# 35th Annual Graduate Research Conference

*Presented by the University of Maryland, Baltimore, Graduate Student Association*

## April 11th, 2013

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GSA Graduate Student Association

# 35th Annual Graduate Research Conference

Cover Design by Mark Mazaitis

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presented by

GSA Graduate Student Association

## Contents:

# Foreword

Greetings, salutations, and welcome to the 35th Annual Graduate Research Conference (GRC), presented by the Graduate Student Association (GSA). Since its establishment in the 1970s, the GRC has been an opportunity for students and postdoctoral fellows at the University of Maryland, Baltimore (UMB), to present their research in a friendly and encouraging environment in preparation for their attendance at major international conferences and meetings held throughout the year. The interdisciplinary format allows the exchange of ideas between basic scientists, informaticists, social scientists, nurses, and policy researchers, and showcases the depth and breadth of research undertaken within the UMB Graduate School.

This year's program has grown to include nearly one hundred abstracts presented by students and postdoctoral fellows involved in a wide range of studies. The updated format now includes multiple oral and poster presentation sessions along with a lunchtime keynote by Dr. Jonathan Yewdell of the National Institute of Allergy and Infectious Disease, vendor showcase, and a social hour and reception following the completion of the scientific program. As in past years, all students exhibiting abstracts are eligible for awards for outstanding presentation. Furthermore, we are pleased to continue to offer two special awards. 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 be sponsoring its 6th Annual UM Graduate Translational Research Award in recognition of important translational research performed by a UMB graduate student or postdoctoral fellow. This award embodies OTT's mission to translate outcomes from basic research into real-world uses. We thank the GGEAR/ORC and OTT for their continued support of GRC and the outstanding research being conducted by students and postdoctoral fellows on campus.

The entire GSA team has been working tirelessly for months to present GRC to the campus community. We would like to give particular thanks to Dr. Bruce Jarrell, Chief Academic and Research Officer (CARO), Senior Vice President and Dean of the Graduate School; Dr. Erin Golembewski, Associate Dean of the Graduate School; as well as all of the staff of the Graduate School Office. We

*are indebted to our sponsors: Life Technologies, Elsevier, NanoString Technologies, and Bio-Rad. Our keynote speaker, Dr. Jonathan Yewdell, deserves special thanks for his continued mission to empower graduate students; we appreciate his participation today. Furthermore, an event such as this requires many faculty members to act as judges, and the GSA would like to thank each of you for your dedication to educating and advancing the careers of your students. The departmental representatives of the GSA deserve thanks for much behind the scenes work in the organization of GRC. Finally, the GRC Organizing Committee of the GSA deserves special recognition for their many months of hard work to bring together the entire campus community for the Graduate Research Conference.*

*We hope you enjoy today's program. It is our pleasure to have you attend, and we encourage you to participate in all of the events scheduled today. It is a privilege and honor to present to you the 35th Annual Graduate Research Conference.*

*GSA Executive Board:*

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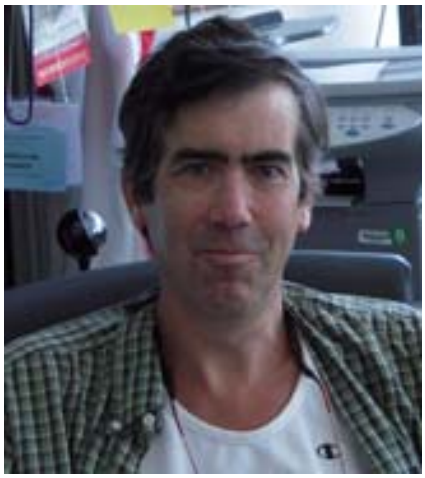
# Keynote Speaker



## Jonathan W. Yewdell, MD, PhD

*Chief of Cellular Biology and Viral Immunology Section*
*Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, NIH*

Dr Yewdell received his BS from Princeton University and obtained his MD and PhD from the University of Pennsylvania, where he worked under Dr. Walter Gerhard at the Wistar Institute creating an antigenic map of the influenza virus hemmaglutinin with monoclonal antibodies. After a post-doc at the Imperial College in London, UK, Dr. Yewdell returned to the Wistar Institute as an Assistant Professor. At the Wistar Institute, Dr. Yewdell and Dr. Jack Bennink began a collaboration that later moved to NIAID. Together they have contributed greatly to the field of immunology and virology by researching antigen presentation of viral proteins. This includes the discovery of Cytotoxic T cell recognition of intracellular viral proteins and the effects of brefeldin A on Golgi to ER trafficking and antigen presentation. Dr. Yewdell is currently a section chief in NIAID at the NIH in Bethesda, MD. In addition to his research, Dr. Yewdell has been giving advice lectures to young scientists based on his series of manuscripts in *Nature Reviews Molecular Cell Biology* in 2008. His advice spans from the beginnings of graduate school to post-doctoral fellowships and beyond. He addresses topics essential to the success of graduate students and post-docs including how to select a lab and how to deal with day-to-day science.

# SCHEDULE OF EVENTS

## SMC Campus Center

## April 11th, 2013

| | | |
|---|---|---|
| 8:00-9:00am | Breakfast and Registration | Second Floor |
| 9:00-10:30am | Oral Presentations | |
| | Basic Science "A" Policy/Informatics/Social Science "A" | Elm Ballroom<br>Room 351 |
| 10:30-11:45am | Poster Presentations | |
| | Basic Science "E", "G", "H" | Room 349 |
| | Policy/Informatics/Social Science "B", "D" | Room 349 |
| 12:00-1:15pm | Lunch & Keynote Address by Dr. Jonathan Yewdell | Elm Ballroom |
| | Vendor Showcase | |
| 1:30- 2:45pm | Poster Presentations | |
| | Basic Science "D", "F" | Room 349 |
| | Policy/Informatics/Social Science "C", "E" | Room 349 |
| 2:45-4:00pm | Oral Presentations | |
| | Basic Science "B" | Elm Ballroom |
| | Basic Science "C" | Room 351 |
| 4:00-4:30pm | Awards and Closing Remarks | Elm Ballroom |
| 5:00-7:00pm | Social Hour | Pratt Street Ale House 206 W.Pratt St |

# Abstracts

### 1. Development of a Novel *In-Vitro* Xenoperfusion Assay

Donald G. Harris, Prabhjot Benipal, Xiangfei Cheng, Agnes M. Azimzadeh and Richard N. Pierson III

Oral presentation; Elm Ballroom

Basic Science A

Pig to human xenotransplantation may relieve the critical shortage of organs available for treating patients with end-stage organ failure, but is currently limited by acute thrombotic inflammatory xenograft failure. Current models provide limited ability to study the complex cellular interactions between the recipient and xenograft under physiologic flow conditions. We developed a novel *in-vitro* pig to human xenoperfusion assay to enable efficient modeling and characterization of cellular adhesion and aggregation under shear flow.

Wild type (WT) or gal transferase knock-out (Gal-KO, which resist hyperacute xenorejection) pig aortic endothelial cells were cultured to confluence in 350µm x 75µm microfluidic perfusion channels (Fluxion Biosciences). Fresh, heparinized (19 IU/mL) whole human blood was treated with 20 µM calcein-AM to fluorescently label leukocytes and platelets; 0.2 – 1.6 mg/mL bivalirudin was added in 5 experiments. Blood was perfused over the monolayers under constant flow at 5 dynes/cm$^2$ and 37ºC. Serial fluorescent microscopy of each channel was performed at 100x magnification at 30 second intervals for 50 minutes.

Cell binding was captured by serial imaging and processed using the MetaMorph (Molecular Devices) engine. Results were visualized by 3D surface plot rendering using ImageJ (NIH) and data analyzed in Excel (Microsoft) by peak percent surface area coverage (SAC) and fluorescent intensity per surface area (FI) as markers of adhesion and aggregation, respectively. Perfusion of WT monolayers resulted in significant SAC (64.2 ± 8.8%, n=7) and FI (113.6 ± 10.4au, n=7), indicating high-grade human platelet and neutrophil adhesion to and aggregation upon the porcine monolayers. Compared to WT controls, Gal-KO monolayers displayed less SAC (31.8 ± 16.7%, n=6; $p < 0.005$) but similar FI (108.6 ± 16.9au, n=6; p=0.53), indicating less cellular adhesion but similar levels of aggregation. Similarly, perfusion of WT monolayers with blood treated with bivalirudin, a direct thrombin inhibitor, demonstrated less SAC (34.3 ± 24.5%, n = 5; p = 0.02) but similar FI (110.4 ± 10.9au, n=5; p=0.53) compared to controls.

This high-throughput novel model enables detailed characterization of the processes that result in thrombosis and graft injury during pig to human transplantation. These findings are consistent with the results of in-vitro static assays as well as existing whole-organ ex-vivo xenotransplantation models, demonstrating the validity of this microfluidic assay. Further, the model indicates the Gal-KO genotype inhibits xenogeneic cellular adhesion but has little effect on aggregation, which may enable more targeted and rational genetic or pharmacologic manipulation of xenotransplantation. The model is a promising platform for mechanistic and high-throughput studies and can be applied to other systems involving cellular interactions under conditions of shear flow.

### 2. CLEARANCE OF *STAPHYLOCOCCUS AUREUS* NASAL CARRIAGE IS T-CELL DEPENDENT AND MEDIATED THROUGH IL-17A EXPRESSION AND NEUTROPHIL INFLUX

Archer N and Shirtliff ME

Oral presentation; Elm Ballroom

Basic Science A

The anterior nares of humans are the major reservoir for *Staphylococcus aureus* colonization. Approximately 20% of the healthy human population is persistently and 80% intermittently colonized with *S. aureus* in the nasal cavity. Previous studies have shown a strong causal connection between *S. aureus* nasal carriage and increased risk of nosocomial infection, as well as increased carriage due to immune dysfunction. However, the immune responses that permit persistence or mediate clearance of *S. aureus* on the nasal mucosa are fundamentally undefined. Here we developed a carriage model in C57BL/6J mice and showed that clearance begins 14 days post-inoculation. In contrast, SCID mice that have a deficient adaptive immune response are unable to eliminate *S. aureus* even after 28 days post-inoculation. Furthermore, decolonization was found to be T-cell mediated, but B-cell independent by evaluating carriage clearance in TCR-β/δ KO and IgH-μ KO mice, respectively. Up-regulation of the cytokines IL-1β, KC, and IL-17A occurred following inoculation with intra-nasal S. aureus. IL-17A production was crucial for clearance since IL-17A-deficient mice were unable to effectively eliminate *S. aureus* carriage. Subsequently, cell differential counts were evaluated from nasal lavage fluid obtained from wild type and IL-17A-deficient colonized mice. These counts displayed IL-17A-dependent neutrophil migration. Antibody-mediated depletion of neutrophils in colonized mice caused reduced clearance compared to isotype treated controls. Our data suggest that the Th17-associated immune response is required for nasal decolonization. This response is T-cell dependent and mediated via IL-17A production and neutrophil influx. Th17-associated immune responses may be targeted for strategies to mitigate distal infections originating from persistent S. aureus carriage in humans.

