution services in courts, communities, schools, and government makes high quality of service increasingly important. Although participant satisfaction with mediation and dispute resolution are well-researched, only one study has examined the measurement properties of participant evaluations. Post-mediation evaluations from 998 mediation participants in community-based mediation are analyzed using exploratory and confirmatory factor analysis. Using a well-fitting four-factor, nine-item model, responses measured four distinct dimensions of satisfaction: process, understanding, endorsement, and satisfaction. Of those empirically-defined latent variables, participants' increased understanding of each other was most closely correlated with satisfaction.

5. TOTAL HEALTHCARE EXPENDITURES ASSOCIATED WITH BIOLOGICAL ANTI-RHEUMATIC DRUG USE AMONG MEDICARE BENEFICIARIES WITH RHEUMATOID ARTHRITIS

Priyanka Gaitonde

Gaitonde, P. and Shaya, F. T.

Session A; Oral Presentation; Ballroom A

Objectives: Medicare coverage rules regarding infusible biological disease modifying anti-rheumatic drugs (bDMARDs) under Part B (medical benefit) and self-injectable bDMARDs under Part D (drug benefit) have stimulated the use of these drugs. Our objective is to assess overall utilization and compare healthcare costs associated with infusible vs. self-injectable bDMARDs, among rheumatoid arthritis (RA) Medicare beneficiaries.

Method: We analyzed the 5% Medicare Chronic Conditions Warehouse database (2006-2015) using a retrospective cohort study design. The study cohort consisted of continuously enrolled, fee-for-service beneficiaries with RA. Healthcare costs for both infusible and self-injectable bDMARDs were attributed to all RA-related drug and direct medical costs incurred during the treatment duration. The incremental cost of infusible bDMARDs was derived in the multivariate analysis, using a generalized liner model.

Results: Among 39,224 Medicare beneficiaries with RA who were treated with anti-rheumatic drugs between 2006 and 2015, 14.6% (N=5,727) used infusible and 11.5% (N=4,527) used self-injectable bDMARDs. The average annual total healthcare cost for beneficiaries using infusible bDMARDs was $ 7,116.5 and $ 7,742 per person for those using self-injectable bDMARDs ($p<0.05$); with an average duration of 26.2 months and 23.7 months respectively. The medical cost was 9.3% higher among infusible bDMARD users ($p<0.05$) while the drug cost was equivalent among the two classes.

Conclusion: Overall, bDMARDs accounted for about one third of RA treatment for Medicare beneficiaries with RA. Although the drug cost was equivalent, infusible bDMARDs were associated with significantly higher medical costs as compared to self-injectable treatments.

6. Optimizing Binge Eating Disorder Drug Development using a Quantitative Disease-Drug-Trial Model

Shamir Kalaria

Kalaria S.N., McElroy S., Gobburu J., and Gopalakrishnan M.

Session A; Oral Presentation; Ballroom A

Objectives: The development of drugs to treat binge eating disorder is challenged by high dropout rates due to lack of efficacy and long follow up times. The objective of this analysis is to inform future BED clinical trials using a quantitative disease-drug-trial framework.

Methods: Longitudinal normalized binge frequency (BF) from a double blind, randomized placebo controlled, titration trial (N=61) that evaluated the use of topiramate for BED, was used to develop the disease-drug trial model. Model building consisted of (1) developing a placebo effect model that describes longitudinal data from the placebo group, (2) adding a dose effect to the placebo model to evaluate the impact of varying treatment doses on BF, (3) using a kinetic-pharmacodynamic (K-PD) model to justify the delay in changes in BF, and (4) creating a parametric time to event model to characterize patient dropout patterns. Secondary efficacy variables were predicted based on individual predicted BF scores.

Results: The placebo effect on normalized BF over time demonstrated a maximum decrease in BF of 50% by 4 weeks. Baseline global severity of illness scores was found to be a significant covariate on baseline BF. The K-PD model adequately explained the delayed effect on changes in BF with a time to reach maximum decrease in BF of 80% by 7.5 weeks. Patients were found to have a higher drop-out probability if they gained weight.

Conclusion: The developed comprehensive disease-drug-trial model will be used to simulate different clinical trial designs to optimize topiramate and similar BED drug development programs.

7. P47 Restricts Borrelia burgdorferi Colonization of Ixodes scapularis Ticks

Erin McClure

McClure, E. E., Wang, X., and Pedra, J. H. F.

Session B; Oral Presentation; Ballroom B

The black-legged tick Ixodes scapularis transmits the Lyme disease spirochete Borrelia burgdorferi to humans. Over 300,000 cases of Lyme disease occur annually in the United States alone. Despite the public health burden of this tick, detailed knowledge of vector-pathogen interactions is lacking. One interface between the tick vector and B. burgdorferi is the tick immune system. The immune deficiency (IMD) pathway leads to nuclear factor (NF)-κB-mediated production of antimicrobial peptides upon stimulation. The central regulator of the IMD pathway in ticks is the E3 ubiquitin ligase X-linked inhibitor of apoptosis (XIAP). We hypothesized that substrates of XIAP regulate the IMD pathway in I. scapularis. Coimmunoprecipitation of XIAP and associated proteins followed by mass spectrometry led to the identification of p47, a protein canonically involved in regulating membrane biogenesis. Silencing of p47 in I. scapularis nymphs led to increased B. burgdorferi acquisition. We showed that p47 molecularly interacts with XIAP. Together, these results indicate that p47 and XIAP interact and that p47 may function as a positive regulator of the IMD pathway in ticks. Future directions include determining if XIAP ubiquitylates p47 and elucidating the mechanism of p47-mediated inhibition of B. burgdorferi colonization of I. scapularis.

8. The Muscle Xenograft, a Humanized Model of FSHD

Amber Mueller

Mueller, A.L., O'Neill, A., Lach-Martinez, A., Sakellariou, P., and Bloch, R.J.

Session B; Oral Presentation; Ballroom B

Aberrant expression of DUX4, a gene unique to humans and primates, causes Facioscapulohumeral Muscular dystrophy (FSHD), yet the pathogenic mechanism is unknown. Transgenic mouse models have failed to reproduce the FSHD phenotype, therefore studies of endogenously expressed DUX4 have been limited to patient biopsies and myogenic cell cultures. Our laboratory developed a method to xenograft immortalized human muscle precursor cells from patients with FSHD and controls into the tibialis anterior of immune-deficient mice, generating pure human muscle xenografts. We found that intermittent neuromuscular electrical stimulation increases myofiber size, quantity, and quality within xenografts. We also showed that FSHD cells mature into organized and innervated human muscle fibers, and also reconstitute the satellite cell niche within the xenografts. Recently, we modified the method

to produce chimeric human/mouse xenografts to study genetic dysregulation by way of nuclear translocation of human proteins from human to mouse myonuclei. We are using these models to test the hypothesis that DUX4 expression activates pathogenic gene targets that alter the structural physiology of muscle, inducing local muscle wasting, and leading to FSHD. Our results show that xenografts express DUX4 and DUX4-gene targets in a DUX4-dependent manner. Furthermore, the FSHD xenografts exhibit a distinctly slow-type muscle phenotype switch, compared to controls. Finally, results from our cHMX show that several mouse genes are up-regulated in response to DUX4 expression from human myonuclei, indicating that DUX4 induces a nuclear translocation cascade which may explain how relatively low expression of DUX4 causes the debilitating effects we observe in patients with FSHD.

9. Targeting the ERK1/2 Pathway to Prevent Airway Smooth Muscle Cell Proliferation and Tissue Remodeling in Asthma

Amy Defnet

Defnet, A.E., Huang, W., Kane, M., Deshpande, D., and Shapiro, P.

Session B; Oral Presentation; Ballroom B

Increased airway smooth muscle (ASM) cell mass and secretory functions are hallmark characteristics of airway inflammatory diseases, such as asthma. To date, there are no effective therapies to combat ASM cell proliferation that contributes to hyperresponsive airways and debilitating bronchoconstriction. Targeting transcription factors presents a therapeutic opportunity to treat asthma. Previous studies suggest that inhibition of the activator protein-1 (AP-1) transcription factor could prevent the activation of ASM cells during inflammation. In the current studies, we evaluated a novel function-selective extracellular signal-regulated kinase (ERK2) inhibitor, referred to as SF-3-030, in regulating platelet-derived growth factor (PDGF) induced AP-1 activity and ASM cell proliferation. PDGF treatment induced active ERK and the transcription factors FosB, c-Fos, c-Jun, and Fra-1 over time. SF-3-030 only inhibited Fra-1, consistent with its function selective mechanism of action. Despite only Fra-1 being inhibited, SF-3-030 inhibited AP-1 activity and ASM cell proliferation. These data suggest that partial inhibition of ERK2 signaling through AP-1 with novel compounds such as SF-3-030 is sufficient to inhibit the proliferation of primary human ASM cells and may overcome therapeutic limitations of inhibitors that block all enzymatic activity of kinases with multiple cellular functions.

10. Interrogating the Role of Interleukin-1 Receptor-Associated Kinases (IRAKs) in Mediating Response to Immunotherapies for Solid Tumors

Jackline Joy Lasola

Lasola, J. J. M. and Davila, E.

Session B; Oral Presentation; Ballroom B

Cancer care in recent years has faced compelling breakthroughs in approaches to patient management with the advent of immunotherapies for cancer. In particular, checkpoint inhibitors such as ipilimumab and nivolumab have been life-changing in a subset of patients with solid tumors that have otherwise been unresponsive to therapy. These therapies work by blocking inhibitory signals sent by the tumor cells and other cells in the tumor microenvironment to allow a sustained antitumor T cell response against the cancer.

Interestingly, when evaluating early responses to checkpoint inhibitors two patterns of response arise. In the subset of patients who do respond to checkpoint inhibitor regimens the response is dramatic and sustained (as noted by progression-free and overall survival), while for those who do not respond to checkpoint inhibitor therapy there is no difference in survival from the previous standard of care. This suggests other markers of immunotherapy response that have yet to be identified. Specifically, this study takes a bioinformatics approach to evaluating clinical trials to determine the status of IRAKs in responders and non-responders for checkpoint inhibitor therapy. In doing so, this study aims to evaluate the potential of IRAK status as a predictor of immunotherapy response and as a druggable target to augment current immunotherapy regimens.

11. Novel model of Francisella novicida intradermal infection using microneedle arrays

Courtney Chandler

Chandler, C.E., Harberts, E.M., Laemermann, T., Zeng, Q., Opene, B., Germain, R.N., Jewell, C., Scott, A.J., and Ernst, R.K.

Session B; Oral Presentation; Ballroom B

Infectious diseases propagated by arthropod vectors, such as tularemia, are commonly initiated via dermal infection of the skin. However, due to the technical difficulties in achieving accurate and reproducible dermal deposition, intradermal models are less commonly used than intranasal or subcutaneous routes of infection. To overcome these limitations, we used microneedle arrays (MNAs), which are micron-scale polymeric structures, to temporarily disrupt the barrier function of the skin and deliver a bacterial inoculum directly to the dermis of an animal. MNAs efficiently eliminate injection-associated pain and increase reliability by eliminating leakage of the inoculum or blood form the injection site, thereby providing a more biologically relevant model for arthropod-initiated disease. Here, we characterize a murine intradermal infection model using Francisella novicida (Fn) delivered by MNAs. We show targeted delivery to the dermal layer leading to innate immune cell infiltration and lethality in a dose dependent manner in C57BL/6 mice. After deposition, bacteria remain viable and disseminated to the spleen, liver, blood, and lungs 24 and 48 hours post-infection, leading to tissue damage in the spleen and liver and lethality. The immune profile of infected mice via MNAs mirrors that of other Fn infection models with markedly increased serum levels of IL-6 and KC, splenic T-cell depletion, and an increase in splenic granulocytes confirming that MNAs can be used to reproducibly induce tularemia-like pathogenesis in mice and provide a novel avenue to study intradermal-induced disease in mice.

12. Immediate Mechanical Stability of New Dental Nano-sealant Formulations with Calcium and Phosphate Ion-recharge Properties

Maria Ibrahim

Ibrahim, M.S., Weir, M. D., Melo, M. A. S., and Xu, H. H. K.

Session B; Oral Presentation; Ballroom B

Background and Objectives: The application of nanotechnology and polymer development in dental materials have enabled amorphous calcium phosphate (NACP) and dimethylaminohexadecyl methacrylate (DMAHDM), respectively, to emerge as an anti-

caries strategy via resin-based materials. There is currently no DMAHDM-NACP-based dual antibacterial and re-mineralizing sealant agent for caries prevention. The objectives of this study were to develop various formulations of rechargeable DMAHDM-NACP dental sealants, and evaluate their physical properties, mechanical properties and calcium (Ca) and phosphate (P) ions-release and re-chargeability.
Materials and Methods: Four formulations of the novel dental sealants were developed using Pyromellitic Dimethacrylate (PMGDM), Ethoxylated Bis Phenol A Dimethacrylate (EBPADMA), 2-hydroxyethyl methacrylate (HEMA) and bisphenol-A glycidyl dimethacrylate (Bis-GMA) with different percentages of DMAHDM, NACP and Boroaluminosilicate glass. Virtuoso flowable composite was used as a commercial control and the resin matrix with 50% glass fillers was used as an experimental control. Specimens were tested for flexural strength, elastic modulus, flowability within 24h to establish immediate mechanical performance. Acid neutralizing ability, and calcium and phosphate ions release and re-chargeability were also assessed.
Results: The novel dental sealants showed comparable results of flexural strength, elastic modulus and flowability to the controls. The new formulations showed abilities to release Ca and P ions over a period of 70-day. In addition, the new formulation showed the abilities to re-release Ca and P ions after exposing the specimens to recharging solutions.
Conclusions: This novel rechargeable calcium phosphate dental nano-sealant showed promising remineralization and anti-caries properties with satisfactory immediate physical and mechanical properties.

13. Sex Differences in In-Hospital In-Hospital Complications among Older Adults Following Traumatic Brain Injury

Timileyin Adediran

Adediran, T., McCunn, M., Stein, D., and Albrecht, J.S.

Session C; Poster Presentation; Room 349

Introduction: Older adults have the highest rates of hospitalization and mortality following traumatic brain injury (TBI) and suffer poorer outcomes compared to younger adults with similar injuries. Evidence suggests that women have reduced mortality and may be at decreased risk for complications after TBI, yet in-hospital complications among older women following TBI have not been studied. The objective of this study was to assess sex differences in in-hospital complications following TBI among adults aged 65 and older. Methods: We conducted a study of adults aged 65 and older treated for isolated TBI at the R Adams Cowley Shock Trauma Center between 1996-2012. We identified the following in-hospital complications: acute kidney failure, acute respiratory failure, thrombocytopenia, coagulopathy, myocardial infarction, cardiac arrest, and arrhythmia. We assessed the adjusted odds of each in-hospital complication separately as a function of sex and potential confounders. Results: Of 2,584 patients meeting criteria, 1,339(51.8%) were men and 685(26.5%) developed an in-hospital complication. In the adjusted analysis, men were more likely to have any in-hospital complication (odds ratio (OR): 1.49; 95% confidence interval (CI): 1.23, 1.81). Men were more likely to have thrombocytopenia (OR: 2.23; CI: 1.52, 3.27), acute kidney failure (OR: 2.52; CI: 1.35, 4.70), and acute respiratory failure (OR: 1.26; CI: 1.00, 1.59). Associations with other complications were not statistically significant. Discussion: In-hospital complications were common among older adults with TBI. Older men were more likely to have in-hospital complications, especially

thrombocytopenia, acute kidney failure and acute respiratory failure following isolated TBI.

14. A Quantitative Approach to Optimize Levetiracetam Dosing in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration

Shamir Kalaria

Kalaria S. N., Armahizer M., McCarthy P., and Gopalakrishnan M.