### 3. MYD88 PLAYS A ROLE IN DECIDING BETWEEN APOPTOTIC AND NECROPTOTIC CELL DEATH AFTER UV IRRADIATION.

Erin Harberts, Rita Fishelevich, Juan Liu, Sergei P. Atamas, and Anthony A. Gaspari

Oral presentation; Room 351

Basic Science C

Ultraviolet irradiation (UV) induced cellular damage is classically associated with apoptosis and known to result in systemic immunosuppression. How the cell fate decision to undergo apoptosis is made following UV irradiation is not fully understood. Our previous finding that toll-like receptor (TLR) signaling regulates DNA repair and cell survival after UV led us to hypothesize that a central mediator of TLR signaling, MyD88, contributes to determining cell fate after UV. Survival following UV of immortalized bone marrow-derived macrophages (BMM) from MyD88 germline-deficient mice ($MyD88^{-/-}$) was significantly higher than that of wild-type (WT) BMM. UV-induced apoptotic morphology was less pronounced in $MyD88^{-/-}$ BMM than in WT. DNA from peritoneal macrophages (PM) and epidermis of $MyD88^{-/-}$ animals, compared to WT, showed decreased UV-induced DNA laddering. In $MyD88^{-/-}$ PM, decreased cleavage of a pro-necroptotic protein RIP1, suggests that necroptosis rather than apoptosis has been initiated. Furthermore, mRNA levels of RIP1 and RIP3 were elevated and TNF-α production increased in $MyD88^{-/-}$ PM compared to WT PM, further suggesting necroptotic rather than apoptotic fate. *In vivo* studies using UV-irradiated mice showed significantly less TUNEL-positive cells and more profound inflammation in skin sections of $MyD88^{-/-}$ than in WT animals. Using a contact sensitization model, $MyD88^{-/-}$ mice, compared to WT, are also found to be resistant to UV-induced immunosuppression. Considering that MyD88 participates in multiple TLR pathways, $TLR2^{-/-}$, $TLR4^{-/-}$, and WT BMM were compared for evidence of UV-induced apoptosis. Only $TLR4^{-/-}$ BMM had a similar phenotype to $MyD88^{-/-}$, suggesting that the TLR4-MyD88 axis importantly contributes to cell fate decision. Our study begins to describe a new cellular consequence of MyD88 signaling after UV-irradiation, and may provide rationale for the development of a MyD88 modulating therapy that could potentially be used to mitigate UV-induced immunosuppression.

**4. THE ROLE OF BST-2/TETHERIN IN SARS PATHOGENESIS**

Justin Taylor and Matthew Frieman PhD

Oral presentation; Elm Ballroom

Basic Science A

Severe Acute Respiratory Syndrome (SARS) is an acute respiratory disease caused by a novel human coronavirus (SARS-CoV). SARS-CoV is a positive-sense single-strand RNA virus with a 30kb genome. BST-2, also known as tetherin, is an interferon-inducible membrane protein that acts as an anti-viral restriction factor by inhibiting release of enveloped viruses by tethering the virus to the host cell. Several viruses have been show to encode BST-2 antagonists, such as HIV-1 VPU and Ebola GP1,2. Next

generation sequencing of SARS-CoV-infected mouse lungs shows upregulation of BST-2. Since BST-2 restricts many enveloped viruses and many viruses encode BST-2 antagonists, we hypothesize that SARS-CoV may antagonize BST-2. We screened 22 SARS-CoV proteins for effects on BST-2 expression and found 4 proteins that potentially antagonize BST-2. Co-transfection of BST-2 and SARS-CoV PLP, nsp1, ORF6, or ORF7a led to lower levels of BST-2 expression. We tested the SARS-CoV effects on BST-2 mRNA and found that nsp1 downregulates BST-2 mRNA expression, which is consistent with other groups findings that nsp1 degrades host mRNA.

### 5. LOCALIZATION AND INTERFERON ANTAGONIST ACTIVITY OF THE ACCESSORY PROTEINS OF THE NOVEL CORONAVIRUS HCOV-EMC

Christopher Coleman, Krystal Matthews and Matthew Frieman

Oral presentation; Elm Ballroom

Basic Science A

The recently emerged novel beta-Coronavirus, hCoV-EMC, from the Middle East is associated with severe pneumonia and renal failure with a lethal outcome in over half of those infected. The environmental origin of the virus is unknown however its genome sequence is closely related to 2 other Coronaviruses isolated from bats in China, named HKU4 and HKU5. A hallmark of highly pathogenic respiratory viruses is their ability to evade the host's innate immune response. Accessory proteins, which are proteins encoded in each Coronavirus and unique to that particular virus, have been shown for several other Coronaviruses, SARS-CoV in particular, to encode proteins that block anti-viral signaling pathways. In this work, we characterize the sub-cellular localization of the accessory proteins of hCoV-EMC, HKU4 and HKU5 using GFP tagged proteins and show, for example, ORF4B proteins from all 3 localize to the nucleus.We also demonstrate that the accessory proteins of hCoV-EMC, HKU4 and HKU5 can inhibit various pathways in the host innate immune response to viral infection.

Further work will link localization to function and we hypothesize that the accessory proteins of these viruses will be important for viral pathogenesis and, potentially, important therapeutic targets

### 6. ANTI-ARTHRITIC EFFECT OF CELASTRUS EXTRACT AND ITS ACTIVE COMPONENT CELASTROL

Shivaprasad H. Venkatesha, Brian C. Astry and Kamal D. Moudgil

Oral presentation; Elm Ballroom

Basic Science A

Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation, bone erosion and cartilage destruction in the joints. Pro-inflammatory cytokines, antibodies, and matrix-degrading enzymes orchestrate the pathogenic events in autoimmune arthritis. Accordingly, these mediators of

inflammation are the targets of several anti-arthritic drugs. However, the prolonged use of conventional anti-inflammatory drugs is associated with severe adverse effects. This limitation has necessitated the search for less toxic natural plant products that possess anti-arthritic activity. Using the rat adjuvant-induced arthritis model of human RA, we demonstrate that celastrol derived from Celastrus has potent anti-arthritic activity. This suppression of arthritis is mediated via modulation of the key pro-inflammatory cytokines (IL-17, IL-6, and IFN-γ), of chemokines (RANTES, MCP-1, MIP-1α, and GRO/KC) in response to the disease-related antigens, of the IL-6/IL-17-related transcription factor STAT3, of antibodies directed against cyclic citrullinated peptides and Bhsp65, and of the activity of matrix metalloproteinase-9 and phospho-ERK. The protective effects against bone damage are mediated primarily via the inhibition of defined mediators of osteoclastic bone remodeling (e.g., receptor activator of nuclear factor-κB ligand (RANKL)), the deviation of RANKL/osteoprotegerin ratio in favor of anti-osteoclastic activity, and the reduction in osteoclast numbers. Most of the clinical and mechanistic attributes of celastrol are similar to those of Celastrus extract. These results provide a strong rationale for further testing and validation of the use of celastrol and Celastrus extract as adjuncts (with conventional drugs) or alternative modalities for the treatment of RA. (This work was supported by National Institutes of Health Grant R01AT004321)

## 7. LOSS OF THE TUMOR SUPPRESSOR PROTEIN PTEN CONTRIBUTES TO INCREASED NRF2 SIGNALING

Phillip M. Shelton, Michele I. Vitolo, Stuart S. Martin and Anil K. Jaiswal

Oral presentation; Elm Ballroom

Basic Science A

Nrf2 is a master regulator of cyto-protective genes involved in the maintenance of cellular redox balance. In recent studies, the PI3K/Akt pathway is reported to positively regulate the Nrf2 pathway. The protein phosphatase PTEN counteracts the action of PI3K by removing the phosphate from PIP3. This led us to hypothesize that loss or mutation of PTEN, an event that occurs frequently in cancers, might increase Nrf2 activity that promotes the survival and proliferation of cancer cells. In our study we investigated the role of PTEN in prostate and breast cancer, commonly reported to have either loss of heterozygosity or mutations in PTEN. Using the PTEN-null human prostate cancer cell line PC3, we found that expression of wild-type but not mutant PTEN decreased the basal and anti-oxidant induced expression of Nrf2 target genes. More common clinically, patients have loss of a single allele of PTEN. Therefore, we also investigated the Nrf2 pathway in cells heterozygosity for the PTEN gene. Using a murine prostate tumor cell line with a spontaneous loss of a single allele in PTEN (PTEN-P8, +/-) and an isogenic cell line that had deletion of the second allele (PTEN-CaP8, -/-) we found that complete loss

of PTEN resulted in higher expression of the Nrf2 target genes. In order to fully address the role of PTEN haploinsufficiency that could mimic the cellular progression from benign to malignant we also looked at Nrf2 activity in the immortalized breast epithelial cell line MCF-10a that had both alleles intact (+/+), deletion of a single allele (+/-), or deletion of both alleles (-/-) of PTEN. As expected, we found that both the basal and inducible expression of the prototypical Nrf2 target gene NQO1 inversely correlated with PTEN status. Together this suggests that the loss of PTEN contributes to increased Nrf2 transcriptional activity, which likely provides cells with an altered proteome that favors oncogenesis.

### 8. Association between Psychological Distress and Unintentional Non-occupational Injuries among U.S. Adults

Jana McAninch, Christina Greene, and Gordon Smith

Oral presentation; Room Elm Ballroom

Basic Science B

Background: Previous studies have demonstrated that individuals with mental illness have an elevated risk of intentional injuries, but the association between poor mental health and unintentional injuries is not well understood.

Methods: We used the 2010 National Health Interview Survey to assess the association between psychological distress and the 3-month prevalence of unintentional non-occupational injury in adults. Psychological distress was measured by the Kessler Psychological Distress Scale, a validated scale that identifies community-dwelling persons with serious mental illness. Multivariable logistic regression was used to estimate adjusted odds ratios (AOR) and 95% confidence intervals.