Session C; Poster Presentation; Room 349

Objectives: Limited data exist on the effect of continuous renal replacement therapy (CRRT) methods on antiepileptic drug pharmacokinetics (PK). Patients who undergo CRRT may experience refractory seizures from underexposure of therapy, while serious adverse effects may appear in those who are overexposed. This study aims to assess the impact of continuous venovenous hemofiltration on key pharmacokinetic parameters in critically ill patients receiving levetiracetam.

Methods: Nine patients receiving levetiracetam and continuous venovenous hemofiltration (CVVH) in various ICUs at a large academic medical center were enrolled to investigate the need for dosing adjustments. Pre-filter, post-filter, and ultrafiltrate samples were taken before dosing, after the completion of the infusion or 1 hours post oral dose, and 6 additional time points. Plasma concentrations were determined using a validated HPLC-UV bioanalytical method. Pharmacokinetic analysis was conducted using Phoenix WinNonlin® 7.1 (Pharsight Corporation).

Results: The average sieving coefficient was 0.90 ± 0.1 and the average volume of distribution was 0.75 ± 0.08 L/kg. Six out of the nine patients experienced concentrations outside the reported therapeutic range (12-46 mg/L) of levetiracetam. Average total drug clearance for patients taking 750 mg, 1000 mg, and 2000 mg were 3.27, 5.18, and 4.38 L/hr respectively, suggesting that differences in clearance can be attributed to differences in ultrafiltration flow rates.

Conclusion: Preset ultrafiltrate rates need to be taken into consideration when determining an appropriate dose. Patients with higher ultrafiltrate rates will have increased drug clearance. Therefore, individualized dosing recommendations should be based on CRRT flow parameters and drug specific sieving coefficients.

15. Age-associated changes in neuromuscular and kinematic landing responses to sudden loss of ground support while standing

Ozell Sanders

Sanders, O. P., Hsiao, H., Savin, D.N., Creath, R.A., and Rogers, M.W.

Session C; Poster Presentation; Room 349

With advancing age, the capacity to maintain balance after perturbations deteriorates due to a number of age-related sensorimotor deficits, and likely increases the risk for falls. The unexpected nature of falls triggers startle-like whole body postural responses. Startle responses are characterized by exaggerated whole body postural responses with increased muscle co-activity causing co-contraction during the first trial response (FTR) and normally diminish with repeated exposure due to behavioral habituation. Because all falls

involve a downward motion of the body with gravity which may trigger a startle response, understanding whether these responses are also superimposed onto the landing response will be important to determine. Our central hypothesis is that age-related abnormalities of exaggerated startle responses and habituation will influence control of drop landing movement strategies. Understanding whether the FTR during sudden drop perturbations influences the landing response will be important to determine whether it enhances balance recovery or is problematic and precipitates falls. Whole body postural muscle activation patterns, movement kinematics, and landing impact forces were assessed by electromyographic (EMG) recordings, motion capture, and force platform recordings. The specific aims are 1) Compare changes in landing responses to unexpected and expected drop perturbations in relation to age during a) FTRs and b) subsequent trials. Our primary finding of increased incidence of early SCM activity across, a surrogate marker for startle response, and greater hip flexion upon landing demonstrate age-related differences in balance recovery during drop perturbations, which is likely to have been influenced by startle.

16. Fall Prevention Using Purposeful Hourly Rounding in the Long Term Care Setting

Jennifer Linehan

Linehan, J.

Session C; Poster Presentation; Room 349

Background: Individuals who reside in Long Term Care (LTC) facilities are at an increased risk from suffering from falls. Falls can lead to injury, diminished functional ability, loss of independence, and sometimes death. A large retirement community in Baltimore, Maryland has identified falls on the LTC floor as a safety concern.
Objective/Aim: The objective of this DNP project was to incorporate hourly rounding (HR) focused on the 4 P's: Pain, Positions, Possessions in close proximity, and Pottying/Toileting into the current fall prevention practices within a 23-bed LTC unit. The anticipated outcomes of this project are to reduce fall rates and call light usage. Additional objectives include analyzing staff perceptions about HR pre- and post-intervention and sustaining HR into routine practice.
Results: The preliminary results from the data obtained revealed staff compliance with the rounding intervention ranged from 35% to 56%. Low staff compliance is likely correlated to decreased staffing numbers. During the 5-week intervention there was only one reported fall, which did not result in any injuries. Fall data from the sixth week has not been reported by the facility at this time. Furthermore, data is still being gathered on post-intervention staff surveys and call light usage.
Conclusion: With much of the literature on hourly rounding being based in the hospital setting this project can help in the spread of implementing hourly rounding to the LTC setting to enhance resident safety and satisfaction. High resident to low staffing ratios will likely impact sustainability with hourly rounding in this setting.

17. Racial Differences in Discharge Location Following a Traumatic Brain Injury among Older Adults

Aparna Vadlamani

Vadlamani, A., Perry, J. A., McCunn, M., Stein, D. M., and Albrecht, J. S.

Session C; Poster Presentation; Room 349

OBJECTIVE:

The highest rates of TBI related-hospitalization and injury-related disability occur in older adults. Rehabilitation following TBI improves functional outcomes. Evidence suggests that discharge to rehabilitation following TBI differs by race among younger adults, but whether this is true among older adults is unknown. We assessed the association between race and discharge location among older adults treated for TBI.

METHODS:
We conducted a retrospective cohort study of older adults treated at the R Adams Cowley Shock Trauma Center for TBI between 1998-2012 who survived to hospital discharge. Home without services included discharge to home without services or shelter. Inpatient rehabilitation included inpatient rehabilitation, inpatient out of state, and inpatient in state. Race was restricted to white or black.

RESULTS:
2,902 older adults with TBI met our inclusion criteria. Of these, 2,487 (86%) were white and 415 (14%) were black. A total of 1,513 (52%) were discharged to inpatient rehabilitation and 1,389 (48%) were discharged home without services.

In unadjusted analysis, there was no significant difference in discharge location between blacks and whites (Odds Ratio (OR) 1.19, 95% Confidence Interval (CI) 0.97-1.47). In the adjusted model, blacks were significantly more likely to be discharged to inpatient rehabilitation than whites (OR 1.28, 95% CI 1.03-1.58).

CONCLUSIONS:
In this group of Medicare-eligible older adults treated for TBI at an urban trauma center, blacks were more likely to be discharged to inpatient rehabilitation than home without services compared to whites.

18. PATIENT STAKEHOLDER INVOLVEMENT IN THE CLINICAL PRACTICE GUIDELINE DEVELOPMENT PROCESS

Bansri Desai

Oehrlein, E.M., Desai, B., Ngo, M., Tang, L., Love, T.R., and Perfetto, E. M.

Session C; Poster Presentation; Room 349

Background: The 2011 Institute of Medicine report, "Clinical Practice Guidelines We Can Trust," recommends patient and public involvement during clinical practice guideline (CPG) development. Involving patients can help improve recommendation transparency and incorporation of patient perspectives. Yet actual involvement is still limited.

Objective: To identify if and how professional organizations active in developing CPGs involve patients in the development processes.

Methods: An organization list was generated based on: 1) the Guidelines International Network membership roster; 2) publication of more than 3 CPGs on the U.S. National Guideline Clearinghouse's website; or 3) recommendation by an expert committee. Research staff searched Google and organizations' websites for CPG development methodology reports. Information on patient involvement in CPG development, type of patient stakeholder, and inclusion of patient-centered data sources was extracted.

Results: A total of 125 organizations met inclusion criteria; 67/125 had publicly available CPG-development methodology documentation. Of these, 34 (51%) included patient and/or patient advocate participation: 16 (24%) organizations involved patient stakeholders in an active role, such as a position

on CPG committees; 5 (7%) involved patient stakeholders in a passive role, such as reviewing CPG recommendations; and 13 (19%) included them in both. A pre/post IOM report release sub-analysis showed 56% (33/57) included patients, versus 20% (2/10) prior to the report.

Conclusions: Engagement efforts display wide variation across organizations. Guiding principles for patient engagement in CPG development could help increase meaningful engagement and consistency. Further research is needed to assess patient input methods in CPG development.

19. KYNURENIC ACID MODULATION OF EXCITATORY AND INHIBITORY SYNAPSES AND IMPLICATIONS IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

Kaia Amoah

Amoah K.M., Contreras M., Schwarcz R., Blanpied T., and Tang A.

Session C; Poster Presentation; Room 349

Glutamate is a major excitatory neurotransmitter in the mammalian brain and its dysregulation has been linked to the pathophysiology of neurological diseases such as Schizophrenia. Kynurenic acid (KYNA), a product of tryptophan degradation, is naturally occurring and can modulate glutamate function by acting as an antagonist to NMDA-type glutamate receptors. While we can assume the direct role of KYNA in the pathophysiology of Schizophrenia, recent evidence suggests that a shift in the excitatory to inhibitory balance of neural circuitry also leads to cognitive deficits related to Schizophrenia. Because the effect of KYNA at a cellular level is not fully understood, in this study, we analyze the effects of KYNA on the formation and function of brain synapses. We hypothesize that KYNA induces the symptoms of Schizophrenia by shifting excitatory and inhibitory neural circuitry ratios. Cultured rat hippocampal neurons were co-transfected with DNA plasmids expressing GFP and FingR-PSD-95 or FingR-Gephyrin(GPHN) to show the dendritic morphology, excitatory synapses and inhibitory synapses, respectively. Cells were either treated with KYNA 10 μM or left untreated as a control. Using confocal microscopy, we observed changes in the spine density and excitatory/inhibitory synapse density upon exposure to KYNA. We conclude that there is an increase in both the excitatory and inhibitory postsynaptic density of cells with prolonged KYNA exposure. However, these changes in the postsynaptic density do not shift excitatory to inhibitory neural circuitry ratios. Using the results from this study, we can explain how KYNA alters synapses during the pathophysiology of Schizophrenia.

20. CAPTURING VAR GENE DIVERSITY IN MALARIA INFECTIONS USING WHOLE GENOME SEQUENCE DATA

Emily Stucke

Stucke, E. M., Dara, A., Matsumura, J., Adams, M., Moser, K. A., Coulibaly, D., Daou, M., Dembele, A., Diarra, I., Kone, A. K., Kouriba, B., Laurens, M. B., Niangaly, A., Traore, K., Tolo, Y., Thera, M. A., Djimde, A. A., Doumbo, O. K., Plowe, C. V., Silva, J. C., and Travassos, M. A.

Session C; Poster Presentation; Room 349

Plasmodium falciparum is the parasite that is the major cause of the most severe forms of malaria and is responsible for nearly all cases of malaria in Africa. Plasmodium falciparum erythrocyte membrane protein-1s (PfEMP1s),

expressed on the surface of parasite-infected erythrocytes, play a critical role in immune evasion by mediating cytoadhesion and sequestration in host capillaries. PfEMP1s are encoded by var genes, with each parasite genome containing ~40-60 copies. Sequencing and assembling these genes has been a challenge, and full var repertoires are known for only a few reference genomes and clinical isolates. This lack of knowledge has posed a challenge for studying var gene expression, particularly in clinical samples. We previously sequenced var gene repertoires from malaria infections in 12 Malian children. Before studying var expression in these samples, we first evaluated the ability of published degenerate primer sets targeting the DBL-α region to optimally capture these repertoires. The DBL-α tag primer set captured 95% of DBL-α sequences and >90% of DBL-α sequences across the 12 samples. Additional primers are needed to capture var2csa and var3, two conserved vars which are present in the var repertoires of these clinical infections. This will form the basis of a high-throughput next-generation sequencing approach to determine proportions of var subtypes expressed in asymptomatic and symptomatic infections in a cohort study of malaria incidence in Malian children. We plan to use this approach to correlate changes in var gene expression with the development of particular clinical syndromes of malaria.

21. MUSCARINIC ANTAGONISTS AND ANTI-DEPRESSANT-LIKE EFFECTS IN RODENTS: SOME CHEMICAL FORAYS TOWARD NEW COMPOUNDS

Chad Johnson

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Session D; Poster Presentation; Room 349

Scopolamine, a non-selective muscarinic antagonist, is an effective antidepressant compound in humans. In rat models, it is clear that scopolamine's antidepressant-like effects may be mediated through an antimuscarinic effect. Unfortunately, scopolamine can produce cognitive impairment including memory disturbances in humans. These effects (antidepressant-like and cognitive impairment) are separable in principle. It is important to identify a muscarinic antagonist that may be able to relieve depression without disrupting cognitive effects. The 3-exo-1-azabicyclo[2.2.1]heptane, (3R)-1-bicyclo[2.2.2]octane, and N-methyltetrahydropyidine 1,2,4-oxadiazoles appear to be excellent chemical scaffolds for the generation of potent muscarinic agonists. Interestingly, addition of a methyl group to the 3-position of the 1,2,4-oxadiazole yields some of the most potent muscarinic agonists currently known. Yet, addition of a cyclopropyl group (3-position) to the 1,2,4-oxadiazole moiety appears to reduce efficacy and confer antagonist action at muscarinic sites. We are evaluating cyclopropyl analogs as antagonists of the muscarinic agonist, arecoline, in behavioral assays in anticipation of separating antidepressant-like activity from cognitive impairment.

22. EXPLORING THE ROLE OF THE ENDOCANNABINOID SYSTEM IN SPATIAL MEMORY CONSOLIDATION USING IN VIVO CALCIUM IMAGING OF ACETYLCHOLINE INPUT IN MICE WITH HIPPOCAMPAL CB1 DELETION

Edith Hernandez

Hernandez, E., Covey, D. P., and Cheer, J. F.

Session D; Poster Presentation; Room 349

The hippocampus is well-known as the limbic center for memory consolidation and spatial navigation, receiving input from a wide array of neuronal circuits. Acetylcholine input to the hippocampus is critical during memory formation, with abnormal cholinergic activity exhibiting major implications in memory-related disorders, such as Alzheimer's disease. The endocannabinoid (eCB) system, known for modulation of marijuana's psychoactive and reinforcing aspects in the brain, is a wide neurochemical network that also plays a major role in memory consolidation. Specifically, we recently found dense expression of the cannabinoid type 1 (CB1) receptor on cholinergic neurons that innervate the hippocampus, suggesting an important role in memory formation. To assess eCB regulation in memory development, we monitored short-term spatial memory consolidation using a novel object recognition task within a transgenic mouse line bearing a selective deletion of CB1 receptors on cholinergic neurons. Spatial memory capacity was quantified by measuring the rodents' innate tendency to recognize a novel objects as different from familiar objects within an open field. Previous studies in the Cheer Lab have tested spatial memory in transgenic mice lacking the CB1 receptor, showing an increase in short-term memory function. To further understand cholinergic signaling in the hippocampus, we will employ in vivo calcium imaging through miniature endoscopes to visualize the spatial distribution of these genetically-defined neuronal populations with single cell resolution in freely behaving mice. Results will elucidate the extent to which abnormal cholinergic activity in the eCB system regulates memory function within the hippocampus and may lead to memory-related disorders.

23. Role of Palmitoylation in the Function of the Apical Sodium Dependent Bile Acid Transporter (ASBT;SLC10A2;IBAT)

Ebehiremen Ayewoh

Ayewoh, E. N., Czuba, L. C., and Swaan, P. W.

Session D; Poster Presentation; Room 349

The human apical sodium bile acid transporter (ASBT; SLC10A2;IBAT) is a key player in the enterohepatic circulation system that is responsible for maintaining bile acid and cholol homeostasis. Transporter abnormalities in the enterohepatic circulation system have been linked to diseases such as Cholestasis, Necrotizing enterocholitis, Gastrointestinal cancer, and Barret's esophagus. Recent studies have been made to characterize and understand the structure-function relationship of ASBT in order to guide treatment for cholesterol disorders.

Lipidation is a biological process that improves protein hydrophobicity and its affinity for cell membranes and membrane domains. Palmitoylation, a form of lipidation that attaches to cysteine residues, has been implicated in membrane and peripheral-membrane protein assembly, trafficking, and degradation. The objective of this research is to determine the site of ASBT palmitoylation and investigate the effect that inhibiting palmitoylation has on ASBT expression and function.

24. Implementation of Obstructive Sleep Apnea Screening in Primary Care Setting

Stephanie Catalano

Catalano, S.

Session D; Poster Presentation; Room 349

Purpose: The purpose of this project is to identify patients at risk for Obstructive Sleep Apnea (OSA) by implementing an OSA screening program in a primary care practice, using the STOP-Bang Questionnaire.
Background: Approximately 5.9 million people in the United States are diagnosed with OSA, and it is estimated that 23.5 million people are undiagnosed. The significance of undiagnosed OSA has been recognized by several healthcare organizations as deleterious to the medical management of multiple co-morbidities, such as hypertension, chronic obstructive pulmonary disease, and asthma.
Methods: The Ottawa Model of Research Use (OMRU) was utilized in developing a quality improvement project implementing the STOP-Bang questionnaire in a primary care setting. The STOP-Bang questionnaire was modified for this QI project by the addition of the following two questions: 1.) Was a referral made for a positive screen and 2.) If co-morbidities of diabetes, CHF, COPD, or asthma were present.
Results: A total of 88 people were screened. 9 people (10.2%) had a documented history of OSA. 19 people (21.5%) had a positive screening score; of those who screened positive, 9 people (10.2%) refused a referral for a sleep study and 10 people (11.3%) accepted a referral. Regarding the comorbidities of those screening positive for OSA, there were zero patients with COPD or CHF. Whereas, 17 people (89.4%) had HTN, 8 people (42.1%) had DM, 3 people (15.7%) had asthma.
Conclusions: Utilization of the STOP-Bang questionnaire increases awareness of patients at risk for OSA in the primary care setting.

25. GLUTAMATERGIC VENTRAL PALLIDAL NEURONS MODULATE ACTIVITY OF THE HABENULA - TEGMENTAL CIRCUITRY AND CONSTRAIN REWARD SEEKING

Jason Alipio

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Session D; Poster Presentation; Room 349

The ability to appropriately integrate and respond to rewarding and aversive stimuli is essential for survival. The ventral pallidum (VP) plays a critical role in processing both rewarding and aversive stimuli. However, the VP is a heterogeneous structure, and how subpopulations integrate into larger reward networks to ultimately modulate these behaviors is not known. We identify a noncanonical population of glutamatergic VP neurons that play a unique role in constraining inappropriate reward seeking in response to aversive stimuli. Using neurochemical, genetic, and electrophysiology approaches, we characterized glutamatergic VP neurons. We performed patch clamp and in vivo electrophysiology recordings in the lateral habenula, rostromedial tegmental nucleus, and ventral tegmental area to determine the effect of glutamatergic VP neuron activation in these target regions. Finally, we optogenetically stimulated glutamatergic VP neurons in a real-time place preference task and ablated these neurons using a virally expressed caspase to determine their necessity for reward seeking. We found that glutamatergic VP neurons innervate and increase firing activity of the lateral habenula, rostromedial tegmental nucleus, and gamma-aminobutyric acidergic ventral tegmental area neurons. While nonselective optogenetic stimulation of the VP induced a robust place preference, selective

activation of glutamatergic VP neurons induced a place avoidance. Viral ablation of glutamatergic VP neurons increased reward responding and abolished taste aversion to sucrose. We conclude that glutamatergic VP neurons constitute a noncanonical subpopulation of VP neurons and increase activity of the lateral habenula, rostromedial tegmental nucleus, and gamma-aminobutyric acidergic ventral tegmental area neurons to adaptively constrain reward seeking.

26. THE ELUSIVE LABILE IRON: BIOANALYTICAL TECHNIQUES TO MEASURE IRON SPECIATION IN HUMAN PLASMA

Heather Nu

Neu, H. M., Alexishin, S. A., Brandis, J. E. P., Williams, A. M. C., Polli, J. E., Kane, M. A., and Michel, S. L. J.

Session D; Poster Presentation; Room 349

Iron deficiency anemia is the most common nutritional deficiency worldwide, affecting nearly 1 billion people. There are currently 6 brand and 1 generic FDA approved intravenous iron products on the market. These products are colloidal nanoparticles composed of a polynuclear iron(III)-(oxy)hydroxide core, stabilized by carbohydrate ligands. There is concern that the generic iron formulations may have a different safety profile from their reference listed drug (RLD) products.

Under normal conditions, the iron released by the IV iron drug is bound to the protein transferrin and then transported into the cell via the transferrin receptor pathway. Under iron overload conditions, however, transferrin becomes saturated, and the remaining iron called “labile iron” is taken up by the cell via non-iron specific pathways. Labile iron, once it enters the cell, can promote the production of reactive oxygen species which can damage proteins, DNA, and lipids. Thus, it is critical that the IV iron products do not produce excessive labile iron in circulation.

A key gap in our understanding is how iron is released from iron nanoparticle drugs. Current methods do not allow for the iron speciation of the nanoparticle drug nor the quantification of labile iron to be measured. We have developed novel approaches using inductively coupled plasma mass spectrometry (ICP-MS) and liquid chromatography (LC) coupled ICP-MS. LC-ICP-MS allow for the simultaneous identification and quantification of all iron species in blood plasma in their native form. This assay will be presented along with pilot data on plasma from patients treated with SFG.

27. USP24 REGULATES AUTOPHAGY THROUGH THE ULK1 AND TYPE III PI3-KINASE PATHWAY

Julia Thayer

Thayer, J. A., Hegdekar, N., Awad, O., Sarkar, C., Burt, C., Tesfay, H., Feldman, R. and Lipinski, M. M.

Session D; Poster Presentation; Room 349

Autophagy is a lysosome-dependent intracellular degradation pathway, essential for neuroprotection. Defects in autophagy are linked to neurodegenerative diseases, including Parkinson’s disease (PD), but the mechanisms causing its disruption are not fully understood. The deubiquitinating enzyme USP24 is located on chromosome 1 in the PARK10 locus, associated with late-onset PD, and was identified as a negative regulator of autophagy by our lab. We confirmed increased USP24 protein and mRNA levels in the substantia nigra of a subpopulation of idiopathic PD patients. In human cell lines and iPS cell

derived dopaminergic neurons, USP24 knock-down led to up-regulation of cellular autophagy flux, assessed by increased LC3-II levels and lysosomal translocation of the mCherry-GFP-LC3 autophagy reporter. To determine where USP24 functions in the autophagy pathway we studied its effect on upstream regulators of autophagy. USP24 knock-down caused accumulation of PtdIns3P (type III PI3-kinase product), demonstrated by quantification of the FYVE-dsRed reporter. Induction of autophagy by USP24 knock-down was attenuated by treatment with inhibitors of type III PI3-kinase. Furthermore, USP24 knock-down lead to ULK1 protein stabilization and increased ULK1 activity. As ULK1 is positively regulated by K63 ubiquitination, our data suggests that USP24 may deubiquitinate ULK1, therefore de-stabilizing it and inhibiting autophagy. Together our data demonstrate that USP24 regulates autophagy via ULK1 and the type III PI3-kinase pathway. Interestingly, USP24 knock-down enhanced long-term survival and increased neurite length of iPS cell derived dopaminergic neurons, suggesting potential neuroprotective function. Our data highlight the mechanisms of USP24 in regulation of autophagy and its potential role in PD.

28. SKELETAL MUSCLE CONTRACTION ALTERS MICROTUBULE PROPERTIES THAT IMPACT FUNCTION

Camilo Vanegas

Vanegas, C., Joca, H., Vandermeulen, J., Khairallah, R., Lederer, J.W., Stain, J., and Ward, C.

Session D; Poster Presentation; Room 349

We discovered a microtubule (MT) dependent mechanotransduction pathway linking contraction/stretch to NADPH oxidase 2 (Nox2) derived reactive oxygen species (ROS) signals (X-ROS) in skeletal muscle. We further showed that X-ROS target calcium (Ca2+) channels to regulate Ca2+ influx. Our work in healthy muscle aligned the properties of the MT (i.e., density and stability) to the stiffness of the cytoskeleton (CSK) which regulated the magnitude of mechano-activated X-ROS and Ca2+ influx. In dystrophic muscle (dystrophinopathy, dysferlinopathy) we linked the disease driven increase in MT dependent cytoskeletal stiffness to the deleterious excess in contraction elicited X-ROS and Ca2+ responsible for contraction injury. In recent work, we sought to reveal mechanisms that regulate these MT properties in skeletal muscle and further define how these MT alterations impact function. Using well described in vivo and in vitro contraction paradigms (non-injurious and injurious contractions), we show MT alterations align with the functional deficits in healthy muscle; deficits previously linked to altered Ca2+ and ROS signaling. Further experiments identified ROS and pro-inflammatory cytokines as signals that promote these contraction induced MT alterations in WT and diseased muscle. Extending our evidence for contraction/stretch as a activator of X-ROS, we now show that alterations in MT dependent CSK stiffness increases X-ROS signaling and Ca2+ influx independent of stretch/contraction. Together our discoveries add important insight the MT network as a dynamic regulator of skeletal muscle function in health and disease.

29. TRISTETRAPROLIN TARGETING BY CADMIUM: A POTENTIAL MECHANISM OF CADMIUM TOXICITY

Joel Brandis

Brandis, J. E. P., Ok, K., and Michel, S. L. J.

Session D; Poster Presentation; Room 349

Humans are exposed to cadmium, a toxic metal, on a daily basis from environmental sources including cigarette smoke, car exhaust, and industrial production of plastics and batteries. Cadmium is a potent carcinogen that targets major organs including the kidney, liver, lungs, and pancreas, and causes oxidative stress and DNA damage. Although classified as a potent carcinogen, the mechanism(s) of cadmium toxicity are not well understood. However, there has been some evidence for cadmium targeting zinc co-factored proteins. We have previously reported in vitro cadmium binding to apo-Tristetraprolin (TTP) (a Cys3His type zinc finger protein that regulates inflammation by targeting cytokine mRNA for degradation) in addition to the retention of TTP's RNA binding ability. We now seek to determine how cadmium interacts with zinc bound TTP in vitro and in cells as well as its effect on RNA binding. By furthering our understanding of cadmium-TTP interactions, we may be able to expand our understanding of the mechanism(s) of cadmium toxicity

30. Fluorine-Labeled Bile Acid Live-Animal Magnetic Resonance Imaging (MRI) Detects Bile Acid Malabsorption in FGF15 Knockout Mice

Melissa Metry

Metry, M., Felton, J., Cheng, K., Shang, A. C., Xu, S., Vivian, D., Raufman, J-P., and Polli, J. E.

Session E; Poster Presentation; Room 349

Bile acid malabsorption, a prominent cause of chronic bile acid diarrhea (BAD), is frequently misdiagnosed as diarrhea-predominant irritable bowel syndrome. Fibroblast growth factor-19 (FGF19 in humans; FGF15 in mice) is a key hormonal regulator of hepatic bile acid synthesis; FGF15/19 deficiency results in excess spillage of bile acids into the colon, the most common cause of BAD. As current methods of diagnosing BAD are limited, we developed a novel test involving oral administration of fluorine (19F)-labeled bile acids (19FBA) for detection in live mice using dual 1H/19F magnetic resonance imaging (MRI). Fgf15-deficient and WT mice were gavaged with a solution containing two 19FBA (CA-lys-TFA and CA-sar-TFMA). A time-course of 19FBA accumulation in the gallbladder was determined where gallbladder contents were extracted after euthanization to measure concentrations by LC/MS/MS. Using the time of peak 19FBA as a guide, mice were gavaged with CA-lys-TFA and underwent live-animal dual 1H/19F MRI for abdominal imaging. For both Fgf15-deficient and WT mice, peak gallbladder 19FBA concentrations were detected by LC/MS/MS 8.5 h after dosing. Nonetheless, peak concentrations of 19FBA were >4-fold higher in WT compared to Fgf15-deficient mice. Based on these findings, we imaged mice ~8.5 h after oral gavage with CA-lys-TFA. As anticipated from the LC/MS/MS data, whereas we detected a 19FBA signal emanating from the WT mouse gallbladder, no signal was detectable from an Fgf15-deficient mouse gallbladder. 19FBA-MRI has great potential as a diagnostic test to identify FGF15/19 deficiency and other forms of bile acid malabsorption as the cause of bile acid diarrhea.

31. Utilizing a Yeast Knockout Library to Identify Host Factors Effecting MERS Coronavirus Replication

Kayla Rayford

Rayford, K. J., Weston, S., and Frieman, M.

Session E; Poster Presentation; Room 349

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged from bat and camel reservoirs in the Middle East to infect humans around the world, with a case fatality rate of 35%. We sought to identify host factors that are required for MERS-CoV replication as a way to identify novel targets for therapeutic development. We have used expression of MERS-CoV proteins in yeast as a tool to identify host factors that interact with viral proteins. Saccharomyces cerevisiae is a great model organism due to its conserved cellular functions with humans and rich tools for genetic analysis. In this model, we find that yeast expressing the MERS-CoV ORF4a protein display a slow growth phenotype compared to control yeast. Using this phenotype, we performed a suppressor screen with the yeast knockout library for yeast deletion mutants that no longer grow slow. We hypothesize that deletion mutants that grow like wildtype yeast even when the ORF4a gene is expressed are either direct or indirect interactors with the ORF4a protein. The mammalian homologues of the yeast genes identified in the screen are being tested in mammalian cells for their effect on MERS-CoV growth. In addition, we are testing whether the yeast knockouts are able to suppress other viral proteins identified to cause yeast to grow slow as well, including the Chikungunya virus NSP2 and the SARS Coronavirus Papain Like Protein (PLP). We hope to identify common host factors that regulate replication of a variety of viruses to use as targets for future therapeutic development.

32. Potentially Bioactive or Toxic Metals in Common Cigalike E-cigarette Liquids

Angela Lee

Lee, A., Neu, H., Patel, V., Schneider, A., Kane, M. A., Michel, S. L. J., and Dalby, R. N.

Session E; Poster Presentation; Room 349

With the plethora of electronic cigarettes (e-cigarettes) that are now available worldwide for their intended use to administer nicotine to the lungs, there is a need to evaluate potential toxicants that might be present in the aerosol. Because e-liquids are frequently packaged in metal cartridges of uncertain origin, composition and grade, and encounter metal or metal-containing device components, and are heated by a metal coil, it seems likely that testing for potentially bio-reactive or harmful metals is necessary for learning about the potential toxicity and metal exposure. Popular e-cigarette refill cartridges were purchased serially over the Greater Baltimore Metropolitan area for metals analysis. The e-liquids were extracted from the cartridges through forceful rupture of the cartridge packaging within plastic bags, and centrifugation when necessary. USP grade propylene glycol (PG) and vegetable glycerol (VG), which are used alone or in combination as the vehicle for many e-liquids were analyzed for comparison. The identity of metal ions and their concentrations were measured by inductively coupled plasma mass spectrometry (Agilent 7700x ICP-MS, Santa Clara, CA). Nickel and chromium occurred at higher levels than were found in USP grade propylene glycol and vegetable glycerol across a range of brands. Lead levels between 23-175 ppb were associated with Blu Magnificent Menthol e-liquid, four orders of magnitude higher than the other products tested.

33. Dendritic Cell Derived IL-12p40 Binds Extracellular Proteins to Make Heterodimeric Cytokines

Allison Gerber

Gerber, A. N., Abdi, K., and Singh, N. J.