Results: Of the 27,157 participants, 2.5% (weighted %) reported a medically-attended unintentional injury in the past three months. Those with moderate and severe levels of psychological distress had 1.5 [1.2-1.9] and 2.1 [1.5-3.0] times higher odds of injury, respectively, as compared to those with low distress levels, after adjusting for age, sex, race, marital status, education level, alcohol use, physical functional limitation, presence of chronic disease, employment status, and health insurance status. Severe psychological distress was significantly associated with falls [AOR 2.3 (1.5-3.7)] and overuse/strain injuries [AOR 3.4 (1.4-8.1)] but not transportation-related injuries [AOR 1.7 (0.7-4.2)].

Conclusion: Among community-dwelling U.S. adults, psychological distress is significantly associated with unintentional non-occupational injury, and the magnitude of association increases with severity of distress. The association between psychological distress and injury may be particularly strong for fall and overuse/strain injuries. Screening for psychological distress to identify and intervene in high-risk groups should be considered as part of prevention

strategies for both intentional and unintentional injuries.

### 9. Inhibition of Nrf2 Signaling Decreased Drug Resistance in Aromatase Inhibitor (AI)-Resistant Breast Cancer Cells

Raju Khatri, Preeti Shah, Angela Brodie and Anil K. Jaiswal

Oral presentation; Elm Ballroom

Basic Science B

The stress-response transcription factor, NF-E2-related factor 2 (Nrf2), is a master regulator of cytoprotective genes. Under basal condition, inhibitor of Nrf2 (INrf2 / Keap1) constantly facilitates the ubiquitination-mediated degradation of Nrf2. Upon exposure to xenobiotics, radiation and oxidative stress, Nrf2 is stabilized, and translocates into the nucleus and coordinately induces 200 plus cytoprotective gene expression. Previous studies have shown that Nrf2 regulates the expression of phase II detoxification enzymes, antioxidants, and drug efflux transporters that collectively help defend the normal cells against oncogenesis. The increased activation of Nrf2 signaling in cancer cells is thought to provide cancer cells with increased cytoprotective gene expression, and therefore, Nrf2 has been implicated in chemoprevention, cell survival and drug resistance. Treatment with Aromatase inhibitors (AI), the first-line therapeutic option for breast cancer in post-menopausal women, is associated with acquired resistance. Little is known about the underlying mechanisms for the development of AI-resistance. We hypothesized that the persistent treatment of AI upregulates Nrf2 mediated-drug-resistance factors in breast cancer cells. Our studies showed that AI-resistant breast cancer cells expressed lower INrf2 and higher Nrf2 protein levels as compared to AI-sensitive cells. We also observed that Nrf2 gets less ubiquitinated and degraded slowly in long term letrozole treated breast cancer (LTLT) cells. We found higher levels of Nrf2-regulated biotransformation enzymes, drug-transporter and anti-apoptotic proteins in the AI-resistant breast cancer cells. The removal of letrozole from the medium of LTLT cells led to an increase in INrf2 protein level, a decrease in Nrf2 protein level and increased sensitivity to doxorubicin. To investigate the role of Nrf2 in AI-resistance, we knocked down the Nrf2 in the AI-resistant LTLT cells (LTLT-Nrf2 KD) and evaluated the doxorubicin-induced cell death, the protein levels of Nrf2-mediated biotransformation enzymes, drug-transporters and anti-apoptotic proteins. Interestingly, the LTLT-Nrf2 KD cells expressed lower levels of ALDH, a marker of Tumor Initiating Cells (TIC) and formed less mammospheres as compared to LTLT cells, implying that the levels of Nrf2 in the LTLT cells positively correlated with the mammosphere formation and ALDH expression. These results together suggest that persistent AI treatment stabilized Nrf2 and activated the Nrf2-mediated gene expression that led to drug resistance. Understanding the mechanisms for Nrf2-regulated drug resistance is important to develop more effective anticancer drugs. In addition,

identification of compounds inhibiting Nrf2 signaling will improve the therapeutic effect of anti-cancer agents.

### 10. Design and Synthesis of HIV-1 Capsid Core Inhibitors Using SAR Analysis

Joshua D. Brown and Michael F. Summers

Oral presentation; Elm Ballroom

Basic Science B

The human immunodeficiency virus (HIV) has caused a serious epidemic. It has killed over 25 million people from the time it was discovered in 1981 to 2006. In the virus replication life cycle, thousands of copies of the viral Gag polyprotein of the HIV associate at the cell membrane during the assembly stage. The virus buds to form an immature, non-infectious virion and then Gag is cleaved by protease. Capsid protein is released and assembles into the capsid core, creating a mature, infectious virus. The capsid protein is an attractive inhibition site because its formation of the capsid core is crucial for viral infectivity. A compound, CAP-1, has been identified that binds to the N-terminal domain of the capsid protein (CAN) and inhibits capsid formation in vitro and in vivo, but the dissociation constant (Kd) is not within an acceptable range for clinical use. We have been working with CAN and testing new compounds for potential inhibition and affinity with a Kd in the nanomolar range. NMR HSQC titrations have been used to test the affinity of the compound to CAN and thus calculate the corresponding Kd. The computer program, PyMOL, has been used as a method to give a visual representation of the binding pocket conformation of the new compounds bound to the capsid protein. A correlation has been found between the amount of unoccupied space within the pocket by the compound and the Kd. The more space occupied within the binding pocket the lower the Kd. Using this information, several compounds' PyMOL pocket conformations and Kd values were screened. Along with this, the environment of the binding pocket produced by PyMOL was analyzed. Taking a structure activity relationship (SAR) approach, four potential inhibitors were formulated from this data. The four targets have shown good PyMOL results. All four targets are currently in the synthesis phase. The results of the future NMR HSQC titrations will provide the data needed for the next steps in the drug design.

### 11. Ontogeny of the Splenic White Pulp

Harold R. Neely and Martin F. Flajnik

Oral presentation; Elm Ballroom

Basic Science B

The spleen is the most evolutionarily ancient secondary lymphoid organ, and is unique in its histological and functional segregation into two discrete areas, the red pulp and the white pulp. Both the establishment and maintenance of the splenic white pulp is absolutely dependent on the presence of B cells. In the developing

embryo, B lymphopoiesis occurs initially in the yolk sac, followed by the fetal liver, and the B cells produced from these sites of lymphopoiesis are predominantly of the B-1 lineage. During embryogenesis, the spleen contains only red pulp, and at or around birth, B cells begin to accumulate around the splenic arterioles, followed by the recruitment and/or differentiation of APC, and finally the recruitment of T cells and formation of the marginal zone. Also at birth, the site of hematopoiesis shifts from the fetal liver to the bone marrow, which predominantly generates follicular or B-2 cells. The coincident developmental timing of the establishment of splenic white pulp microarchitecture and the shift in the site and type of B lymphopoiesis raises a fundamental question: which lineage of B cells, B1 cells from the yolk sac/fetal liver or B2 cells from the bone marrow, initially seed the spleen and orchestrate white pulp formation? To address this hypothesis, we have begun a timecourse analysis of perinatal murine spleens, including immunohistochemical analysis of the spleen to visualize cellular recruitment and localization, and flow cytometric analysis of splenocytes to determine their developmental origins. Preliminary results show a random distribution of B-1 cells throughout the red pulp of the fetal spleen, and the anticipated accumulation of B cells, both B-2 cells and developing (IgM-) B cells, around splenic arterioles in newborn mice. We are currently investigating which population is the first to accumulate around the splenic vasculature and provide signals necessary for the initiation of the establishment of white pulp microarchitecture.

## 12. IncA BAR domain-mediated transluminal folds of the inclusion membrane support contact-dependent development of *Chlamydia psittaci*

Daniel Phillips, Andrew Craig, Roger Rank, Ru-ching Hsia, David Wilson, Jacques Ravel and Patrik Bavoil

Oral presentation; Elm Ballroom

Basic Science B

Background and Significance: The contact-dependent hypothesis of chlamydial development, which predicts that the developmental status of the *Chlamydia trachomatis* (Ctr) inclusion is dependent on type III secretion-mediated contact with the inclusion membrane (IM) such that IM-associated reticulate bodies (RBs) are replicating while luminal RBs are committed to late differentiation into infectious elementary bodies (EBs), is inconsistent with the *Chlamydia psittaci* (Cps) inclusion configuration where apparently actively replicating RBs are observed in the inclusion lumen.

Objectives: We propose that the Cps IM forms transluminal folds that enable contact between luminal RBs and the IM.

Methods: Late Ctr/Cps inclusions grown with/without a sphingolipid biosynthesis inhibitor were stained using IncA-specific immunofluorescent antibody. A

liposome-based *in vitro* assay was used to demonstrate IncA-induced membrane curvature.

Results: Cps inclusions stained with anti-IncA/Cps displayed IM folds extending into the lumen of the inclusion. Similar folds were not observed in Ctr inclusions stained with anti-IncA/Ctr. Inhibition of sphingolipid biosynthesis caused the formation of smaller, rounded Cps inclusions devoid of luminal folds. Bioinformatic analysis of IncA orthologs revealed a eukaryotic BAR domain, uniquely present in Cps IncA. Purified recombinant IncA/Cps induced the formation of tubules from liposomes *in vitro*, confirming that the IncA/Cps BAR domain can bind lipids and induce membrane curvature, as do its eukaryotic counterparts.

Conclusions: The BAR domain of IncA/Cps is the first such domain identified in prokaryotes. We hypothesize that in Cps, IncA has evolved to cause transluminal IM folds, enabling contact of replicating RBs with the IM and reconciling the Cps inclusion configuration with the contact-dependent hypothesis of chlamydial development.

## 13. TOLERANCE INDUCTION CHANGES LYMPH NODE STRUCTURE AND FUNCTION

Aparna Baxi, BE, Bryna B Burrell, Ph.D. and Jonathan S Bromberg, MD,Ph.D.

Oral presentation; Elm Ballroom

Basic Science B

Background

Costimulatory blockade plus donor-specific splenocyte transfusion (DST) induces long-term graft acceptance, however the mechanism by which this tolerance occurs remains incompletely defined. The lymph node (LN) contains a basic scaffolding structure comprised of collagens, laminins and stromal fibers such as ER-TR7. These fibers form a protein meshwork foundation for cell interactions and bind chemokines that guide cells to specific, instructive microdomains. This study tested the hypothesis that tolerance induction involves modification of lymph node structure and chemokine expression.