Session E; Poster Presentation; Room 349

IL-12 and IL-23 are heterodimeric cytokines which share a common subunit, p40. Binding of p40 to p35 results in IL-12, while binding to p19 generates IL-23. Assembly of these cytokines is thought to occur when both relevant subunits are expressed inside a dendritic cell (DC) allowing for covalent linkage and secretion. Intriguingly, the p40 subunit is released from DCs as a monomer with unknown function. We previously hypothesized that monomeric p40 can bind p35 (or p19) released by another cell in the extracellular space. Consistent with this, recombinant p40 and p35 were shown to assemble in cell free extracts. In vitro and in vivo assays were performed by mixing p40-/- and p35-/- cells; since no one cell can make both subunits, the only way IL-12 can be present is through extracellular assembly. In vitro bioassays for IL-12 showed proliferation and IFNγ production in response to mixing. In vivo, mixed bone marrow chimeras infected with Leishmania major were able to induce IFNγ production by T cells. These results suggest that functional IL-12 assembly can occur in the extracellular milieu from component peptides. Importantly, this mechanism may allow non-hematopoietic tissues to direct T cell differentiation by releasing proteins capable of binding to DC-derived p40. In order to identify novel heterodimeric cytokines capable of fulfilling that paradigm, we have used a panel of proteins that can bind p40, identified from an unbiased mass spectrometry based analysis. Recombinant versions of these proteins expressed as dimers with p40 are being evaluated for functional activity.

34. WHOLE GENOME DNA SEQUENCE CAPTURE APPROACH REVEALS TREMENDOUS GENETIC DIVERSITY IN INTRACELLULAR PATHOGEN THEILERIA PARVA

Nicholas Palmateer

Palmateer, N.C., Tretina, K.T., Pelle, R., Awino, E., Gotia, H.T., Nene, V., Daubenberger, C.A., Bishop, R.P., and Silva, J.C.

Session E; Poster Presentation; Room 349

Theileria parva is a tick-transmitted apicomplexan parasite that causes East Coast fever, a fatal disease of cattle in sub-Saharan Africa. A vaccine for this disease exists, which is effective against cattle-transmissible strains but less effective against those originating from the African Cape buffalo, the natural reservoir of T. parva. Understanding genetic variation in both cattle- and buffalo-derived T. parva strains is critical for the design of next-generation vaccines against infection. The biology of T. parva presents an obstacle to the acquisition of DNA in sufficient quantity and quality for whole genome sequencing. DNA extracted early in the infection cycle is contaminated with host DNA and parasite DNA from late-stage infections cannot be obtained sustainably on a large scale. We adapted a DNA capture approach to select T. parva from a mix of parasite and bovine DNA obtained from T. parva-infected bovine lymphocytes. In order to gain access to variable genomic regions that cannot be characterized through read mapping approaches, we assembled the captured reads de novo. From starting material of <1%-4% parasite DNA in a mixed sample from host and parasite, >98% of sequence reads post-capture mapped to the parasite genome, reflecting the method's high specificity. Assemblies generated from these

data correspond to >97% of the reference genome. This approach is successful even when applied to highly divergent T. parva isolates from buffalo. The ability to characterize genome-wide polymorphism based on de novo genome assemblies allows us to identify highly divergent genes and characterize differences between cattle- and buffalo-derived infections.

35. TUNING OF TCR SIGNALING PATHWAYS IN CHRONICALLY STIMULATED CD4+ T CELLS IN VIVO

Courtney Matson

Matson, C.A. and Singh, N.J.

Session E; Poster Presentation; Room 349

Prolonged antigenic stimulation is known to tune down a T cell's ability to respond to antigen. It is not yet fully understood at what level this tuning occurs. Using an adoptive transfer model where transgenic T cells are continuously stimulated by a persistent self-antigen in vivo, we have previously found that tuned T cells show poor responses to antigen-restimulation; however, stimulation with PMA and ionomycin is mostly intact. This implies the negative regulation during tuning operates mostly on the TCR proximal signaling machinery; upstream of PKC activation and Ca2+ flux. Ex vivo, tuned T cells show decreased Zap70 kinase activity. Additionally, downstream of Zap70, chronically stimulated cells have reduced expression of both c-Fos and c-Jun leading to decreased assembly of the AP-1 transcriptional complex. Finally, chronically stimulated cells have increased expression of IκBβ, which contributes to a decrease in NFκB signaling. An important characteristic of T cells in this model is that the loss of responsiveness is mostly reversible. Tuned T cells, when adoptively transferred into an antigen-free host recover most of their functionality and can re-respond to antigen. However, acute antigen removal for at least 48 hours in vitro retains an unresponsive state suggesting the negative regulation is stable for a significant period after removal from antigen. Importantly, the stability of tuning ex vivo allows us to screen for pharmacological agents capable of improving antigen responsiveness in these T cells. Such agents may prove therapeutic for increasing T cell responses in cancer and chronic infections.

36. A SINGLE SESSION OF PHYSICAL ACTIVITY IMPACTS COGNITIVE FUNCTION IN SURVIVORS OF CHRONIC STROKE

Cecilia Najera

Najera, C., Saffer, M., Rietschel, J., Macko, R. Ivey, F., and Dux, M.

Session E; Poster Presentation; Room 349

Evidence suggests that cognitive function improves immediately following a single bout of aerobic exercise in healthy people of all ages. The potential for an acute bout of exercise to confer cognitive benefits has not been systematically investigated in survivors of chronic stroke. This study examined elements of post-stroke cognition before and after acute, moderate intensity aerobic exercise and non-aerobic stretching. METHODS: 12 chronic (> 6 months) stroke participants (6 females) and 13 age-matched healthy controls (6 females) completed two single 20-minute exercise sessions (treadmill aerobic and non-aerobic stretching), with each exercise session separated by approximately one week (counter-balanced by random ordering). Average age of both groups (stroke and control) was 61.8 (+/- 9.4). Global index, along with domain-specific

scores for memory, attention, information processing speed, visual-spatial processing, and motor skills were assessed before and after each exercise session using a computerized neuropsychological battery with strong psychometric properties (NeuroTraxÔ). RESULTS: Stroke participants displayed reduced global cognitive function compared to age-matched healthy participants prior to engaging in physical activity. Both the stroke and matched control groups experienced improvements in global cognitive function regardless of acute exercise type (aerobic vs. non-aerobic), and there were no differences between groups in terms of degree of change (Time x Group interaction, $f(1, 23) = 9.23$, $p < .01$). CONCLUSION: Acute structured physical activity (aerobic and non-aerobic) improves global cognitive function in those with chronic stroke disability.

37. Role of 2-Alkyl-4-quinolones in Pseudomonas aeruginosa

Luke Brewster

Brewster, L.

Session E; Poster Presentation; Room 349

Cystic fibrosis is a hereditary disease that is characterized by acute and chronic pulmonary infections. These infections are frequently polymicrobial in nature, and typically involve early colonization of the lung by *Staphylococcus aureus*, followed by later colonization by *Pseudomonas aeruginosa*. *P. aeruginosa* is able to out-compete *S. aureus* and persist as a chronic infection, an event that is correlated with worsening lung function. While the dynamics of this transition are not well understood, *P. aeruginosa* is known to produce several alkyl-quinolone (AQ) metabolites that confer antimicrobial activity toward *S. aureus* during co-culture. Previous studies in our lab demonstrated that antimicrobial activity of these AQs against *S. aureus* increases in iron-limiting environments, although the mechanism of this iron-mediated activity has not been determined. In these studies, I developed a novel liquid co-culture system to study the genetic mechanisms mediating iron-regulated AQ activity against *S. aureus*. I show that 2-Alkyl-4-quinolone N-oxides (AQNOs) are primarily responsible for the AQ antimicrobial activity of *P. aeruginosa*. HQNO, an AQNO species with a seven carbon alky chain, demonstrates iron-mediated antimicrobial activity against multiple strains of *S. aureus*. Moreover, iron mediated antimicrobial activity correlated with changes in *S. aureus* gene expression in response to iron depletion. These studies provide novel insights into polymicrobial interactions that contribute to worsening disease in CF lung infection.

38. The Factors Associated With the Respite Service Use by Informal Caregivers of Older Adults

In Seo La

La, I.

Session E; Poster Presentation; Room 349

Objectives: Informal caregivers (CGs) play an important role in caring for their loved ones as people live longer. It is estimated that about 34 million adults in the U.S. provide unpaid care to older adults. Respite services are recommended as an important means of supporting caregivers. However, there are a limited number of studies that focus on caregiving and respite services. Thus, this study adopted the Andersen and Newman behavioral model to examine associations between factors and respite care use.
Methods: Data for this secondary analysis was provided by the National Alliance for

Caregiving and American Association of Retired Persons (Weight adjusted n = 1036). Descriptive statistics and multiple logistic regression were conducted. Three blocks of variables were entered to illustrate the contribution of each block to respite use.
Results: Only 16% of CGs reported that caregiving have received respite services. In final model, the results revealed that older adults having more ADLs need (OR=1.317, p <.001), presence of Alzheimer's dementia/mental confusion (OR=1.95, p =.002), race (OR=1.95, p =.01), use of paid support (OR=4.40, p < .001), self-reported CG health (OR= 1.42, p = .001), and CG burden (OR = 1.43, p=.001) were significantly associated with the likelihood of use of respite services.
Conclusion: Characteristics related to older adults and CGs were closely associated with their planned break. Since supporting caregivers and reducing caregiving load are important issues for public health. It is required to understand factors related to use of respite service and to facilitate appropriate services for CGs.

39. Synthetic alpha-Helix Mimetics as Dual Inhibitors of Bcl-2/Mcl-1 and MDM2 Oncoproteins

Ivie Conlon

Conlon, I. L., Falat, A., Bowen, N. G., and Fletcher, S.

Session E; Poster Presentation; Room 349

Protein protein interactions play a key role in cell differentiation, proliferation, and apoptosis. Notably, the Bcl-2 protein family members, key regulators of the intrinsic pathway of apoptosis, govern the life and death of a cell. Dysregulation of the pathway via upregulation of pro-life proteins such as Bcl-2, Bcl-xL, and Mcl-1 can lead to many diseases including cancer. P53, a tumor suppressor also termed the "guardian of the genome" also has a pivotal role in apoptosis. It is negatively regulated by the E3 ubiquitin ligase MDM2, whose overexpression has also been linked to cancer. Interestingly, there is cross-talk between the two protein pathways. p53 can transcriptionally regulate Bcl-2 family proteins and has been shown to bind in the hydrophobic clefts of pro-life proteins. Both the transactivation domain of p53 and the BH3 "death domain" of the Bcl-2 pro-death proteins present a similar α-helical interface, with key hot spot residues in the i, i+3/4, and i+7 residues on the peptide. We hypothesize that a potentially highly efficacious antineoplastic may be realized by a universal α-helix mimetic that can target both protein families and induce apoptosis in the cancerous cells.

40. The Impact of the Worksite Heart Health Improvement Project on Clustering of Cardiovascular Risk Factors among Long-term care workers

Hamzah Alghzwai

Alghzawi, H. M., Doran, K., Resnick, B., and Zhu, S.

Session F; Poster Presentation; Room 349

Background: Current evidence suggests that health care workers, including long-term care (LTC) workers, are at greater risk for CVD than the general population. Hence, worksite health promotion programs (WHP) is needed to increase heart-healthy behaviors. Despite the fact that LTC workers are ideal candidates for WHP, little is known about their health and even less is known about their clustering of CVD risk factors or the impact of WHP programs with LTC workers' clustering of risk

factors over time. Purpose: This study aims to describe the clustering of CVD risk factors among LTC workers and to assess the impact of a WHP intervention on the clustering of risk factors over time. Methods: Data were collected from 98 LTC workers in four long-term care facilities in the Baltimore metro area. We hypothesized that LTC workers that participated in WHP would reduce their composite CVD risk score (clustering of risk factors) over time when compared to those in the education-only control group. The poster will show the clustering of CVD risk factors at the baseline by groups as well as the treatment effect and time on the composite CVD risk score. Results: The present study shows that 19%, 29.5%, 31%, 16%, and 4% of LTC workers had 0, 1, 2, 3, 4 CVD risk factors, respectively. There was no significant treatment effect for the WHHIP on composite CVD risk scores over time. Conclusion: This study provides a valuable source of information for the implementation of a WHP program with long-term care workers.

41. SEARCHING GENE VARIANTS FOR "GENERIC BRITTLENESS" IN EPILEPSY PATIENTS

Sharmila Das

Das, S., Guo, D., Shu, Y., Pu, X., Jiang, X., Jiang, W., Ting, T. Y., and Polli, J. E.

Session F; Poster Presentation; Room 349

Some epilepsy patients cite sensitivity (e.g. worsened seizures or side effects) to generic antiepileptic drug (AED) formulation compared to brand, which we denote such patients as generic brittle (GB). The objective was to elucidate genes that differentiate GB patients from not GB patients. Subjects were outpatients from an epilepsy clinic at the U of MD Medical Center. GB status for these patients was based on: intractable seizures or AED adverse events history; opinion about generic brittleness in general or in their personal experience; whether they were taking brand or generic AED. 24 single nucleotide polymorphisms (SNPs) and two copy number variants (CNVs) in 12 genes were genotyped in 148 subjects. The SCN1A: rs2298771 ($p=0.051$) and ABCC2:rs3740066 ($p=0.048$) showed some level of association in single SNP analysis, however did not pass the criteria of $p<0.0042$. For each of these two SNPs, although not statistically significant, there was a trend for the less frequent allele (i.e. variant allele for ABCC2 SNPrs3740066 and reference allele for SCN1A SNPrs2298771) to be correlated with GB. Hardy-Weinberg equilibrium analysis found two variants, CYP3A5:rs776746 and CHRNA4:rs1044397, were significant ($p<<0.001$ and $p=0.0043$ respectively), where in each case the epilepsy cohort observed homozygous variant was greater than expected. Interestingly, there were 47 patients who possessed the variant CYP3A5*3 allele and were GB. All 11 of these 47 patients had history of carbamazepine exposure, an AED metabolized by CYP3A5, and were GB. Results suggest that a study powered to detect rare variants may find gene associations for GB status.

42. OLDER ADULTS' EXPERIENCE USING PATIENT PORTALS IN COMMUNITIES: CHALLENGES AND OPPORTUNITIES

HyoJin Son

Son, H. J., and Nahm, E.-S.

Session F; Poster Presentation; Room 349

Patient portals can be beneficial for older adults in managing their health by reviewing health records, communicating with health care providers, and using other convenient

functions. However, there is a lack of research on older adults' experience using patient portals in the community. The aim of this study was to assess older adults' usability of patient portals that they are using. This was a secondary data analysis using selected baseline data from an online trial that tests the effects of a patient portal learning program, which included 272 older adults recruited online. Data were analyzed using descriptive statistics and content analysis. Majority of participants owned portal accounts (n = 194, 71.3%). Self-efficacy for using patient portals was relatively low (mean, 27.1, range: 0-40), and perceived usability of patient portals was also low (mean, 28.7, range: 6-42). Most favored features of patient portals were review of medical information and eMessaging. Main difficulties in using patient portals were associated with login/access and specific functions of patient portals such as appointment set-ups and prescription renewals. Managing multiple patient portals was a particular challenge for many participants, and there are strong needs for more research in improving interoperability of patient portals. Findings from this study indicate importance of proving proper levels of training and technical support to older adults, along with federal-level efforts to maximize the outcomes of patient portal implementation. Further investigation is needed to identify barriers to patient portal use among various older adult populations and develop strategies to mitigate the problems.

43. TAILORING NONINVASIVE BRAIN STIMULATION TO ENHANCE BIMANUAL ARM COORDINATION IN INDIVIDUALS WITH CHRONIC STROKE

Wan-wen Liao

Liao, W-W., Whitall, J., Barton, J. E., and McCombe Waller, S.