Methods

Tolerance was induced by treating C57BL/6 mice with BALB/c DST + anti-CD40L mAb, while immunity was induced by treating mice with DST only. Mice were euthanized 3 to 7 days post-treatment and quantitative immunohistochemistry of LN defined the amount and location of the structural elements collagen III, ER-TR7, desmin, laminin, the high endothelial venules (HEV), and the chemokines CCL19 and CCL21.

Results

LN in tolerant and immune mice displayed distinct structural modifications and chemokine expression. In the LN of tolerant mice, ER-TR7 increased and peaked at day 5 post-tolerance induction. Laminin decreased initially following tolerance induction, with expression increasing 5 days later. In contrast, ER-TR7 in the LN peaked 3 days following immunization, and laminin expression

decreased to levels below that observed in naïve LN. Following tolerance induction or immunization, an increase in both desmin and collagen III occurred. With respect to chemokine expression, CCL19 expression increased gradually after day 3 in tolerant mice. In contrast, CCL19 expression peaked at day 3 in immune mice. Interestingly, CCL21 expression decreased following both tolerization and immunity.

Conclusion

Tolerance induction results in structural changes within the LN. ER-TR7 and laminin are essential LN structural stromal fibers, and CCL19 is important for T cell and dendritic cell LN chemoattraction. Hence, these results suggest that tolerance induction leads to changes in both LN structure and function. These changes can subsequently affect T cell migration, homing and differentiation in the LN. Hence, this remodeling choreographs the encounters and interactions between antigen reactive cells and their cognate antigen resulting in tolerance as opposed to immunity. These findings suggest that the LN is a malleable structure, and changes in both physical structure and chemokine expression affect LN function.

### 14. Resting State and Task-Related Network Analysis Using Multi-Channel EEG to Assess Brain Functional Connectivity in Chronic Stroke Patients

Ozell Sanders, Ron Goodman, Brian Jung, Jeremy Rietschel and Jason Diaz

Oral presentation; Elm Ballroom

Basic Science B

The human brain is a complex system comprised of several highly interconnected regions. Recently graph theory has emerged as a valuable tool for analyzing functional and structural connectivity in the human brain. Within graph theory, a network is defined as a set of nodes or vertices and the edges/lines (i.e., the connections) between them. Networks can be computed from electroencephalographic signals recorded from the scalp using the individual electrodes to represent the nodes and various measures of connectivity (cross correlation, coherence, and synchronization likelihood) to represent the edges or links between them. Once the network is constructed, graph theory metrics such as small-worldness are computed to study potential changes in the information transfer (e.g., efficiency) within the network. This study compares changes in graph theory derived networks before and after 3 weeks of seated ankle robotics training designed to improve paretic ankle motor control. EEG from 10 chronic hemiparetic stroke survivors was recorded during resting-state and active ankle robotics training (task-related). Functional networks were constructed for each condition pre vs. post. For the ankle robotics training

participants played a videogame while seated by moving their ankle in dorsi-plantar-flexion ranges to attempt to navigate a cursor through gates that moved across the screen. The training participants were randomly assigned

to a high- or low-reward group (monetary rewards). EEG coherence was computed offline from all possible pairs of electrodes and used to calculate correlation matrices between different brain regions. Each correlation matrix was weighted using the amplitude coherence values and then used to construct association matrices. From these association matrices graph theory metrics such as clustering coefficient and path length were calculated. Results showed that interregional connections derived from coherence values were different between the task and resting conditions. Furthermore, during active ankle robotics training (task condition), participants in the high-reward group had higher small-worldness values pre vs. post compared to the low-reward group. These findings indicate that knowledge of functional connectivity can be used to probe behavioral impairments, group differences (high- vs. low-reward motivation) and task-related vs. resting state brain dynamics in clinical populations. Further studies in stroke may advance our basic understanding of the sequelae of brain injury and may eventually aid in the design of individualized and more efficacious neurorehabilitation strategies.

### 15. THE LDL RECEPTOR-RELATED PROTEIN 1 (LRP1) REGULATES THE PDGF SIGNALING PATHWAY BY BINDING THE PROTEIN PHOSPHATASE SHP-2 AND MODULATING SHP-2- MEDIATED PDGF SIGNALING EVENTS

Julie Craig, Irina Mikhailenko, Nathaniel Noyes, Molly Migliorini, Dudley Strickland

Oral presentation; Room 351

Basic Science C

Background: The PDGF signaling pathway plays a major role in several biological systems, including vascular remodeling that occurs following percutaneous transluminal coronary angioplasty (PTCA). Recent studies have shown that the LDL receptor-related protein 1 (LRP1) is a physiological regulator of the PDGF signaling pathway. The underlying mechanistic details of this relationship have yet to be resolved. Activation of the PDGF receptor β (PDGFRβ) leads to tyrosine phosphorylation of the LRP1 cytoplasmic domain and generates an LRP1 molecule with increased affinity for adaptor proteins involved in signaling pathways such SHP-2, a ubiquitous tyrosine phosphatase. SHP-2 positively regulates the PDGFRβ pathway, and is required for PDGF-mediated chemotaxis. We investigated the possibility that LRP1 may regulate the PDGFRβ signaling pathway by binding SHP-2.

Methodology/Principle Findings: To quantify the interaction between SHP-2 and phosphorylated forms of the LRP1 intracellular domain, we utilized an ELISA with purified recombinant proteins. These studies revealed high affinity binding of SHP-2 to phosphorylated forms of both LRP1 intracellular domain and the PDGFRβ kinase domain. By employing the well characterized dynamin inhibitor, dynasore, we established that PDGF-induced SHP-2 activation primarily occurs within endosomal compartments, the same

compartments in which LRP1 is tyrosine phosphorylated by the PDGFRβ. Immunofluorescence studies revealed colocalization of LRP1 and SHP-2 following PDGF stimulation of immortalized mouse smooth muscle cells. To define the contribution of LRP1 to SHP-2-mediated PDGF chemotaxis, we employed fibroblasts expressing LRP1 and deficient in LRP1 and a specific SHP-2 inhibitor, nsc-87877. Our results reveal that LRP1 modulates SHP-2-mediated cell migration.

Conclusions/Significance: Our data demonstrate that phosphorylated forms of LRP1 and PDGFRβ compete for SHP-2 binding, and taken together, the data implicates a critical role for LRP1 in attenuating SHP-2-mediated PDGF signaling events.

### 16. BLUNTING THE PERMISSIVENESS OF TH17 CELLS TO HIV INFECTION

Aaron Christensen-Quick, Mark K. Lafferty, Marco Goicochea and Alfredo Garzino-Demo

Oral presentation; Room 351

Basic Science C

HIV preferentially depletes IL-17-producing, CD4+ "T helper 17" (Th17) cells from the gut during the acute phase of infection, and this process aggravates disease progression. Th17 cells play a key role in mucosal barrier maintenance and protection against opportunistic infections commonly associated with HIV/AIDS. In response to cytokines secreted by Th17 cells, epithelial cells of mucosal barriers secrete β-defensins - a family of secreted, cationic peptides with potent and broad-range antimicrobial activity against bacteria, fungi, and viruses including HIV. Our laboratory has shown that the expression of human β-defensin 2 (hBD2) is markedly decreased in the oral mucosa of HIV+ subjects, and that β-defensins, in addition to direct antimicrobial activity, upregulate the HIV restriction factor APOBEC3G via the chemokine receptor CCR6, which is expressed on Th17 cells. Our experimental system characterizes HIV infection in the Th17 subset of human peripheral blood CD4+ T cells. Negatively-selected CD4+ T cells are activated, infected, washed, and then treated with media, hBD2 or other agents that target Th17 signaling pathways. Five days post-infection, cells are characterized by flow cytometry. Our results show that IL-17A+ cells from peripheral blood are highly permissive to HIV, are preferentially infected during in vitro infection, and that Th17-polarizing cytokines enhance HIV infection. Our data also suggest a post-entry mechanism of viral permissiveness among IL-17A+ cells. Currently we are determining if hBD2 treatment or the disruption of Th17 signaling pathways can inhibit infection. Our studies examining the permissiveness of Th17 cells may yield new therapeutic targets to selectively protect the Th17 compartment from HIV infection.

### 18. A COMMUNITY GENOMICS APPROACH TO STUDY THE DYNAMICS OF THE VAGINAL ECOSYSTEM DURING VULVOVAGINAL CANDIDIASIS

L. Latéy Bradford, Vincent Bruno, Steven Smith, Jacques Ravel

Oral presentation; Room 351

Basic Science C

The human vagina is a dynamic ecosystem where physical and chemical interactions between host, commensal microbes and pathogens occur frequently and impact vaginal health. Although the significance of these interactions has not been well-characterized, it is widely accepted that the vaginal microbiota play an essential role in maintaining homeostasis in the vagina by regulating pH and protecting against vaginal infections. Using next-generation sequencing-based genomic approaches we are attempting to further understand the role of the microbiome during states of vaginal health and disease by studying community composition and function before, during and after vulvovaginal candidiasis (VVC) events. A cohort of 135 women was recruited for a 10-week longitudinal study; vaginal swabs were self-collected on a daily basis, and each participant kept a detailed daily diary of medications, health and sexual behaviors. At present, two women who were clinically diagnosed and treated for yeast infection during the study, have been selected for analyses of the vaginal microbiota and Candida strains using 16S (or 18S) rRNA sequencing as well as community transcriptomic analysis of mRNA expression before and during episodes of yeast vaginitis. Results from our 16S genomic analyses provide information about changes in relative abundance of bacterial species present in the community, and community transcriptomic data informs our understanding of bacterial activity and function. Subject 40 maintained a community state dominated by Lactobacillus crispatus over the course of the study, while the microbiota of Subject 12, mainly dominated by L. iners, demonstrated more frequent fluctuations in microbial composition. Community transcriptomic analysis revealed increased peptidoglycan biosynthesis in the presence of yeast, 15X increase in bacteriocin production by L. crispatus (Subject 40), and up-regulated expression of the cholesterol-dependent cytolysin, inerolysin (100X) and CRISPR-related genes during yeast infection (Subject 12). Genomic and transcriptomic analyses of C. albicans isolated during VVC is in progress and will characterize the genome of these isolates and clarify the activity of the causative pathogen. Lastly, parallel transcriptomic analysis of host gene expression is on-going and will complement this study by providing understanding of host activity and responses to the microbiota and pathogen.