Session F; Poster Presentation; Room 349

Using non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS) as an adjunctive therapy has emerged as a promising approach in stroke rehabilitation. Few studies have examined the effects of rTMS on bimanual arm function. The purpose of this study was to examine the neuromodulation effects of ipsilesional primary motor cortex (iM1) vs. contralesional dorsal premotor cortex (cPMd) on bimanual arm coordination and cortical function in individuals with chronic stroke. Subjects: Eight subjects with chronic stroke. Methods: Subjects received a single session of 5-Hz rTMS on either iM1 or cPMd. During each session, subjects performed isometric elbow flexion tasks with both arms while matching a visual target corresponding to 20% of their maximal voluntary contraction. Outcomes included motor evoked potential amplitude (MEPs) of M1, as well as, interlimb force and neuromuscular coordination during the bimanual task. Results: Six subjects showed increased MEPs in the lesioned hemisphere, and decreased MEPs in the non-lesioned hemisphere after iM1-rTMS ($p<.05$). Their interlimb force correlation/intermuscular coordination also increased after iM1-rTMS ($p<.05$). In contrast, two subjects demonstrated greater MEPs in the lesioned hemisphere after cPMd-than iM1-rTMS. Their interlimb force correlation/intermuscular coordination also increased after cPMd-rTMS. Our regression model showed the changes of MEP of the lesioned hemisphere was significantly correlated with wrist/hand function of the paretic arm ($p=.03$, $R2=.63$). Conclusion: Our study identified two different patterns of response to iM1- and cPMd-rTMS in subjects with chronic stroke, indicating that brain stimulation protocols should be individualized to each subject to achieve optimal effects.

44. Genetic Risk for Hearing Difficulty is Enriched in Evolutionarily Conserved Cochlear Enhancers

Gurmannat Kalra

Kalra, G., Milon, B., Casella, A., Song, Y., Ament, S.* and Hertzano, R.*

Session F; Poster Presentation; Room 349

Age-related hearing loss affects approximately 25% of those aged 65-74 and 50% aged 75+. Family studies suggest that heritable factors contribute strongly to hearing loss, yet specific loci remain largely unknown. In this study, we tested the hypothesis that heritability for hearing loss is enriched in regions of open chromatin conserved in human and mouse cochlear epithelial cells. We identified open chromatin regions in neonatal mouse cochlear epithelial and non-epithelial ATAC-seq cell samples. We mapped homologous open chromatin regions to the human genome and tested for enrichment of heritability in these conserved regions using stratified LD score regression in GWAS of hearing loss traits in 323,978 individuals from the UK Biobank. Heritable risk for hearing difficulty was enriched 10-fold in these regions; 2.08% of all SNPs are in the annotated regions, and these SNPs capture 21.59% of the total SNP heritability. Similarly, heritability of hearing aid use was enriched 15-fold in these regions; these SNPs capture 32.82% of the total SNP heritability. Given the enrichment of heritability in these conserved cochlear open chromatin regions, we hypothesized that age-related hearing loss involves changes in the binding sites and target genes of specific transcription factors. We performed genomic footprinting analysis with our ATAC-seq data from mouse cochleae to predict the genome-wide binding sites of target genes for transcription factors in epithelial and non-epithelial cells from the mouse cochlea. Using these data, we aim to characterize the relationship between cochlear enhancers, gene expression in the inner ear, and risk for age-related hearing loss.

45. Regional Variations in the Prevalence of Opioid Use Disorders, Treatment Among Pregnant Women, and Newborns with Adverse Outcomes in a Commercially Insured Pregnant Population

Laura Gessler

Gressler L.E. and Shaya F.T.

Session F; Poster Presentation; Room 349

OBJECTIVES: To evaluate regional variations in the prevalence of opioid use disorder (OUD), treatment among pregnant women, and the prevalence of adverse outcomes among newborns, in a commercially US insured population.
METHODS: The study was a retrospective cohort analysis using the IMS Lifelink database with electronic records from 2007-2015. Pregnant women were identified and classified as having an OUD if they had that diagnosis before or during their pregnancy. Receipt of treatment was recorded if an NDC code for the methadone, buprenorphine, or a combination of buprenorphine/naloxone was present. Newborns with diagnoses codes for fetal alcohol syndrome, presence of hallucinogenic agents or narcotics, withdrawal symptoms or neonatal abstinence syndrome were classified as having an adverse outcome. Based on the state of residence, women and newborns were placed into 4 different regions: South, Midwest, West, and Northeast.
RESULTS: Of 310,861 pregnant women, 1247 (0.41%) had OUD, 329 (0.11%) received treatment, and 1369 (0.39%) of newborns had

an adverse outcome. In the North, there was a higher prevalence of OUD (0.57%) among pregnant women and adverse outcomes (0.75%) among newborns, but a lower prevalence of treatment (0.14%). In contrast, the South had a lower prevalence of OUD (0.34%) among pregnant women, similar prevalence of treatment (0.13%) and lower prevalence of adverse outcomes (0.18%) among newborns.
CONCLUSIONS: These results show significant regional variations in the patterns of OUD diagnosis, treatment, and newborn adverse outcomes, and suggests a need to further explore the source of these variations.

46. Targeted Memory Reactivation during a Daytime Nap to Enhance Sensorimotor Skill Performance in Healthy Young Adults

Brian Johnson

Johnson, B. P. and Westlake, K. P.

Session F; Poster Presentation; Room 349

Introduction: Neural networks involved with memories are strengthened throughout the course of sleep via spontaneous 'replaying' in activity-related local brain regions. Non-invasive methods of sensory stimulation during sleep have been developed to enhance this process. The most widely used method is known as targeted memory reactivation (TMR), involving classical conditioning of an auditory cue paired with task performance during motor skill acquisition, followed by replaying the same cue during sleep. Application of TMR during sleep, but not wake, activates brain regions involved with initial skill acquisition leading to increased functional connectivity within related brain networks. We have previously demonstrated that TMR throughout the first two slow wave cycles of sleep feasible to enhance non-dominant arm throwing accuracy. However, it is unknown whether TMR application throughout a one-hour daytime nap is sufficient to produce measurable effects in performance. Methods: Fifty-two right-handed individuals were randomized into groups differentiated by between-session activity: Wake+NoTMR, Wake+TMR, Sleep+NoTMR, Sleep+TMR. The protocol involved two sessions of repetitive left arm throwing to unique visuospatial targets with distinct auditory cues paired with each target. Results: Between-group differences found in absolute error change score ratios between-sessions, where negative ratios indicate improved accuracy ($p=0.002$). Post-hoc analyses indicated that Sleep+TMR had a greater decrease in absolute error change scare ratio than Wake+NoTMR ($p=0.001$), Wake+TMR ($p=0.045$), and Sleep+NoTMR ($p=0.042$). Conclusions: These results indicate that auditory cues enhanced spatial accuracy across the one-hour sleep interval. A follow-up study is planned to enhance upper extremity training protocols in individuals post-stroke.

47. Impaired Posture and Movement Preparation during Standing Voluntary Reach in the Paretic and Nonparetic Arms Following Stroke

Chieh-ling Yang

Yang, C.-L., Rogers, M. W., and McCombe-Waller, S

Session F; Poster Presentation; Room 349

Delivering a loud acoustic stimulus (LAS) during the preparation phase of an intended action can trigger an early initiation of the planned movement, a phenomenon called startReact (SR) response. The purpose of this study is to investigate posture and movement

preparation during a standing reach task by using SR response in individuals with chronic hemiparesis and healthy controls. Nine subjects with stroke 10 healthy controls participated in this study. Subjects were standing on two separate force platforms and received a warning light cue followed 2.5s later by a go light cue to "reach as quickly as you can". An LAS was delivered at 500 or 200 ms before the go cue. The incidence of SR response in anticipatory postural adjustment and goal-directed reaching movement was calculated. One-way ANOVA was used to compare the differences between the paretic and nonparetic arms in stroke subjects and healthy controls. Significant difference in the incidence of full SR response was found ($F(2,25) = 4.855$, $p = .017$). Post-hoc analysis revealed that healthy controls has significantly higher incidence of SR response (0.63 ± 0.23) compared to stroke subjects during the paretic arm reaching (0.27 ± 0.29, $p=.032$) and a trend toward significance during the nonparetic arm reaching (0.31 ± 0.32, $p=.061$). These findings indicated impairments in posture and movement preparation following stroke during not only the paretic but also nonparetic arms reaching. To promote functional independence in individuals with stroke, intervention strategies should emphasize posture-reach coordination for both the paretic and nonparetic reaching in standing.

48. Pain Perception In The Brain - EEG

Nandini Raghuraman

Raghuraman, N., Schenk, L., and Colloca, L.

Session F; Poster Presentation; Room 349

Background: Placebo effect is the beneficial outcome of treatment due to context and not just the action of drugs. In the field of pain, the reduction of pain perception due to placebo effects is called placebo analgesia or expectancy-induced analgesia. Research shows that placebo analgesia can be generated by conditioning, verbal instruction, or by observing others. Previously conditioning paradigms were primarily used to understand how placebo effects arise and are maintained although human behaviors are affected by social learning. Social learning refers to gaining information about one's environment by observing others. Recent research suggests that observational learning can also induce placebo analgesia, however, the neural underpinnings of observationally-induced placebo analgesia are yet to be investigated.
Research Plan: Healthy study participants will be recruited and asked to complete an observation and test phase during EEG acquisitions.Observation phase will have pictures of a demonstrator experiencing pain on two inert creams on the forearm described as active analgesic and control. Each cream is linked with colored cues. The demonstrator showed painful expression for the control cue and neutral expression for the treatment cue. During the test phase, same treatment will be applied to the participants and will receive medium pain along with both the cues to determine observationally induced pain modulation.
Expected outcome: Observationally acquired benefits of treatment in another person will result in placebo analgesic responses which concord with specific EEG band- frequency changes namely the alpha and gamma oscillation in the medial prefrontal cortex that associate with pain.

49. Assessing Cultural Competence in Professional Curriculum

Ester Kimani and Hannah Oseghlae

Kimani, E. and Oseghale, H.

Session F; Poster Presentation; Room 349

Aim.
The purpose of our research is to conduct a literature review in order to assess cultural competence among pharmacy students throughout their professional curriculum as well as their Advanced Pharmacy Practice Experiences.
Background.
Our communities are full of a diverse pool of people; therefore, it is imperative for the pharmacist that serve these communities to have the necessary trainings in order to offer optimal services to patients. One way to assess cultural competence is by engaging pharmacy students with diverse patient populations during APPEs.
Methods.
A comprehensive search using Embase, PubMed, and American Journal of Pharmaceutical Education, was completed based on a wide range of key terms including cultural competence, APPE, curiculum, pharmacy education, assessment and perceptions of cultural competence. After reviewing the relevance of the articles to the question, 13 articles published from 2003-2018 were eligible for this study.
Results.
Most pharmacy students demonstrated awareness and experience of cultural competence. Pharmacy students who had more cultural competency encounters during their rotations, have been shown to be more successful in different sociocultural groups. By implementing cultural competence activities in curriculums, students are able to provide exceptional care to patients.
Conclusions.
The literature review shows that pharmacy students have shown some progression towards cultural competence and also based on their experiential rotations, when given case scenario group there was a significant positive change in the culture awareness component. However, there were still students who had low knowledge and moderate skills in dealing with socio-cultural issues and cross-cultural issues.

50. COST-EFFECTIVENESS ANALYSIS OF HYDROGEL SPACER DURING PROSTATE CANCER RADIOTHERAPY

Rahul Khairnar

Khairnar, R., Levy, J., and Mishra, M. V.

Session G; Poster Presentation; Room 349

BACKGROUND: A hydrogel rectal spacer is an FDA-approved medical device used to increase the separation between the rectum and the prostate. We conducted a cost-effectiveness analysis of spacer use in prostate cancer (PC) patients undergoing intensity modulated radiation therapy (IMRT).

METHODS: A multi-state Markov model was constructed to examine the cost-effectiveness of spacer in men with localized PC receiving IMRT in the US (arms: IMRT alone vs. IMRT + hydrogel rectal spacer). Data on toxicity incidence, as well as potential risks associated with spacer implantation were obtained from a recently published clinical trial. Health utilities and costs were derived from the literature and 2018 Physician Fee Schedule. Quality-adjusted life years (QALYs) and costs were modeled for a 5-year period from receipt of RT. Probabilistic sensitivity analysis (PSA) and value-based threshold analyses were conducted. Costs and utilities were discounted at 3% annually.

RESULTS: The per-person 5-year incremental cost for spacer administered in a hospital was $4,008 and the incremental effectiveness was 0.0273 QALYs. The incremental cost-effectiveness ratio (ICER) was $143,741 for

PC patients undergoing spacer insertion in a hospital vs. $71,851 for patients undergoing spacer insertion in an ambulatory facility. For men with good erectile function (EF), the ICER was $50,749 and $25,755 in hospital vs. ambulatory facility.

CONCLUSIONS: Based on the current Medicare Physician Fee Schedule, spacer is cost-effective in men with good EF at a willingness to pay threshold of $100,000 and it is marginally cost-effective for the entire population depending on the facility where the spacer is inserted.

51. THE REGULATION AND MECHANISM OF HEME MEDIATED SIGANLING BY THE HEME ASSIMILATION SYSTEM (HAS) OF PSEUDOMONAS AERUGINOSA

Alecia Dent

Dent, A. T., Mourino, S., Huang, W., and Wilks, A.

Session G; Poster Presentation; Room 349

Iron is an essential nutrient required for the survival and virulence of Pseudomonas aeruginosa. Due to iron limitation during infection, Pseudomonas utilizes extracellular heme via the Phu (Pseudomonas heme uptake) and Has (Heme assimilation system) systems. Previously our lab has characterized the Phu as the primary heme uptake pathway and the Has functions as the heme sensor. The hemophore HasA through interactions with the outer membrane receptor HasR comprise the cell surface signaling (CSS) that transmits the extracellular heme signal to the extra cytoplasmic function (ECF) anti-sigma and sigma factor, HasS and HasI respectively. Although it is assumed the ECF system is similar to that of the previously characterized S. marcescens Has system and acts to autoregulate the levels of HasA, HasR and HasS, the downstream targets in P. aeruginosa have not been determined. Furthermore, the mechanism by which heme bound HasA activates the ECF system has not previously been investigated. Herein we report on the regulation of the has system through the ECF sigma factor and activation of the CSS system using bacterial genetics and biophysical techniques. Together these results suggest that the has operon functions significantly different than that of the S. marcescens system. Our studies show that HasI is not the only regulator of the has operon and through separate mechanisms such as a riboswitch or a metabolite of heme degradation (e.g. biliverdin), HasA can rapidly activate or downregulate its response to its environment. Also HasA mutants show that HasR activation is dependent on the ligand-bound hemophore.

52. HIGH RESOLUTION SNAPSHOTS INFORM THE CATALYTIC MECHANISM OF G/T GLYCOSYLASE ACTIVITY FOR HUMAN METHYL BINDING DOMAIN IV

Hilary Bright

Bright, H., Pidugu, L. S. M., Pozharski, E., and Drohat, A. C.

Session G; Poster Presentation; Room 349

Deamination of 5-methylcytosine (mC) generates G·T mispairs, and, upon replication, C->T transitions, which are among the most prevalent point mutations associated with cancer and genetic disease. The mammalian repair protein MBD4 (methyl-CpG-binding domain IV) protects against this threat by excising thymine from mutagenic G·T mispairs, and follow-on base excision repair (BER) proteins yield a G·C base pair. MBD4 has also been implicated in active DNA demethylation, by initiating BER on G·T

mispairs generated by a deaminase enzyme. We report two high-resolution (1.21 and 1.24 Å) crystal structures of the glycosylase domain of human MBD4 (residues 427–580) bound to abasic DNA. The structures provide a highly detailed snapshot of the enzyme–product complexes generated by MBD4 action on DNA containing a G·U or a G·T mispair. Remarkably, both structures clearly reveal a natural abasic site, with the C1'-hydroxyl existing as an alpha anomer. Our results do not support the provocative claim that either a transient (highly reactive) reaction intermediate, or a covalent enzyme-substrate intermediate, was trapped in a lower resolution (2.84 Å) structure of the MBD4 product complex. Our findings question the proposal that the MBD4 reaction proceeds through a covalent enzyme-substrate intermediate. Rather, they are consistent with an expected stepwise reaction mechanism, as demonstrated for other DNA glycosylases. We are attempting to obtain a high-resolution structure of MBD4 bound to a transition-state analog, to further explore the reaction mechanism.

53. HISTOMORPHOMETRIC ANALYSIS OF MOUSE GROWTH PLATE DURING MATURATION AND SENESCENCE

Kimberly Wilson

Wilson, K. B. and Enomoto-Iwamoto, M.

Session G; Poster Presentation; Room 349

The growth plate (GP), an essential tissue for endochondral bone formation during growth of long bones, ribs and vertebrae experience changes with overall height , width, zone proportion, cell density and cell size during skeletal growth. The GP has a repair or renewal capacity, but is exhausted when damaged by injury or impaired by metabolic disorders, leading to growth plate senescence and eventually inhibition of long bone growth. The mechanisms involved in physiological and pathological changes in the GP has been actively investigated. However, there is limited data available on microscopic changes of the GP from neonatal to adult. We wanted to establish histomorphometric parameters describing GP changes throughout skeletal maturation. We analyzed the proximal tibia's GP of C57Bl/6J mice at seven different stages: infant (P6 and P9), child (P13, P21) adolescent (P28), young adult (P42), and adult P70. Sagittal sections of the medial tibial plateau (n=3 each) were used and the sections stained with Hematoxylin & Eosin. Histological images of the GP were quantitatively analyzed regarding total and zone height, width and area. The results show an increase of width, height and area up to adolescence before a decline at adulthood. We also studied proliferation activity of the GP using Edu staining and found that proliferation activity of chondrocytes was highest at P13 and decreased from P21 when the longitudinal bone growth rate was still high. The results of this study will provide groundwork that will aid skeletal research by providing a firm understanding of GP maturation and senescence.

54. TWO-FACED SYNTHETIC A-HELIX MIMETICS BASED ON HETEROCYCLIC CORES AS DUAL BCL-2/MDM2 INHIBITORS

Brandon Drennen

Conlon, I. L., Drennen, B., J., Lanning, M.,E., Chen, L., Hughes, S., J., Wilder, P., T., and Fletcher, S.

Session G; Poster Presentation; Room 349

Overexpression of the anti-apoptotic proteins of the BCL-2 family, specifically Bcl-2, Bcl-xL and Mcl-1, leads to tumorigenesis through the sequestration of neutralization of their pro-

apoptotic counterparts through their BH3 α-helical "death" domains. Likewise, MDM2 and MDMX sequester and inhibit the tumor suppressor p53 through its α- helical transactivation domain. It is noteworthy that both members of the BCL-2 and MDM2 families are co- upregulated in many cancers, including acute myeloid leukemia. Significantly, the recognition patterns presented by the hydrophobic faces of both the BH3 and p53 α-helical domains are similar; Bak-BH3: Leu62, Ile65 and Phe69; p53: Phe19, Trp23 and Leu26. On the opposing faces, there are conserved aspartates between the i and i+4 residues; while this plays a functional role in the BH3 α-helices in the recognition of their target proteins, its role in the p53 α- helix is only to ensure proper folding into the secondary structure. Therefore, towards more efficacious anti-cancer agents, we have designed small-molecule α-helix mimetics based on heterocyclic scaffolds to co-emulate both faces of the BH3 and p53 α-helices. Preliminary evaluations have validated our polypharmacology design rationale, and we will present an investigation into the structure–activity relationships of our novel α-helix mimetics across the BCL-2 and MDM2 families of proteins.

55. CHARACTERISTICS OF QUIESCENT MELANOCYTES IN BULGE AND SUB-BULGE REGIONS OF ANAGEN HAIR FOLLICLE

Bishal Tandukar

Tandukar,B., Joshi, S. S., Pan, L., Huang, J., and Hornyak, T. J.

Session G; Poster Presentation; Room 349

Melanocyte stem cells (McSCs) are key components of the hair follicle (HF) stem cell system that are derived from neural crest during embryogenesis and are responsible for regeneration of differentiated melanocytes during successive HF cycles. Our analysis of McSC quiescent and proliferative properties throughout the HF cycle using BrdU surprisingly revealed quiescent melanocytes maintained outside of the HF bulge region throughout the anagen. This observation has implications for maintenance of McSCs throughout successive follicular cycles. Here, we wanted to characterize more fully these quiescent anagen melanocytes.

Our Dct-H2BGFP bitransgenic doxycycline-regulated mouse model permits accurate identification of the McSCs and melanocytes in murine HFs through GFP expression. To confirm the existence of quiescent GFP expressing cells during anagen, we treated the animals with doxycycline from P19 to P30 to extinguish the expression of GFP. The results show a subpopulation of Ki67- GFPHigh melanocytes predominately in the HF outer root sheath (ORS), confirming their quiescence compared to proliferating and differentiated melanocytes located at the HF bulb with low GFP retention and higher Ki67 expression. Further investigation shows existence of Kit+ Nestin+ quiescent melanocytes at the HF bulge and Kit+ Nestin- quiescent melanocytes below the bulge area. Both subpopulations of quiescent melanocytes express lower levels of melanocyte differentiation markers Mitf, Dct, Tyrp1 and Tyr compared to proliferating Kit- Nestin- melanocytes located at HF bulb. These results suggest that quiescent melanocytes localized in the ORS above the HF bulb in anagen retain the stem cell phenotype observed in quiescent McSCs during telogen.

56. DETERMINATION OF THE MECHANISM OF RNA REGULATION BY CPSF30, A ZINC FINGER/IRON SULFUR CLUSTER PROTEIN INVOLVED IN RECOGNITION OF THE POLYADENYLATION SIGNAL DURING PRE-MRNA PROCESSING

Jordan Pritts

Pritts, J. D., Oluyadi A. A., Shimberg, G. D., Michalek, J. L., Beth E. Zucconi, Stemmler, T. L., Rodrigues, A. V., Wilson, G. M., and Michel, S. L. J.

Session G; Poster Presentation; Room 349

Zinc finger (ZF) proteins are the most common type of metal regulated transcription factor found in eukaryotes. ZFs have high specificity in DNA and RNA recognition and play important roles in transcription and translation. ZF proteins contain one or more domains with four conserved cysteine and/or histidine residues that serve as ligands for zinc. ZFs are classed based upon the number of cysteine and histidine residues in the domain and the spacing between amino acids. We are studying a ZF named Cleavage and Polyadenylation Specificity Factor 30 (CPSF30). CPSF30 contains five CCCH domains and is required for pre-mRNA processing. We have recently reported the first direct evidence that CPSF30 is an RNA binding protein. We discovered that CPSF30 regulates pre-mRNA by selectively binding to an AU-rich hexamer present in all pre-mRNAs (PAS signal). Unexpectedly, we discovered that CPSF30 has been shown to harbor a 2Fe-2S cluster, in addition to zinc. This is one of a few known examples where zinc fingers have been incorrectly annotated by sequence homology after the genome sequencing boom in the early 2000's. Our current work is focused on understanding how mutations in the PAS signal related to disease affect CPSF30/RNA recognition. We will present these results along with current efforts to decipher the role of the 2Fe-2S cluster in RNA recognition.

57. The Relationship between the soluble heme binding protein PhuS and iron-responsive small regulatory RNA's prrF/H in Pseudomonas aeruginosa

Tyree Wilson

Wilson, T., Reyes-Caballero, H., Mourino, S., A. and Wilks, A.

Session G; Poster Presentation; Room 349

Pseudomonas aeruginosa is a gram-negative opportunistic pathogen that can cause life threatening nosocomial infections in immune compromised patients. Most bacteria require iron for survival and virulence. P. aeruginosa can acquire iron through several mechanisms including iron siderophores, the ferrous iron uptake system and via heme uptake and metabolism. This pathogen encodes two interdependent heme uptake systems, the pseudomonas heme utilization (Phu) and heme assimilation system (Has). Our laboratory has shown the Has and Phu system have non-redundant roles in heme sensing and uptake, respectively. However, once internalized in the cytoplasm heme flux is through the iron-regulated HemO to release iron and biliverdin IX alpha/beta is regulated by the cytoplasmic heme binding protein PhuS.
A link between PhuS and the iron-regulated sRNAs, PrrF1 and PrrF2, has been uncovered. The prrF1 and prrF2 sRNAs are arranged in tandem arrangement upstream of the phu operon, and is only found in Pseudomonas strains that encode PhuS. The tandem arrangement also allows for heme-dependent read through of prrF1/2 to give PrrH. Analysis of knockouts, prrF1/F2 and PhuS, showed an increase in PhuS expression and PrrH, respectively. We hypothesize that PhuS acts as a regulator of intracellular heme and iron homeostasis linking heme metabolism to the iron and heme-dependent sRNA regulatory network. We will test this hypothesis in vitro and in vivo by creating PhuS mutants that shift

the apo- to holo-PhuS equilibrium. We will determine heme binding affinities and rate of transfer by spectroscopic methods, and the PhuS-prrF1 promoter affinities by EMSA and fluorescence anisotropy.

58. THE INVESTIGATION OF INTERACTIONS OF PROTEIN TARGETS WITH GOLD COMPLEXES AND GOLD NANOCLUSTERS

Kiwon Ok

Ok, K., Neu, H. M., Li, W., Brandis, J. E. P., Liang, D., Zalesak, S., and Michel S. L. J.

Session G; Poster Presentation; Room 349

Gold complexes have potential as anti-inflammatory and anti-cancer agents, however their mechanisms of action is poorly understood. Similarly, gold has been shown to stabilize protein nanoclusters as protein stabilized gold nanoclusters. These new materials have unique fluorescence properties that have the potential to be employed as novel biological sensors. However, the fundamental physiochemical and biochemical properties of protein stabilized gold nanoclusters are not well known. My research is focused on characterizing the interactions of gold complexes with protein targets and on determining the fundamental properties of protein stabilized gold nanoclusters. My approach includes biophysical and mass spectrometric methods along with cellular studies. My findings in both areas will be presented.

59. DIFFERING CONTEXT SPECIFICITY FOR THYMINE DNA GLYCOSYLASE (TDG) SUBSTRATES

Jake Dow

Dow, J. and Drohat, A.C.

Session G; Poster Presentation; Room 349

Thymine DNA glycosylase (TDG) excises T from G•T mispairs that arise via deamination of 5-methylcytosine (5mC), with specificity for mispairs within a CpG sequence context. TDG can also excise 5-formylcytosine (fC) and 5-carboxylcytosine (caC), oxidation products of 5mC that are generated by TET (ten-eleven translocation) enzymes, during active DNA demethylation. Remarkably, we find that TDG activity for fC and caC shows no significant dependence on a CpG context, revealing a major difference in specificity for excision of fC and caC relative to T. The stringent CpG context specificity for excision of T might reflect the need for TDG to minimize excision of T from the vast background of A•T pairs, an aberrant activity that could be mutagenic and cytotoxic. Our goal is to understand the molecular basis of substrate specificity for TDG. Using 19F NMR, we determined that base-flipping equilibria for G•T mispairs into TDG's active-site is strongly affected by CpG context.

60. LOSS OF BINDING BETWEEN GIANT OBSCURIN AND TITIN RESULTS IN CARDIAC MALADAPTATION

Alyssa Grogan

Grogan, A., Hu, L. R., and Kontrogianni-Konstantopoulos, A.

Session G; Poster Presentation; Room 349

Giant obscurin is a modular protein that plays key structural and regulatory roles in striated muscle. It was originally discovered as a binding partner of canonical titin and novex-3, a "small" splice variant of titin. Immunoglobulin (Ig) domains Ig58/Ig59 of obscurin mediate binding to Ig9/Ig10 domains

of titin and to a unique 198 amino acid sequence of novex-3. Although the direct binding of obscurin to both titin isoforms has been known for over 15 years, the physiological significance of these interactions is still elusive. To assess the effects of obscurin/titin binding in vivo, we generated a constitutive deletion mouse model (Obscn-ΔIg58/59) that carries truncated obscurin lacking the Ig58/Ig59 region. By 1-year of age, male Obscn-ΔIg58/59 animals develop left ventricular dilation, whereas females do not exhibit any obvious alterations. Interestingly, electrocardiography reveals the presence of arrhythmia in both genders, with males exhibiting more frequent and longer episodes. The distinct phenotypes of the female and male populations clearly indicate the presence of sex dimorphism in the Obscn-ΔIg58/59 model at least in response to the physiological process of aging. Given that stress often exacerbates the harmful effects of molecular alterations, we subjected young wild type and Obscn-ΔIg58/59 mice to a physiological stress via treadmill exercise and evaluated their running performance and cardiac function. Both male and female Obscn-ΔIg58/59 mice exhibited poorer running ability compared to gender-matched wild types. Furthermore, male Obscn-ΔIg58/59 mice develop significantly larger atria, suggesting that strenuous exercise is leading to cardiac remodeling in young male Obscn-ΔIg58/59 animals as well.

61. DYSFERLIN MUTANTS: DEFECTS IN TRAFFICKING AND ASSOCIATION WITH PROTEINS OF THE TRANSVERSE TUBULE

Daniel Garman

Garman, D. D., Muriel, J. M., Lukyanenko, V., and Bloch, R. J.

Session H; Poster Presentation; Room 349

Dysferlinopathies are a class of muscular dystrophies caused by a loss of function or expression of dysferlin, a 237 kDa single-pass transmembrane protein expressed in skeletal muscle. Dysferlin has been implicated in sarcolemmal and T-tubule repair and in the regulation of calcium signaling during mechanical stress. Dysferlin binds to several proteins associated with the transverse tubules, including the dihydropyridine receptor (DHPR) and Caveolin 3, to stabilize the triad junction and possibly serve as a scaffold for repair machinery. Mutations disrupting these interactions may lead to disruption of Ca signaling mechanical stress, which in turn leads to fiber loss, inflammation and muscle atrophy associated with muscular dystrophy. Mutations to dysferlin have also been shown to lead to aberrant trafficking, causing accumulation in compartments other than the T-tubules and sarcolemma, therefore removing or reducing the ability of dysferlin to function. We are studying several point mutations found in dysferlinopathy patients, in addition to domain and exon deletion mutants, to determine their effects on trafficking, association with other membrane proteins, and dimerization.

62. MECHANISTIC STUDY OF A NOVEL THIENYL NAPTHALENESULFONATE MOLECULE THAT SELECTIVELY INHIBITS MELANOMA CELLS WITH CONSTITUTIVELY-ACTIVE ERK1/2

Ramon Martinez III

Martinez III, R., Huang W., Centola, G., Samadani, R., Chen, L., Scheenstra, J., Fletcher, S., Kane, M., Mackerell, A., and Shapiro, P.

Session H; Poster Presentation; Room 349

The uncontrolled proliferation of cancer cells is often a result of constitutive activation of the extracellular signal-regulated kinase (ERK 1/2)

signaling pathway. Current trends in the design of kinase inhibitors for the ERK1/2 pathway employ the use of ATP-competitive scaffolds, targeting the catalytic core of the proteins. As an alternative, we used computer-aided drug design (CADD) to identify a novel thienyl napthalenesulfonate compound that selectively inhibits ERK2 at a binding site used by F-site containing substrates, such as members of the Fos family of proteins. This compound has been shown to selectively inhibit the growth of melanoma cells that have constitutively active ERK1/2 via mutations in upstream activators BRaf or NRas. Proteomic and transcriptomic analysis of drug-treated lysates showed inhibition in the expression of important downstream F-site containing substrates of ERK 1/2, such as c-Fos, Fra-1, and c-Myc. In addition, increased expression of Nrf2, which is a regulator of reactive oxygen species (ROS)-mediated cellular responses, suggests that this compound may be involved with impeding melanoma cell growth via upregulation of oxidative stress pathways. However, when treating with compounds known to reverse the effects of the ROS-response, significant reversals in proliferation are not apparent, suggesting that ROS-induction may not be the sole player in this compound's apoptotic effect. In this work, we will attempt to further characterize and validate if ROS-mediated regulatory mechanisms are a result of the apoptotic effects of this novel compound and how it can serve as a promising alternate line of therapy to traditional ATP-competitive kinase inhibitor.