### 19. CELASTRUS-DERIVED CELASTROL MODULATES AUTOIMMUNE ARTHRITIS THROUGH CELLULAR IMMUNOREGULATION

Brian C Astry, Shivaprasad H Venkatesha, Kamal D Moudgil

Oral presentation; Room 351

Basic Science C

Rheumatoid arthritis (RA) is a chronic debilitating autoimmune disease affecting the synovial joints. The target organ pathology in arthritis is

primarily the result of infiltration of IL-17-producing CD4+ T helper 17 (TH17) cells and other leukocytes into the synovial tissue within the joints leading to joint damage. The treatment of RA is aimed at controlling inflammation and limiting tissue damage. Many potent drugs for the management of RA are currently available. However, the severe adverse reactions associated with prolonged use of conventional anti-inflammatory drugs by RA patients have led to a gradual increase in the number of patients who use natural plant-derived medications. One natural product used for the treatment of arthritis is the traditional Chinese medicine Celastrus aculeatus Merr. (Celastrus). However, its mechanism of action is not yet fully defined. We hypothesized that Celastrol, a purified component of Celastrus, would alter the ratio of Th17 vs. CD25+Foxp3+T regulatory (Treg) cells in the synovial tissue, decrease chemotactic migration and antigen-induced proliferation of the draining lymph node cells (LNC), and affect the expression of positive/negative costimulatory molecules on antigen-presenting cells (APCs) in the rat adjuvant-induced arthritis (AA) model of human RA. Celastrol treatment resulted in significant ($p<0.05$) reduction in the arthritis score. Control arthritic rats had higher frequency of TH17 but reduced frequency of Tregs in the synovial tissue than Celastrol-treated arthritic rats. In addition, celastrol was able to reduce both the migration of LNC in response to RANTES and the proliferation of LNC following restimulation with arthritis-related antigens (i.e. mycobacterial HSP65). However, Celastrol treatment increased the expression of PD-L1 and PD-L2 on APCs. The above results demonstrate the mode of action of Celastrol as an anti-arthritic medication. On the basis of these results, we propose that Celastrus should be further evaluated in RA patients as a potential adjunct to conventional medication. (Supported by F31 AT007278 and R01 AT004321 from NIH/NCCAM.)

### 20. Impact of Ribosomal Modification on the Binding of the Antibiotic Telithromycin using a Combined Grand Canonical Monte Carko/Molecular Dynamics Simulation Approach

Meagan C. Small, Pedro Lopes, Rodrigo B. Andrade, Alexander D. MacKerell

Oral presentation; Room 351

Basic Science C

Resistance to macrolide antibiotics is conferred by mutation of A2058 to G or methylation by Erm methyltransferases of the exocyclic N6 of A2058 (E. coli numbering) that forms the macrolide binding site in the 50S subunit of the ribosome. Ketolides such as telithromycin mitigate A2058G resistance yet remain susceptible to Erm-based resistance. Molecular details associated with macrolide resistance due to the A2058G mutation and methylation at N6 of A2058 by Erm methyltransferases were investigated using empirical force field-based simulations. To address the buried nature of the macrolide binding site, the number of waters within the

pocket was allowed to fluctuate via the use of a Grand Canonical Monte Carlo (GCMC) methodology. The GCMC water insertion/deletion steps were alternated with Molecular Dynamics (MD) simulations to allow for relaxation of the entire system. From this GCMC/MD approach information on the interactions between telithromycin and the 50S ribosome was obtained. In the wild-type (WT) ribosome, the 2'-OH to A2058 N1 hydrogen bond samples short distances with a higher probability, while the effectiveness of telithromycin against the A2058G mutation is explained by a rearrangement of the hydrogen bonding pattern of the 2'-OH to 2058 that maintains the overall antibiotic-ribosome interactions. In both the WT and A2058G mutation there is significant flexibility in telithromycin's imidazole-pyridine side chain (ARM), indicating that entropic effects contribute to the binding affinity. Methylated ribosomes show lower sampling of short 2'-OH to 2058 distances and also demonstrate enhanced G2057-A2058 stacking leading to disrupted A752-U2609 Watson-Crick (WC) interactions as well as hydrogen bonding between telithromycin's ARM and U2609. This information will be of utility in the rational design of novel macrolide analogs with improved activity against methylated A2058 ribosomes.

### 21. CHARACTERIZATION OF VAGINAL MICROBIOTA IN NON-INFECTED AND CHLAMYDIA CAVIAE INFECTED GUINEA PIGS

Elizabeth Neuendorf, Pawel Gajer, Patricia X. Marques, Bing Ma, Honqiu Yang, Li Fu, Sara S. K. Koenig, Anne K. Bowlin, Garry A. Myers, Patrik M. Bavoil, Roger G. Rank & Jacques Ravel

Poster presentation; Room 349

Basic Science D

Background and Significance: Chlamydia trachomatis causes the most commonly reported sexually transmitted infection, with over 1.4 million cases reported in the USA by the CDC in 2011. The guinea pig is widely used as a model for the study of C. trachomatis genital tract infection. Previous culture-based studies have given us an incomplete picture of the guinea pig vaginal microbiota.

Objectives: In this study we aim to characterize the vaginal microbiota in non-infected and C. caviae infected guinea pigs using culture-independent methods.

Methods: We used high-throughput sequencing of the 16S rRNA gene to survey the

vaginal microbiota in non-infected and C. caviae infected guinea pigs. Three groups of five guine pigs: 1) non-infected; 2) C. caviae infected and 3) mock-infected guinea

pigs were sampled every two days over two estrous cycles. Bacterial community composition was characterized using pyrosequencing of barcoded 16S rRNA genes,

while total bacteria and C. caviae abundances were established by 16S rRNA gene and major outer

membrane protein (MOMP-ompA) gene quantitative PCR (qPCR).

Results and Conclusions: Our comprehensive characterization of the guinea pig

vaginal microbiota identified the most abundant bacteria as Corynebacterium,

Anaerococcus, Incertae Sedis XI (Family), Porphyromonas, Erysipelotrichaceae

(Family), Peptoniphilus, and Aerococcus. Previous studies found that the most

abundant bacteria were of the genera Corynebacterium and Streptococcus. Unlike the vaginal microbiota of healthy women, Lactobacillus spp. were poorly represented in the guinea pig vaginal microbiota. Total bacterial 16S rRNA gene counts showed a great variability in the number of bacteria ranging between 1.2x109 and 3.4x104, the lowest counts were found during peak infection. Chlamydia-specific qPCR showed that C. caviae was most abundant 5 days post-infection (1x108 cells per swab), and was greatly reduced by day 16. Our results show that the guinea pig vaginal microbiota (infected and non-infected) are distinct from that of the vaginal microbiota of healthy and C. trachomatis-infected women. While C. caviae infection does have an effect on the bacterial composition of the guinea pig vaginal microbiota, it is transitory and appears to reduce bacterial load.

## 22. BASE-DEPENDENT AND -INDEPENDENT DETERMINANTS OF RNA BINDING AND STRUCTURAL REMODELING BY AUF1

Beth E. Zucconi and Gerald M. Wilson

Poster presenation; Room 349

Basic Science D

AUF1 is a family of RNA-binding proteins most closely associated with regulating the decay and/or translation of mRNAs containing AU-rich elements (AREs) in their 3'-untranslated regions (3'UTRs), including many that encode factors involved in inflammation, heart disease, and cell cycle regulation. While many AUF1-associated RNAs have been experimentally identified, bioinformatics and ribonome-wide screening efforts have so far been unable to methodically predict or identify specific RNA targets of AUF1. These approaches, as well as potential drug development strategies targeting AUF1, have been hampered by the lack of information regarding the precise substrate nucleotide requirements for AUF1 association.

Previously we used electrophoretic mobility shift assays and fluorescence anisotropy-based approaches to show that high affinity AUF1 binding and oligomerization requires approximately 34 nucleotides of a single-stranded model substrate RNA based on the canonical ARE from TNFa mRNA. However, our new studies show that the substitution of non-ARE sequences has a negligible effect upon AUF1 binding when placed

at explicit locations relative to the specific AU-rich target. About 16 nucleotides of ARE sequence are required for optimal AUF1 binding, but only when placed downstream of a non-ARE domain. The only 3' element that enhanced AUF1 association was that of a single guanine which strengthened binding significantly. The non-ARE sequences stabilize the AUF1-RNA complex by inducing conformational changes and mediating ionic interactions. AUF1 associates with mRNAs containing these minimal bipartite sequences in cell and regulates their stability. These findings are resolving the minimal sequence requirements for AUF1 recruitment to RNA substrates, which in turn will propel investigation into the ability of local RNA secondary structures, miRNAs, and other RNA-binding proteins to influence the affinity and positioning of AUF1 binding. Our model is that combinatorial, cooperative, and and/or mutually exclusive functions of these factors collectively define the catabolic fate of target mRNA.

### 24. Infant Sucking and Swallowing Kinematics Following Palatal Local Anesthesia

Shaina D. Holman, Regina Campbell-Malone, Peng Ding, Estela Gierbolini-Norat, Stacey Lukasik, Rebecca German

Poster presenation; Room 349

Basic Science D

Objective: Infants with dysphagia risk aspiration and delayed development. It is not known to what extent oral sensation can influence sucking and swallowing in infants. We sought to uncover the role of palatal sensation during the kinematics of the suck-swallow using an infant pig model.

Methods: Radio-opaque markers were inserted onto the hyoid bone, under the palatal mucosa and in the tongue in eight infant pigs. They were fed milk containing barium following one of three treatments: 1) 0.5% bupivacaine hydrochloride (Marcaine) nerve block to the palate (PLA), 2) saline nerve block to the palate (PSA), 3) no treatment. The injections were given using 0.5 ml to the nasopalatine and greater palatine nerves under general anesthesia. We recorded lateral videofluoroscopy during the feeding sessions. Movements of the mandible, tongue and hyoid were digitized from the videos and graphed for analysis. The range of motion of each of these structures was tested for differences between treatments using a general linear model ANOVA and post-hoc Tukey's HSD test.

Results: Four of the pigs were able to suck after PLA (Group A) and four were unable to suck after PLA (Group B). Group was added as a factor in the ANOVA. Group B had increased jaw opening, superior tongue movement and both anterior and superior hyoid movement after PLA ($p<0.05$ for all). Group A had no changes in the range of movement of these structures. Jaw movement was greater during control feedings in Group A compared to Group B.

Conclusions: Palatal sensation has a differential effect on suckling in infants that may be physiologic or

developmental in nature. Trigeminal sensation indeed affects the oral phase of the swallow in infants, especially the kinematics and motor output of the tongue. Feeding therapies for infants with dysphagia should take these findings into consideration when providing oral stimulation therapies.