63. Identification of Inhibitors of the Pseudomonas aeruginosa HasA/HasR Protein-Protein Interaction

Garrick Centola

Centola, G., Jiang, W., Yu, W., Hom, K., Mackerrel, A., Xue, F., and Wilks, A.

Session H; Poster Presentation; Room 349

Pseudomonas aeruginosa encodes the heme acquisition system (Has) as a method of sensing and uptake of extracellular heme in a host environment. In this system, heme is captured by a secreted hemophore, HasA, and delivered to an outer-membrane receptor, HasR. Inhibition of this pathway alters expression of the Has system and the higher-capacity Pseudomonas heme uptake (Phu) system leading to decreased virulence. While some efforts have been made to inhibit the heme binding of HasA, picomolar heme affinity presents a significant competitive challenge. Using a model of the Pseudomonas aeruginosa HasR protein, we have proposed a series of peptide sequences that will bind to HasA, inhibiting the HasA/HasR interaction. Using NMR techniques, computer-aided drug design and development of a high-throughput automated cellular assay, we propose a multi-faceted approach towards the identification of novel HasA binders capable of inhibiting interaction with HasR. This method could lead to the new understanding of the system as well as the development of new antibiotics without the need to penetrate the membranes of gram-negative bacteria.

64. A High Throughput In Vivo Screening Assay for Novel Inhibitors of Extracellular Heme Sensing and Utilization in Pseudomonas aeruginosa

Elizabeth Robinson

Robinson, E., Wilks, A., Xue, F., and Mouriño, S.

Session H; Poster Presentation; Room 349

Iron is an essential nutrient for growth and virulence of Pseudomonas aeruginosa, a

multidrug resistant (MDR) opportunistic pathogen. P. aeruginosa adapts within the host to utilize heme as its primary source of iron. Heme in the extracellular environment is sensed by the secreted hemophore HasAp that triggers the extra cytoplasmic function (ECF) sigma factor, HasI to upregulate transcription of the heme uptake systems. We have recently shown that the terminal metabolite of heme degradation biliverdin IXβ (BVIXβ) is a positive feedback regulator of the Has system. Therefore, targeting heme uptake is a novel therapeutic strategy against P. aeruginosa MDR infections. We hypothesize that inhibition of the iron regulated heme oxygenase (HemO) and hence BVIXβ levels, reduces the capacity of the cell to sense the extracellular environment, while also inhibiting the ability to acquire iron. Here we present a novel in vivo high throughput screen coupling heme sensing by P. aeruginosa to the transcriptional activation of a luciferase gene. The assay can be adapted for the screening of inhibitors of heme signaling at the level of HasAp or heme metabolism by HemO. This assay provides a complementary approach to in vitro binding assays and traditional MIC assays which are less informative when targeting systems required only in the host environment.

65. Clinically and Environmentally Harmonized Oxybenzone Skin Permeation from Three Sunscreen Products

Paige Zambrana

Matern, M. Beirl, A. Ogawa, Y. Song, Y. Elkon, R. Milon, B. Kindt, B. Hertzano, R.

Session H; Poster Presentation; Room 349

The benefit of sunscreen use to reduce skin exposure to UV rays and subsequently reduce skin cancer risk has been well studied and is now widely accepted. The objective of these studies were to develop an in vitro permeation method for quantifying a widely used ultraviolet (UV) filter, oxybenzone, in worst case scenario situations to evaluate the influence heat and reapplication have on the rate and extent of oxybenzone permeation relative to normal testing conditions. Methods: In vitro permeation tests (IVPT) were performed on three sunscreen products using pig skin. Environmental (heat) and clinical (reapplication) factors were evaluated with the sunscreen products tested. Results: All of the three sunscreen products tested showed quantifiable levels of oxybenzone permeation with highest accumulation occurring from Lotion 1 and lowest from the Spray product. With the addition of continuous heat at a representative sun exposure temperature, a 1.4 fold increase in oxybenzone accumulation occurred. Further accumulation, 2 fold, was observed when heat and reapplication were performed simultaneously creating a statistically greater accumulation ($p \leq 0.001$) to occur with the lotion product tested. Conclusion: This work shows that more oxybenzone could be permeating into systemic circulation than previously recorded under normal testing conditions. To determine clinical significance further testing should be performed in humans as the increased risk of oxybenzone accumulation in children and infants is still unknown.

66. Connexins Form Distinct Complexes with Signaling Machinery that Differentially Affect Osteoblast Signaling and Gene Expression

Megan Moorer

Moorer, M. C., Hebert, C., Joca, H., and Stains, J. P.

Session H; Poster Presentation; Room 349

Intercellular communication between osteoblast and osteocytes by connexin43 (Cx43) gap junctions affects bone modeling and remodeling. Our recent work showed the requirement of the Cx43 C terminus (CT) for optimal osteoblast signaling and gene expression in vivo. These data imply that Cx43-containing gap junctions not only exchange signals, but also recruit signaling machinery to the Cx43 CT domain to optimally affect cell function, and bone acquisition. Additionally, different connexins have distinct effects on osteoblast signaling and function, with Cx43 and Cx45 having antagonistic roles. We hypothesized that the function of connexins are dictated not only by their permeability, but also by their protein-protein interactions. By co-immunoprecipitation (co-IP), our preliminary data show that Cx43 complexes with signaling effectors. In contrast, co-IP of a myc-tagged Cx45 results in minimal co-association of these signaling proteins. These data suggest that Cx43 and Cx45 have different interactomes. To confirm the function consequences of these interactions, we used chimeric connexin proteins composed of portions of both Cx43 and Cx45 and examined downstream signaling and gene expression in osteoblasts. We found that, in general, both the Cx43 pore and Cx43 tail are required for optimal osteoblast signaling and gene expression, as replacement of the Cx43 pore or tail domain with that of Cx45 was ineffective for connexin-dependent signaling and gene expression. In summary, these data imply that each connexin can differentially regulate downstream signaling and gene expression by local recruitment of distinct interactomes to each connexin's CT.

67. PROSTAGLANDIN E2 (PGE2) RECEPTOR EP4 AND THE PGE2 TRANSPORTER MRP4 IN OVARIAN CANCER

Mc Millan Ching

Ching, M. N., Fan, C., Staats, P., Roque, D., Rao, G., Fulton, A., and Reader J.

Session H; Poster Presentation; Room 349

Ovarian cancer has the highest incidence of mortality of all gynecologic malignancies in the US. Most ovarian cancer cases lead to recurrent disease which is often incurable due to innate or acquired chemoresistance. Prostaglandin E2 (PGE2), an inflammatory lipid mediator that is functionally linked to progression of many cancers, is exported from the cell via multidrug resistance-associated protein 4 (MRP4) where it acts in a paracrine and autocrine manner by activating a family of four G-protein coupled receptors (EP1-4). EP2 and EP4 activate PKA/cAMP, PI3K and ERK pathways, which can signal cells to have uninhibited growth. We hypothesize that EP4 receptor has increased expression in ovarian cancer and binding of PGE2 will drive ovarian cancer progression. Immunohistochemical analysis of EP4 on the TMA composed of varying histologies revealed that EP4 was expressed in 38.7% of ovarian cancer tissues; whereas, EP4 had no or low expression in 10 normal ovarian tissue samples. Additionally, in comparison to immortalized human ovarian surface epithelial (HOSE) cells, EP4 and MRP4 has increased expression in many high grade serous carcinoma (HGSC) cell lines. Given the role of MRP4 in exporting PGE2 and affecting drug resistance/sensitivity in breast cancer cell lines, we also hypothesize that MRP4 modulates the amount of PGE2; thereby, affecting EP4 receptor signaling. We propose that inhibition of MRP4 with Ceefourin 1 or Probenecid will lead to a

decrease in ovarian cancer growth. A combination of EP4 receptor antagonism and MRP4 inhibition may provide much needed new therapies for the treatment of ovarian cancer.

68. LYMPHOTOXIN BETA RECEPTOR MODULATION ALTERS REGULATORY T CELL DYNAMICS IN LYMPHATIC ENDOTHELIAL CELLS

Vikas Saxena

Saxena, V., Piao, W., Xiong, Y., Wagner, C., Li, L., and Bromberg, J. S.

Session H; Poster Presentation; Room 349

Lymphotoxin beta receptor (LTβR) mediated signaling in lymphatic endothelium cells (LEC) is important for migration of regulatory T cells (Treg) to afferent lymphatic vessels (LV) and lymph nodes (LN), and for Treg suppressive function for allograft survival. To study Treg-LTβR engagement, we crossed LTβRfl/fl mice with Prox1-Cre-ERT2 transgenic mice to generate Prox1-Cre-ERT2+/-LTβRfl/fl (KO) mice, in which LTβR is depleted in LEC by tamoxifen treatment. Mice were analyzed by flow cytometry and histology. In KO mice, LTβR expression by LEC was markedly reduced by 10 days after tamoxifen treatment, while blood vessel endothelial cells and fibroblastic reticular cells (FRC) maintained expression. LTβR depletion did not affect normal immune system homeostasis and overall architecture of LN. Depletion of LTβR did lead, however, to a marked reduction in the accumulation of Foxp3+ Treg and the expression of CCL21 in the LN, and migration of natural Treg across LV. In vitro stimulation assays showed that both LTβR and Treg directly regulated CCL21 expression and secretion by LEC, confirming that Treg-LTβR-LEC interactions are specific and physiologically important. LTβR depletion also reduced LEC expression of non-canonical NFκB kinase (NIK) and the inflammatory and chemotactic lipid sphingosine-1-phosphate (S1P). However, expression of other LEC factors important in Treg migration such as VCAM-1, ICAM-1, and CCL19 were not affected. Taken together, this model allows study of acute and chronic LTβR mediated regulation of Treg migration and function in an otherwise normal environment.

69. TARGETING MEMBRANE-ANCHORED SERINE PROTEASE ACTIVITIES USING ACTIVATED ENGINEERED ANTHRAX TOXINS IN OVARIAN CANCER

Nisha Pawar

Pawar, N. R., Conway, G. D., Martin, E. W., Lapidus, R. S., and Antalis, T. M.

Session H; Poster Presentation; Room 349

Anthrax toxin is a three-component toxin secreted by Bacillus anthracis. The toxin's mechanism of action requires a protective antigen (PA) protein to be proteolytically activated in order to deliver the other two components, lethal factor and edema factor, into the cytosol to induce cytotoxicity. Typically, cleavage and activation of PA is catalyzed by the protease furin on the cell surface, which is ubiquitously expressed on many cell types. PA has previously been engineered to be activated by MMPs and/or uPA as an alternative to furin, and these mutant PA proteins have been used as tumor-selective, protease-activated reagents capable of achieving tumor cell cytotoxicity in vitro and in vivo. We have developed this prodrug strategy to specifically target the proteolytic activities of a group of proteases known as the membrane-anchored serine proteases. These proteases are often found to be over-expressed

and dysregulated on the surface of many types of tumor cells, including ovarian cancer. We have created novel anthrax toxin PA proteins containing sequences that can be cleaved by membrane-anchored serine proteases in vitro and in cell culture. We also show their ability to induce tumor cell cytotoxicity in combination with other anthrax toxin components. Using an orthotopic mouse model of ovarian cancer metastasis, one of the mutant toxins showed significantly reduced ovarian tumor burden that was well tolerated in nude mice. We are currently investigating the effect of this toxin on tumor burden in immune-competent mouse models of ovarian cancer metastasis and potential immune responses to the anthrax toxin.

70. UTILIZATION OF CRISPR FOR THE GENERATION OF ENDOGENOUS NME1-EGFP IN MELANOMA

Devin Snyder

Snyder, D. E., Wang, Y., and Kaetzel, D. M.

Session H; Poster Presentation; Room 349

NME1 is the first discovered metastasis suppressor protein. Metastasis suppressor proteins have been defined by the ability to inhibit metastasis, while having no impact on primary tumor growth. Despite extensive study the specific mechanism by which NME1 prevents metastasis is still unknown. Yet, research indicates that the metastatic process is driven by changes in tumor cell characteristics. At the forefront of metastatic research are the concept of tumor heterogeneity and the identification of subsets of populations, which can exhibit distinct levels of stem-like markers, tumor initiation capacity, and overall metastatic aggressiveness. Therefore, we sought to identify subpopulations of NME1 expression in melanoma cell lines. Flow cytometry of melanoma cell lines, has revealed the presence of a small population of cells with reduced NME1 expression. However, the process of fixing and staining these cell lines for NME1 prevents further phenotypic characterization of the NME1 subpopulations. In order to further analyze living cells within NME1-based populations, we sought to create cell lines that express NME1-EGFP endogenously.

Genome editing with CRISPR/Cas9 has proven advantageous in identifying the functional implications of specific genes. The CRISPR/Cas9 system allows for DNA sequence modifications and gene silencing. Furthermore, CRISPR can be adapted for the insertion of a specific DNA sequence at a designated genomic location - a useful feature that enables fluorescent labeling. Here we present the use of CRISPR/Cas9-D10A in the incorporation of EGFP at the NME1 locus in three melanoma cell lines, WM35, WM9, and WM239.

71. IMPACT OF UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS ON UTILIZATION OF PROSTATE-SPECIFIC ANTIGEN SCREENING IN MEDICARE BENEFICIARIES

Rahul Khairnar

Khairnar, R., Mishra, M. V., and Onukwugha, E.

Session I; Oral Presentation; Ballroom A

BACKGROUND: Previous studies assessing the impact of USPSTF recommendations on utilization of PSA screening have not investigated longer-term impacts of 2008 recommendations nor have they investigated the impact of 2012 recommendations in the Medicare population. This study aimed to

evaluate change in utilization of PSA screening, post 2008 and 2012 USPSTF recommendations, and assessed trends and determinants of receipt of PSA screening in the Medicare population.

METHODS: This retrospective study of male Medicare beneficiaries utilized MCBS data and linked administrative claims from 2006-2013. Beneficiaries aged ≥65 years, with continuous enrollment in Parts A and B for each year they were surveyed were included in the study. Beneficiaries with self-reported /claims-based diagnosis of prostate cancer were excluded. The primary outcome was receipt of PSA screening. Other measures included age groups (65-74 and ≥75), time periods (pre- /post-2008 and 2012 recommendations), and sociodemographic variables.

RESULTS: The study cohort consisted of 11,028 beneficiaries, who were predominantly white (87.56%), married (69.25%), and unemployed (84.4%); 52.21% beneficiaries were aged ≥75. Declining utilization trends for PSA screening were observed in men aged ≥75 after 2008 recommendations and in both age groups after 2012 recommendations. The odds of receiving PSA screening declined by 17% in men aged ≥75 after 2008 recommendations and by 29% in men aged ≥65 after 2012 recommendations.

CONCLUSIONS: The 2008 and 2012 USPSTF recommendations against PSA screening were associated with declines in utilization of PSA screening during the study period. USPSTF recommendations play a significant role in affecting utilization patterns of health services.

72. AN EVALUATION OF IN-VITRO DISSOLUTION PROFILES FROM VARIOUS BIORELEVANT MEDIA

Raqeeb Jamil

Jamil, R. G. and Polli, J. E.