### 25. THE ROLE OF DISULFIDE BONDING IN HIV CAPSID ASSEMBLY AND UNCOATING

Katie Howell, Changqing Li, Marzena Pazgier, Wuyuan Lu

Poster presentation; Room 349

Basic Science E

HIV-1 capsid protein (CA) consists of 231 amino acid residues, which fold into two distinct domains connected by a flexible linker. Data shows that the C-terminal domain of CA (CCA) is an important region for the formation of both immature and mature viral particles. This region contains two conserved cysteines at positions 198 and 218 and a mutation of either to serine results in a defective viral particle, suggesting that they play a structural or functional role in HIV pathogenesis. We hypothesize that the presence or absence of this disulfide bond may play a regulatory role in viral assembly or disassembly.

To test this hypothesis we used solid phase peptide synthesis and native chemical ligation to synthesize CCA of 86 amino acid residues. Chemical protein synthesis allows site-specific fluorophore addition to residues not involved in dimerization so that we can use fluorescence polarization to quantitatively analyze how the presence of the disulfide bond affects CCA's ability to dimerize.

Our results demonstrate that we can synthesize CCA with chemical modifications and fold the polypeptide into its native confirmation. We also show that the presence of the disulfide bond destabilizes CCA despite the fact that oxidized and reduced forms fold into identical confirmations. Further analysis of this phenomenon is needed to determine whether the formation of this disulfide bond plays a regulatory role in HIV pathogenesis.

### 26. LOSS OF GIANT OBSCURINS EXPRESSION IN BREAST EPITHELIUM DISRUPTS EPITHELIAL JUNCTIONS AND PROMOTES CELL MOTILITY AND INVASION

Marey Shriver, Kimberly Stroka, Konstantinos Konstantopoulos and Aikaterini Kontrogianni-Konstantopoulos

Poster presenation; Room 349

Basic Science D

Obscurin A (~720kDa) and B (~870kDa) are giant multidomain proteins, encoded by the single OBSCN gene, originally shown to play important roles in the structural organization and contractile activity of striated muscles. Early studies have indicated that the OBSCN gene is highly mutated in different types of cancers. In light of this observation, our laboratory set forth to examine the expression profile and roles of giant obscurins in normal and cancer breast tissue. Obscurins are readily expressed in breast epithelial cells,

but their expression is dramatically diminished in breast cancer cells. Down-regulation of obscurin A and B using small hairpin RNAs (shRNAs) in non-tumorigenic MCF10A breast epithelial cells resulted in decreased protein expression of β-catenin and E-cadherin, which are major components of adherens junctions and have been heavily implicated in the formation and metastasis of breast tumors. Specifically, β-catenin exhibited a preferential nuclear accumulation accompanied by a concomitant loss from cell-cell junctions. Additionally, loss of obscurins led to alterations in the expression levels and localization of multiple proteins associated with epithelial to mesenchymal transition (EMT). Obscurin-deficient MCF10A cells showed significantly increased motility in 2-Dimensional (2-D) substrata and confined spaces, and invasion through a matrigel coated chamber. Consistent with this, actin filaments re-distributed to extending filopodia-like protrusions where they exhibited increased dynamics. Taken together, our findings indicate that loss of giant obscurins from breast epithelium results in disruption of cell contacts and acquisition of a mesenchymal phenotype that leads to enhanced migration and invasiveness.

### 27. ISOFLURANE IMPEDES THE DEVELOPMENT OF A DEPRESSION-LIKE PHENOTYPE IN RATS

L. WANG, P. L. BROWN, G. I. ELMER, C. L. MAYO, T. D. GOULD, P. D. SHEPARD

Poster presentation; Room 349

Basic Science D

The therapeutic effects of conventional pharmacological treatments for major depressive disorder are slow to develop and are effective in only a subgroup of patients. As such, new therapies are being sought that have rapid action, with increased efficacy in treatment-resistant populations. Subanesthetic doses of ketamine have displayed promise as a rapidly-acting antidepressant with effectiveness in treatment refractory patients (Berman et al., 2000). However, its usefulness is limited by abuse and psychomimetic properties. Clinical studies have shown the volatile anesthetic isoflurane to have rapid and long-lasting antidepressant effects in humans (Langer et al., 1985, 1995, Tadler et al., this meeting). It has yet to be established whether isoflurane has antidepressant-like effects in conventional animal models of depression, limiting studies to define its mechanism of action. We administered isoflurane (2% in 100% $O_2$) to adult male Sprague Dawley rats continuously for two hours through a nose cone attached to a standard stereotaxic apparatus. Two weeks following exposure to isoflurane, rats entered a conventional two-day learned helplessness paradigm. Compared to naïve-controls (n=12), isoflurane-treated rats (n=12) had fewer failure trials (Fig. 1A) and a faster mean escape latency (Fig. 1B) in the shuttle box avoidance task. To specify this effect, a separate group of rats was exposed to an equivalent dose of halothane (1.5% in 100% O2) for two hours, and subsequently evaluated in an identical learned helplessness paradigm after the same two week recovery period. Halothane-

treated rats (n=12) performed similarly to naïve-controls (n=10; Fig. 1C-D), suggesting that the reduced expression of learned helplessness is specific to isoflurane rather than a general effect associated with exposure to volatile anesthetics. These results extend previous findings indicating that isoflurane has antidepressant effects in humans and provide new insights and opportunities regarding alternate targets for development of rapid pharmacological treatments for depression.

### 28. p38 alpha and p38 delta MAPK regulation of p21Cip1 gene expression in human keratinocytes

Kamalika Saha, Richard L. Eckert

Poster presenation; Room 349

Basic Science D

PKC delta increases keratinocyte differentiation via a mechanism that involves activation of p38 delta MAPK. We recently showed that PKC delta also suppresses cell proliferation by increasing expression of the p21Cip1 cyclin-dependent kinase inhibitor. However, the downstream effectors that mediate this PKC delta-dependent regulation are not known. Our present studies suggest that PKC delta activates p38 delta which regulates p21Cip1 promoter activity, as exogenously expressed p38 delta increases p21Cip1 mRNA and protein level in human keratinocytes. Treatment with SB202190, a p38 alpha/beta inhibitor, or dominant negative p38 alpha, leads to a decrease in PKC delta-dependent p21Cip1 promoter activity, implicating p38 alpha as a second mediator of this regulation. p21Cip1 promoter truncation experiments indicate that p38 delta increases the activity via a putative p53 response element. This suggests that p38 alpha and delta may act in conjunction with or thorough p53 to regulate p21Cip1 gene expression. In addition, we show that p38 alpha and p38 delta overexpression increases p53 promoter activity, suggesting that p38 alpha and delta regulate p53 gene expression. We propose that PKC delta activates p38 alpha and p38 delta which in turn activates p53 to increase p21Cip1 expression leading to cessation of keratinocyte proliferation.

### 29. Shiga toxin type 2 dysregulates coagulation cascade in mouse kidney.

Progyaparamita Saha*, Aimee Vozenilek, Tiffany Keepers, Ellen Hailemelecot, Lauren Hippler, Tom Obrig and Fumiko Obata

Poster presentation; Room 349

Basic Science E

We reported a mouse model of hemolytic uremic syndrome (HUS) which is induced by Shiga toxin type 2 (Stx2) and lipopolysaccharide (LPS) injections (Keepers et al., 2006). In this mouse model, the contribution of Stx2 alone is not yet described. Since fibrin thrombi are often seen in Shiga toxin-producing Escherichia coli (STEC) infection-associated HUS, we analyzed Stx2 contribution to fibrin deposition in our mouse model. First, we established fibrin specific

quantification assay from mouse kidney by Western blot. In this assay, we used anti-human fibrin beta chain specific antibody in which thrombin-cleaved neo epitope of fibrin beta chain is used as an antigen. This antibody reacted with fibrin standards that are made from rat or mouse plasma, but did not react with original fibrinogen. We isolated fibrin fractions from lethal dose Stx2 injected mouse kidneys at specific time points until 72 h, and applied fibrin specific Western blot. We detected a basal level fibrin in normal mouse kidney that was reduced significantly at 8 h after Stx2 injection. Platelet accumulation in kidney that is detected by integrin beta III (CD61) immunohistochemistry showed that the number of platelet was reduced prior to fibrin reduction. Platelet counts in blood showed no reduction suggesting there is no thrombocytopenia induced by Stx2. We employed ingenuity pathway analysis (IPA) software to predict coagulation/fibrinolysis cascade activity from a set of microarray data. IPA analysis revealed that coagulation factor II (thrombin), factor VII, urokinase and tissue plasminogen activator are activated in Stx2 injected mice kidney in the later time points (later than 12 h). An increase in fibrin at later time point seemed to correspond with the IPA prediction. Blood urea nitrogen (BUN) in plasma was significantly increased at the later time points. Our data suggests that Stx2 down-regulates coagulation cascade in the beginning but later progresses to induction which associated to renal failure.

## 30. TUMORIGENIC CONSEQUENCES OF RESTORING TTP EXPRESSION IN INVASIVE BREAST CANCER CELLS

Christina R. Ross and Gerald M. Wilson

Poster presenation; Room 349

Basic Science E

Tristetraprolin (TTP) is a tandem zinc finger protein that binds to AU-rich elements (AREs) encoded in select mRNAs and contributes to the rapid turnover of these transcripts. The mRNA-destabilizing activity of AREs is essential for limiting cellular production of many clinically important gene products, including numerous oncogenes. Surveys of TTP expression in human tumors and cancer cell lines indicate that TTP may function as a tumor suppressor in diverse neoplastic contexts. Specifically, TTP expression is suppressed in many human cancers and cancer cell lines relative to non-transformed tissues from many sources. Furthermore, suppression of TTP is a negative prognostic indicator in breast cancer. To determine how diminution of TTP expression may promote breast tumor progression, we have compared selected cellular phenotypes between the highly aggressive breast cancer cell line MDA-MB-231, which does not express TTP, with clonal MDA-MB-231 lines that we have developed which stably express exogenous TTP. Using MTT assays we show that restoring TTP expression in MDA-MB-231 cells significantly slows cell proliferation. Cell cycle analysis by propidium iodide staining and flow cytometry showed significant increases in the G1

population in TTP-expressing cells but no increase in the sub-G1 population, supporting a model whereby TTP slows proliferation by arresting cell cycle progression at the G1/S switch but does not increase apoptosis. qRT-PCR and western blot analyses revealed alterations in the expression of G1/S checkpoint mediators in the MDA-MB-231/TTP cells, but did not identify a clear mechanism for the observed G1 accumulation. However, we observed that TTP induced accumulation of a small (45 kDa) form of the key cell cycle regulator and pro-proliferative transcription factor cMYC in MDA-MB-231 cells. This is consistent with a previously described proteolytic fragment called Myc-Nick, a nucleus-excluded protein that can promote cellular differentiation and slow proliferation. Our working model is that TTP expression enhances cleavage of the cMYC protein, likely by activating components of the calpain family of proteases, and that the resulting decrease in levels of full-length cMYC contributes to the suppression of cell proliferation observed in TTP-expressing cells.