Session I; Oral Presentation; Ballroom A

Aims: Biorelevant media have been devised to simulate fluids in the gastrointestinal (GI) tract in both the fasted and fed states to evaluate tablet and capsule dissolution. Given the increasing utilization of biorelevant media, we sought to evaluate the reproducibility and variability of dissolution data obtained with its use. Due to the complexity of biorelevant media, we hypothesize that drug dissolution profiles in are inconsistent across dissolution study conditions (e.g. different occasions, analysts, locations/universities, post-dissolution analytical methods, and media fabrication methods). Inter-day variability and media fabrication methods are examined here.

Methods: Dissolution studies were performed on ibuprofen and ketoconazole, as representative BCS Class II drug products by two analysts each at three different universities. Each media condition was used on n=2 occasions with n=6 tablets on each occasion. Dissolution samples were analyzed by high performance liquid chromatography and profiles were compared using the f2 similarity factor and ρm analysis.

Results: University of Maryland Analyst 1 data is reported. Across both drugs and various media, comparison of dissolution profiles showed that biorelevant media was consistent across most of the n=12 dissolution study conditions with two exceptions. Also, comparison of results from media derived from commercial powder versus “from scratch” was consistent across most of the n=6 dissolution study conditions with two exceptions.

Conclusions: Although there have been anecdotal complaints that biorelevant media is difficult to fabricate and can provide irreproducible results, preliminary finding here indicate generally good reproducibility.

73. GENOME-WIDE ANCESTRAL CHARACTERIZATION OF 1009 CANCER CELL LINES AND THE NEED FOR INCREASED ANCESTRAL AWARENESS IN TRANSLATIONAL CANCER RESEARCH

Michael Kessler

Kessler, M. D., Bateman, N. W., Dunning-Hotopp, J. C., and O'Connor, T. D.

Session I; Oral Presentation; Ballroom A

While cell lines are an essential resource for studying cancer biology, many are of unknown ancestral origin, and their use may not be optimal for evaluating the biology of all patient populations. Therefore, we used chip-based sequencing data from COSMIC's Cell Lines Project to perform admixture analysis and characterize ancestry genetically for 1009 cell lines. For the 701 cell lines for which ancestry is reported as unknown, we find that 215 are of Asian origin, 30 are of African or African American origin, and 453 are of European origin. In addition to providing quantitative genetic estimates of global ancestry for all cell lines, we identify low but universal levels of contamination or batch effects across the cell lines. We find notable imbalances in ancestral representation across tissue type, with the majority of liver, stomach and billiard tract derived cell lines having Asian ancestral origin, the majority of cell lines deriving from prostate, skin, pleural, and kidney tumors having european ancestral origin, the majority of analyzed tissue types having few cell lines of African American ancestral origin, and Latino ancestry being almost entirely absent across the entire cell line dataset. We also find gene expression and mutational differences across cancer cell lines of differing ancestral origin. These findings underscore the importance of ancestry awareness when studying cancer biology. As investigators consider which cell lines to use for their respective experiments, it is critical that they are armed with accurate ancestry information that can facilitate appropriate comparisons and designs.

74. SEX DIFFERENCES IN INFECTION RISK AFTER HIP FRACTURE

Anthony Herrera

Herrera, A.V., Huang, Y., Lu, W., Magder, L., Gruber-Baldini, A., and Baumgarten, M.

Session I; Oral Presentation; Ballroom A

Previous studies determined that male hip fracture patients had higher 2-year mortality when compared to women. Deaths from infections were primarily responsible for the observed difference. Our objective was to compare sex differences in infection rates during the 12 months after discharge following hip fracture repair using more recent data. We hypothesized that male hip fracture patients would have higher infection rates than females.

The cohort was assembled from community dwelling adults aged 65+ who were admitted to participating hospitals for surgical repair of hip fracture between 2006 and 2011. Females were frequency matched to males. Baseline data was collected from medical records. Monthly health interviews were done by telephone except during months 2, 6, and 12; which were conducted in-person. Descriptive analyses were performed to assess baseline characteristics and the prevalence of infection at each monthly interview. Multivariable

models were constructed to calculate the infection rate between males and females.

296 subjects were included in the final cohort for analysis, with 144 males and 152 female. There was no difference in age or BMI, but males had higher Charleson scores. Males also had a higher proportion of dementia, atrial fibrillation, and myocardial infarction; while females had more thyroid disease, osteoporosis, and non-metastatic tumors. The multivariable analysis did not find a significant difference in infection rates between women and men.

Data from a recent, balanced cohort did not provide evidence of a difference in infection rates between male and female hip fracture patients.

75. Providers' Perspectives on Resources and Strategies to Improve Hospital-to-Home Transitions Among Adult Hispanic Immigrants with Chronic Conditions

Nimasha Fernando and Yolanda Peprah

Peprah, Y. K., Fernando, N. B., Chapin, B. L., Onukwugha, E., and Camelo Castillo, W.

Session I; Oral Presentation; Ballroom A

Background: Immigrant patients face health challenges that become heightened when transitioning from hospital-to-home care. Challenges may include medication adherence and complying with continual care. Providers' awareness of resources and integration of various strategies can help patients overcome these challenges, expand health networks, and combat health disparities amongst immigrant communities.
Objective: To identify resources that providers recognize are available to patients and the strategies that providers use and desire to implement in order to facilitate hospital-to-home care transitions among Hispanic immigrants with chronic conditions.
Approach: For this qualitative study we conducted semi-structured audio-recorded interviews with six providers regarding their experiences with Hispanic immigrant patients in the Baltimore area during the transition from hospital-to-home care for chronic disease treatment. Providers included a physician, nurse, interpreter, community health program director, and immigrant advocates. Interviews were recorded, transcribed, translated (n=2) verbatim, and analyzed using qualitative methodology.
Findings: The list of resources compiled from the Health Networks coding revealed that providers identified both formal resources associated with clinical settings and informal resources unaffiliated with clinical sites. Strategies described also mirrored this formal and informal categorization.
Significance: By identifying the formal and informal resources and strategies providers are aware of to support the Hispanic immigrant community, we can develop a more comprehensive resource list to share with stakeholders and patients to expand health networks, while exposing possible gaps in care. This analysis can help identify similar ways to support other vulnerable communities working to overcome comparable challenges in order to combat health disparities.

76. Generation of mutants in sinC and incA of Chlamydia caviae using TargeTron

Kimberly Filcek

Filcek, K. A.

Session J; Oral Presentation; Ballroom B

Chlamydia psittaci is a neglected zoonosis that is capable of causing high morbidity in humans. Recently, a type III secreted effector protein, known as SinC, has been identified in C. psittaci closely related species Chlamydia caviae, and displays unusual characteristics including localization to the host cell nuclear envelope and translocation to the nuclear envelopes of neighboring, uninfected cells in vitro. Of separate interest is IncA, an integral protein of the inclusion membranes, that is highly conserved among various chlamydial species including C. psittaci and C. caviae, and plays a role in the fusion of inclusion membranes during infection. Here we have generated separate knock-down mutants in the sinC and incA genes in C. caviae using the TargeTron system which introduces a group II intron into a known location within the target gene. We have confirmed both mutants using PCR and immunofluorescence assay and have confirmed a clear morphological phenotype in the incA::GII C. caviae mutant. Ongoing work includes RNA-seq analysis of host cell transcription during infection with wild type, sinC::GII and incA::GII C.caviae mutants and confirmation of C. caviae SinC translocation to neighboring, uninfected cells as previously described in C. psittaci.

77. MAMMOSPHERE BIOLOGY OF MCF-7 CELLS AS DETERMINED BY SINGLE CELL TRACKING

Patrick Bailey

Bailey, P. C., Lee, R. M., and Martin, S. S.

Session J; Oral Presentation; Ballroom B

The mammosphere assay has become widely employed to quantify stem-like cells in a population. Problematically, there is no standard protocol employed by the field. Cell seeding densities of 1000 to 100,000 cells/mL have been reported. These high densities lead to cellular aggregation. To address this, we have individually tracked 1,127 single MCF-7 human breast tumor cells over the course of 14 days. This tracking has given us detailed information for the commonly used endpoints of 5, 7 and 14 days that is unclouded by cellular aggregation. This includes mean sphere sizes, sphere forming efficiencies and a well-defined minimum size. Importantly, we have correlated early cell division with eventual sphere formation. At 24 hours post seeding, we can predict total spheres on day 14 with 96% accuracy. This approach removes cell aggregation and potentially shortens a 5-14 day assay to 24 hours.

78. GAUCHER DISEASE IPSC-DERIVED OSTEOBLASTS HAVE DEVELOPMENTAL AND LYSOSOMAL DEFECTS THAT IMPAIR BONE MATRIX DEPOSITION

Manasa Srikanth

Srikanth, M. P., Panicker, L. M., and Feldman, R. A.

Session J; Oral Presentation; Ballroom B

Gaucher disease (GD) is a lysosomal storage disorder caused by mutations in GBA1 gene that encodes a lysosomal hydrolase β-glucocerebrosidase (GCase), which breaks down glucosylceramide and glucosylsphingosine. Mutations in GBA1 gene result in decreased enzyme activity causing an accumulation of glycoshpingolipids. Patients with GD display hematologic, visceral and bone abnormalities. The skeletal manifestations include bone pain, growth retardation, osteopenia and osteoporosis. However, the exact mechanism behind these skeletal presentations is not understood. Studies using animal models of GD have reported defective osteoblast function. Hence,

an imbalance in bone remodeling could account for bone disease in GD patients.
In order to study the skeletal abnormalities caused by GCase deficiency, we generated GD iPSC-derived osteoblasts. We found that GD-osteoblasts had severe developmental and lysosomal defects that interfered with bone matrix deposition. There was decreased expression of osteoblast specific markers, and defective bone matrix protein and mineral deposition. Concomitantly, GD-osteoblasts also showed down regulation of Wnt/β-catenin signaling. Incubation of osteoblasts with CHIR99021, a pharmacological activator of the canonoical Wnt pathway, was able to rescue GD-osteoblast differentiation and mineral deposition. Additionally, incubation with recombinant GCase (rGCase) reversed the developmental and lysosomal defects of the mutant osteoblasts. Lastly, GD-osteoblasts also displayed defective Ca2+ mediated exocytosis, which is a crucial lysosomal function for bone matrix deposition. This study showed that mutations in GBA1 interfere with normal osteoblastogenesis, which was associated with aberrant Wnt/β-catenin signaling. Our results suggest that pharmacological Wnt activators may be effective therapeutic agents for ameliorating or reversing the bone disease in GD patients.

79. INTERACTION OF SERCA WITH SMALL REGULATORY PROTEINS IN EXCITABLE CELLS

Amanda Labuza

Labuza, A., Desmond, P. F., Muriel, J., Markwardt, M. L., Mancini, A. E., Rizzo, M. A., and Bloch, R. J.

Session J; Oral Presentation; Ballroom B

Sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA) regulates intracellular Ca2+ concentrations by clearing cytosolic Ca2+ into the lumen of the endoplasmic reticulum, and, in muscle, the sarcoplasmic reticulum (SR). Three major isoforms of SERCA include SERCA1, primarily expressed in skeletal muscle, SERCA2A, primarily expressed in cardiac muscle, and SERCA2B, which is ubiquitously expressed. SERCA1 is known to be inhibited by sarcolipin (SLN) and phospholamban (PLN), two small transmembrane proteins. My lab has recently shown that SERCA1 activity is also inhibited by small ankyrin 1 (sAnk1), a ~17kDa transmembrane protein that also binds to the cytoskeletal protein, obscurin. My work is focused on the multi-protein complex of SLN, PLN, and sAnk1 regulating SERCA1 activity. SERCA2B is known to be expressed within the ER of glial cells and neurons, where it is found particularly in dendrites and spines. However, it is unknown if sAnk1 regulates SERCA2B in brain tissue. I am now determining if, like SERCA2B, SLN and sAnk1 are expressed in neurons, and if so, if they regulate the activity of SERCA2B in the same way that they affect SERCA1. These results have significant implications for the development of therapeutic approaches to treat a variety of diseases linked to calcium misregulation such as muscular dystrophies and neuropathies.

80. ROLE OF INTERFERON-γ IN PROMOTING DISEASE SEVERITY IN NEONATAL BORDETELLA PERTUSSIS INFECTION

Ashley Mitchell

Mitchell, A. E. and Carbonetti, N. H.

Session J; Oral Presentation; Ballroom B

Pertussis is an infectious disease caused by the bacterial pathogen Bordetella pertussis. In recent years, there has been a re-emergence of pertussis disease. Pertussis morbidity is extensive and spans across all age groups, but

a higher incidence of severe disease and mortality is exhibited in young infants. Mortality is associated with severe respiratory infection and other systemic secondary co-morbidities. The infant immune system has reduced capacity to generate proinflammatory/T-helper (Th) 1 cell polarizing responses. Secretion of Interferon gamma (IFN-γ), a Th1 polarizing cytokine, by immune cells plays a critical role in macrophage activation and microbicidal activity in the lung. Furthermore, B. pertussis respiratory challenge of adult IFN-γ receptor deficient mice results in systemic dissemination and lethality. We hypothesize that the dissemination and lethality observed in our neonatal mouse model is a result of inadequate IFN-γ signaling or production, which contribute to insufficient control of the infection. We found that B. pertussis infection results in a significantly lower level of transcription of IFN-γ in the lungs and increased bacterial dissemination in neonatal mice when compared to adult mice. Additionally, infected neonatal mice deficient in IL-10, a potent regulator of IFN-γ, showed reduced dissemination and significantly increased IFN-γ and other pro-inflammatory cytokines as compared to age-matched wild type mice. Future studies include characterization of IFN-γ secreting immune cells during infection. Results generated by this work will contribute to a better understanding of severe disease in infants, addressing the limitations of infant immunity and treatment options for pertussis.

81. DNA DEMETHYLATING AGENTS GENERATE A BRCANESS EFFECT: PREDICTION FOR SENSITIVITY TO PARP INHIBITORS IN AML

Aksinija Kogan

Kogan, A.A., Topped, M., Muvarak, N., Creed, T. M., Bentzen, S., Civin, C., Baer, M. R., Kingsbury, T., Baylin, S. B., Abbotts, R.M., and Rassool, F. V.

Session J; Oral Presentation; Ballroom B

AML patients unfit for intensive chemotherapy are treated with DNA methyltransferase inhibitors (DNMTis), but response rates are suboptimal. We derived a novel treatment strategy combining poly (ADP-ribose) polymerase inhibitors (PARPis) with DNMTis, and showed preclinical efficacy of this combination treatment in AML both in vitro and in vivo. Based on these data, we launched a Phase 1/2 clinical trial of DAC/Tal therapy in patients with relapsed/refractory AML that is ongoing.

To study additional mechanisms underlying efficacy of DNMTi/PARPi combination therapy, we explored the hypothesis that Low doses of DNMTis may reprogram the cancer epigenome, by changing gene expression patterns of double strand break (DSB) repair genes, potentially creating a homologous recombination defect (HRD).

Expression arrays of mRNA extracted from AML cells following DNMTi treatment showed one or more HR genes consistently downregulated in all cell lines examined (N=10). QPCR of mRNA validated array data. Notably, functional assays for HR activity showed reduction in RAD51 foci in DAC-treated AML cell lines and clinical trial patient samples, compared to untreated controls. The above HRD-like or BRCAness phenotype with DNMTi treatment translated to significantly increased sensitivity to combination treatment ($p<0.05$) in colony forming assays, compared with single agent treatments. Our data suggests that one of the mechanisms underlying DNMTi/PARPi therapy efficacy in AML is DNMTi-induced BRCAness. In vitro testing for BRCAness with DNMTi treatment could be

a biomarker to predict sensitivity to DNMTi/PARPis and inform selection of AML patients for future clinical trials of this inhibitor combination.

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