### 32. A Role for Bcl-xL in CD1d-mediated Natural Killer T cell responses to B cells

Priyanka Subrahmanyam and Tonya J. Webb

Poster presentation; Room 349

Basic Science D

Lymphomas are a heterogeneous group of malignancies, primarily divided into Hodgkin's and non-Hodgkin's lymphomas (NHL). Unlike other cancers, the incidence of NHL is steadily rising. Natural Killer T (NKT) cells are innate-like lymphocytes that recognize glycolipid antigens in the context of CD1d, an MHC class I- like molecule. They have strong anti-tumor activity and respond by massive cytokine production and/or cytotoxicity. It is known that pro-survival factors are upregulated in B cell lymphomas, but their role in antigen processing and presentation remains unknown. The effect of Bcl-xL on CD1d-mediated antigen presentation was examined utilizing the well-characterized WEHI-231 B cell lymphoma cell line. Bcl-xL expression was modulated via genetic, pharmacologic and biological approaches. We found a concomminant increase in CD1d-mediated NKT cell responses following the induction of Bcl-xL; however, cell surface expression of CD1d molecules remained unchanged. Induction of Bcl-xL in primary B cells led to increased CD1d-mediated activation of NKT cells in response to exogenous antigens, resulting in increased Th1, but not Th2 responses. Taken together, these data suggest that aberrant expression of Bcl-xL may act as a sentry system to alert the CD1d/NKT system to neoplastic transformation.

### 35. Effects of Maternal Chlorpyrifos exposure on Guinea Pig Neurodevelopment

Roger J. Mullins, Su Xu, Edna F.R. Pereira, Jacek Mamczarz, Edson X. Albuquerque, Rao P. Gullapalli

Poster presenation; Room 349

Basic Science E

This study examined the neurodevelopmental effects of an organophosphorus compound, chlorpyrifos (CPF), on the offspring of pregnant guinea pigs exposed to it. Pregnant animals were injected with either chlorpyrifos or vehicle on the 50th day of gestation. Offspring were examined at ~70 PND with the Morris Water Maze (MWM) task and Magnetic Resonance Imaging (MRI) methods including T2-weighted anatomical scans, T2* relaxation time maps, Diffusion Tensor Imaging (DTI), Diffusion Kurtosis Imaging (DKI), and 1H Spectroscopy. Offspring with exposed mothers were impaired on the MWM and showed significant decreases in both body weight and brain volume, particularly in the frontal regions of the brain encompassing the striatum. Diffusion measures revealed decreased myelin integrity within the striatum and amygdala, two frontal brain areas linked to acquisition and modulation of learning, respectively. These strong findings serve to clarify the effects of exposure to CPF in the womb, as well as highlight the danger of mother to child transmission of low levels of CPF in the environment.

### 36. Ectopic Expression of an Obscurin Signaling Cassette Decreases Migration and Invasion of Metastatic Breast Cancer Cells

Nicole A. Perry and Aikaterini Kontrogianni-Konstantopoulos

Poster presentation; Room 349

Basic Science F

The obscurins (~70-820 kDa) are a family of proteins expressed from the 150 kb OBSCN gene, located on human chromosome 1. Sequencing analysis of breast and colorectal cancers, as well as melanoma and glioblastoma, revealed that obscurins are mutated at a substantial frequency and these mutations may be driving tumor formation. Our work has recently demonstrated that obscurins are present in normal breast, skin, and colon cells, but absent in their cancerous counterparts. Downregulation of obscurins' expression is sufficient to allow non-tumorigenic breast epithelial cells to evade apoptosis induced by etoposide. Furthermore, absence of obscurins allows increased migration and invasion of breast epithelial cells. Remarkably though, we observed that ectopic expression of a fragment of obscurin composed of tandem src homology 3-Rho guanine exchange factor-pleckstrin homology (SH3-RhoGEF-PH) motifs was sufficient to decrease monolayer migration and invasion of metastatic breast cancer MDA-MB-231 cells, which are naturally deficient in obscurins, by >20% and >70%, respectively. Based on our observations that 1) absence of obscurins allows increased migration and invasion of breast cells, and 2) expression of an obscurin cassette mitigates this migratory and invasive behavior of metastatic breast cancer cells, we postulate that obscurins may act as metastasis suppressors in breast epithelium. We have therefore begun to investigate how the tripartite obscurin fragment, SH3-RhoGEF-PH, can influence the behavior of the cytoskeleton and therefore affect migration and invasion. We have

found that the RhoGEF domain directly induces guanine nucleotide exchange in RhoA, but not Rac1 or Cdc42. This activity may be allosterically regulated by the adjacent SH3 domain, which interacts with the RhoGEF domain in a yeast two-hybrid assay. Furthermore, the PH domain binds to 3'-phosphorylated inositol lipid headgroups, providing a mechanism for the obscurins to respond to signals generated at the plasma membrane. Together, this evidence suggests that the tripartite signaling cassette can recapitulate the full-length obscurins' metastasis-suppressing activity, and may merit development as a therapy for advanced breast cancer.

### 37. Regulation of *Pseudomonas aeruginosa* PrrF Small RNAs during Anaerobiosis

Alexandria Reinhart and Amanda Oglesby-Sherrouse

Poster presenation; Room 349

Basic Science F

*Pseudomonas aeruginosa* is an opportunistic pathogen that causes chronic pulmonary infections in cystic fibrosis (CF) patients. *P.a.* requires iron for virulence and can obtain this element from heme during infection. Aerobically, excess iron induces oxidative stress; thus, the ferric uptake repressor (Fur) represses expression of genes for iron and heme uptake when iron levels are high. Fur also represses expression of PrrF1 and PrrF2, two small RNAs that block expression of iron-containing proteins in low iron conditions. The prrF genes are arranged in tandem, allowing expression of a third RNA, named PrrH. Oglesby-Sherrouse and Vasil (2010) previously demonstrated that, during aerobic growth, heme represses expression of the PrrH RNA; PrrH in turn represses nirL expression, a part of the nitrite reductase (NIR) gene cluster. NIR catalyzes the reduction of nitrite to nitric oxide as part of the *P.a*. denitrification pathway, the genes for which are induced when oxygen is limiting. Growth in low oxygen is increasingly appreciated as an important factor for *P.a.* pathogenesis in the CF lung. Thus, understanding iron and heme regulatory pathways during anaerobic growth should shed light on how *P.a*. survives during CF lung infections. We therefore sought to define the effects of heme on expression of PrrF, PrrH, and nirL under anaerobic conditions, when nirL is normally transcribed. Our studies show that, while heme represses PrrH expression under aerobic conditions, this regulation is eliminated during anaerobic growth. Moreover, heme-activation of nirL expression is also eliminated under these conditions. These data suggest a distinct mechanism controls PrrH expression in the absence of oxygen. Nitric oxide, the product of NIR, has the potential to induce nitrosative stress in cells via the formation of reactive nitrogen species, such as peroxynitrite, and also functions as a potent signaling molecule. We therefore hypothesize that excess nitric oxide induces PrrH expression, which in turn blocks nirL expression and NIR activity, and that this regulation helps protect *P.a.* against nitrosative stress. We are currently

testing this hypothesis through analysis of PrrF and PrrH expression in response to nitrosative stress, as well as determining the sensitivity of prrF mutants to nitrosative stress.

### 38. Evidence for N-acyl-homoserine Lactone Activity by Rickettsia typhi, the Etiologic Agent of Murine Typhus

Pelc, R.S., Ceraul, S.M.

Poster presentation; Room 349

Basic Science F

Typhus Group Rickettsia (TGR) are insect-borne obligate intracellular bacteria which cause the human febrile diseases epidemic typhus and murine typhus. To date, the molecular mechanisms of TGR pathogenicity remain unclear. Many Gram-negative bacterial species regulate their virulence-associated genes through the production of N-acyl-homeserine lactones (HSLs) and quorum sensing signaling. In this study, we confirm the existence of HSL activity by Rickettsia typhi during its infectious cycle, as part of a larger goal of identifying the mechanisms whereby TGR enter and exit host cells during infection. Bioinformatic analysis confirmed that the genome of R. typhi contains homologs for the known HSL synthase genes hdtS from Pseudomonas fluorescens, and cqsA from Vibrio harveyi. To confirm this potential HSL activity, L929 mouse cells were then infected with R. typhi to high levels of infection. Spent media and cells were collected, sonicated, clarified, and passaged through a 0.2 micron filter. We observe LacZ expression from the HSL reporter strain Agrobacterium tumefaciens KYC55 when T-streaked against this media. The R. typhi HSL synthase homologs, hemA (cqsA) and plsC (hdtS) were then cloned and transformed into Rosetta-gami Escherichia coli cells. Transformed cells were grown overnight in auto-induction media, clarified, and passaged through a 0.2 micron filter. The spent culture media from both putative HSL synthase homologues induce LacZ expression from A. tumefaciens KYC55. Interestingly, transcript abundance for both hemA and plsC increases along with R. typhi burden in L929 cells. We are currently working to identify the HSL molecules produced by hemA and plsC for correlation to the activity we observe in R. typhi infected host cells. We hypothesize that this HSL activity is associated bacteria's preparation for exiting one host cell and entry into the next. Thus, our continued exploration of quorum sensing processes in R. typhi may provide a better understand of virulence factor control by TGR.

### 40. Bacteria-Human Somatic Cell Lateral Gene Transfer Is Enriched in Cancer Samples

Karsten B. Sieber, David R. Riley, Kelly M. Robinson, James Robert White, Ashwinkumar Ganesan, Syrus Nourbakhsh, Julie C. Dunning Hotopp

Poster presentation; Room 349

Basic Science F

Viral DNA frequently integrates in the human genome causing somatic mutations that can promote carcinogenesis. For example,

integrated human papillomavirus (HPV) is found in ~90% of cervical cancers resulting in ~275,000 deaths in 2002. In contrast to viral integrations, the integration of bacterial DNA into the human genome has not been described. Given that there are 10× more bacterial cells in our bodies than human cells, there is ample opportunity for integration of bacterial DNA into somatic genomes. Using publicly available next-generation sequence data from The Cancer Genome Atlas (TCGA), we searched 6.6 trillion base pairs of data for evidence of somatic mutations caused by bacterial integrations. Putative integrations were defined as Illumina paired-end reads with one mate mapping exclusively in the human genome and the other mate mapping exclusively to bacteria. Extensive coverage across specific junctions supports the bacterial DNA integrations into the human somatic genome. Evidence supports that bacterial DNA integrates into the human somatic genome through an RNA intermediate and that such integrations are more frequent in (a) tumors than normal samples, (b) RNA than DNA samples, and (c) the mitochondrial genome than the nuclear genome. Hundreds of thousands of paired reads support random integration of Acinetobacter DNA in the human mitochondrial genome in acute myeloid leukemia samples. Numerous read pairs across multiple stomach adenocarcinoma samples support specific integration of Pseudomonas DNA in the 5′-UTR and 3′-UTR of four proto-oncogenes that are up-regulated in their transcription, consistent with conversion to an oncogene. These data support our hypothesis that bacterial integrations occur in the human somatic genome and may play a role in carcinogenesis. We anticipate that the application of our approach to additional cancer genome projects will lead to the frequent detection of bacterial DNA integrations in tumors that are in close proximity to the human microbiome.

### 41. Disruptions Between Networks: Longitudinal Analysis of Resting State Functional Connectivity and CBF in Mild Traumatic Brain Injury Patients with and without Post Concussive Syndrome

Chandler Sours, Jiachen Zhuo, Steven Roys, Rao P Gullapalli

Poster presenation; Room 349

Basic Science F

Introduction: Following mTBI, some patients exhibit post-concussive symptoms and cognitive deficits. Due to the diffuse nature of the injury, alterations in resting state fMRI and resting cerebral blood flow (CBF) may provide better insights into the cognitive condition of the mTBI patient. Two common resting state networks are the Default Mode Network (DMN) and the Task Positive Network (TPN).[1] These networks ideally are anti-correlated (negative rs-FC). The DMN Interference Hypothesis suggests that an imbalance between the DMN and TPN may result in reduced cognitive performance. [2] The DMN has increased resting CBF compared to the TPN. [3] We hypothesize that following mTBI, especially in those who experience

post concussive syndrome (PCS), the rs-FC between the two networks will be less anti-correlated and that the balance in CBF between the DMN and TPN will be disrupted.

Methods: 28 mTBI patients and 28 matched control subjects received an MRI evaluation in the acute (within 11 days), sub-acute (1 month) and chronic (6 months) stages of injury. mTBI patients were divided into PCS and no PCS groups based on the Modified Rivermead Post-Concussion Symptoms Questionnaire (RPQ). [4] Participants completed a computerized cognitive assessment, the Automated Neuropsychological Assessment Metrics (ANAM). A weighted throughput score was computed which encompasses the accuracy and reaction time from the ANAM. [5] A high resolution T1-weighted-MPRAGE (TE=3.44ms, TR=2250ms, TI=900ms, flip angle=9º, res.=256×256×96, FOV=22cm, sl.th.=1.5mm) was acquired for anatomic reference. The resting state MRI scan used a single-shot EPI sequence (TE=30ms, TR=2000ms, FOV=230mm, res.=64×64) with 36 axial slices (sl.th.=4mm) over 5 min 42s. The perfusion scan used the pulsed arterial spin labeling (PASL) technique based on single-shot EPI (TE=11ms, TR=2500ms, FOV=230mm, res. 64×64) with 16 slices (sl.th.=5mm, 1mm gap). Forty-five pairs of labeled and control volumes were taken over 4 min.

The CONN-fMRI Functional Connectivity toolbox v13.h was used to process the resting state data. The DMN was extracted using a posterior cingulate cortex (PCC) seed and the TPN was extracted using bilateral dorsolateral prefrontal cortex (DLPFC) seed with coordinates.1 ROIs were created using a 10mm sphere centered at correlated clusters for the DMN and the TPN. Rs-FC with DMN and TPN were extracted for each ROI. Average network rs-FC within and between the DMN and TPN was calculated. ASL images were motion corrected. CBF maps were generated using in-house MATLAB program based on [6]. ROIs from the resting state analysis were transformed from MNI space to original space and registered to the ASL data using AFNI. ROIs were masked with GM mask to extract CBF values from each ROI. Average CBF values for the DMN, TPN and a ratio of TPN CBF:DMN CBF were computed.

Results: mTBI patients with PCS performed worse on the ANAM than those without PCS at the acute stage ($p=.003$) (Fig1). mTBI patients had increased DMN-TPN rs-FC at the chronic stage ($p=.023$) (Fig2). Although, the TPN: DMN CBF ratio was similar between mTBI patients as a group and controls, the PCS group however had increased TPN: DMN CBF ratio in the chronic stage ($p=0.022$) compared to those without (Fig3a). There was greater TPN CBF than DMN CBF in the control group ($p=0.002$), and mTBI in the acute and sub-acute stages ($p<0.001$; $p<0.001$), but not in the chronic stage ($p=0.18$) (Fig3b). There was no difference between the TPN CBF and the DMN CBF in the mTBI group with PCS at all three time points (acute: $p= 0.078$; sub-acute: $p= 0.36$; chronic: $p= 0.54$) (Fig3c).

Conclusion: MTBI patients demonstrate increased between network rs-FC and a disrupted balance in CBF within the networks only in the chronic stage in spite of normalized cognitive performance at this stage. However, the mTBI patients experiencing chronic PCS, exhibit alterations in the proportion of resting CBF allocated to each network at all three stages of injury suggesting this may be a possible predictor of patients that will develop chronic PCS among the mTBI population.

References: [1] Fox et al, 2005. [2] Sonuga Barke et al, 2007. [3] Zou et al, 2009. [4] Savola and Hillbom 200). [5] Kane et al, 2007. [6] Wang J et al, 2003.

### 42. INACTIVATING AP1 TRANSCRIPTION FACTOR FUNCTION IN SUPRABASAL EPIDERMIS PRODUCES A LORICRIN KERATODERMA PHENOTYPE ASSOCIATED WITH ENHANCED TH1 CHEMOKINE PRODUCTION

Christina A. Young, Ellen A. Rorke, Janice Babus, and Richard L. Eckert

Poster presenation; Room 349

Basic Science E

The activator protein one (AP1) transcription factors are key controllers of keratinocyte proliferation, differentiation, apoptosis and transformation. To study AP1 factor function in epidermis, we expressed TAM67, a dominant-negative form of c-jun that inhibits the function of all AP1 factors, in the suprabasal epidermis. Suprabasal AP1 blockade results in a progressive symmetric erythrokeratoderma-like phenotype characterized by hyperproliferation, hyperkeratosis, parakeratosis, constriction of the tail and digits, and nuclear localization of loricrin. We hypothesize that TAM67 expression alters epidermal chemokine production and that this is, in part, responsible for the TAM67 impact on epidermal phenotype. Mice were treated for zero to twenty-one days with doxycycline and the phenotype was assayed. This analysis reveals a sequential activation of events beginning with nuclear loricrin accumulation at 24 to 48 h, increased basal keratinocyte proliferation at 48 to 72 h, and enhanced epidermal production of Th1 lymphocyte chemoattractants, CXCL9, CXCL10 and CXCL11 at 8 days. Increased mRNA expression for each of these chemokines were confirmed by qRT-PCR. These findings describe a hierarchy of early and late events in disease development and suggest that increased expression of Th1 chemokines is a late event that may contribute to disease development.

### 43. SURVIVIN AND HEXOKINASE-II EXPRESSION IN ORAL CANCER AND LICHEN PLANUS

Anahita Shaya, Dr. Timothy Meiller

Poster presenation; Room 349

Basic Science G

Objective: The literature reflects numerous anecdotal reports suggesting that oral lichen planus (OLP)/erosive lichen planus (ELP)

may be associated with malignant transformation to oral squamous cell carcinoma (OSCC). With the lack of established diagnostic criteria, however, this correlation has not been confirmed. Molecular studies of biomarker expression suggest that early changes in cancer transformation can be detected by their expression levels. The aim of this study was to evaluate the expression of biomarkers survivin and hexokinase-II in OLP/ELP compared to normal tissue, dysplastic tissue, and tissue from OSCC.

Methods: IRB exempt status was obtained. Archived and de-identified oral biopsy specimens (n=120) from patients with varying diagnoses were sectioned and prepared for immunohistochemical staining.

Monoclonal antibodies to survivin and hexokinase-II and immunoperoxidase-tagged 2° antibody were used to identify expression. The degree of positive expression of biomarkers was quantified by a diagnosis-blinded examiner evaluating 5 separate areas, averaging expression, and comparing between tissue types.

Results: Preliminary results indicate strongly positive expression of both survivin and hexokinase-II in OSCC. OLP specimens show varying levels of expression. Preliminary examination of ELP specimens appear similar to mild dysplasia (representative images not shown here). Upon completion of tissue analysis strength of association will be assessed.

Conclusion: Preliminary results indicate that biomarker expression levels are higher in OSCC compared to OLP and normal tissue. Malignant potential, however, is dependent on the advanced level of tissue damage occurring during transformation. Wound healing in an autoimmune condition such as OLP/ELP is complex and completed data may demonstrate a correlation between the expression of these biomarkers and the extent of stimulated chronic tissue damage/healing.

### 44. MODIFIED LIPID A FROM ACINETOBACTER BAUMANNII IS A UNIQUE BIOMARKER FOR RAPID DETECTION OF ANTIBIOTIC RESISTANCE.

Leila G. Casella, Mark R Pelletier, Jace W Jones, Yohei Doi, and Robert K Ernst

Poster presenation; Room 349

Basic Science G

One of the major challenges in the management of *A. baumannii* infections is the rapid dissemination of multidrug resistant (MDR) strains and diminishing antibiotic choices available to treat this troublesome pathogen. In this context, physicians are turning to the potentially nephrotoxic cationic antimicrobial peptide, Colistin (polymyxin E) to treat patients infected with A. baumannii MDR strains.

Colistin-resistance is rare but the emergence of *A. baumannii* colistin-resistant clinical isolates has raised concerns among physicians as this antibiotic is used as a salvage therapy. More alarming, is the identification of colistin-heteroresistant

subpopulations in susceptible *A. baumannii* clinical isolates that may lead to the development of complete resistance to colistin.

Studies assessing reliability of current susceptibility test methods have suggested poor concordance and revealed a further problem: unreliable detection of heteroresistant subpopulations. Thus, rapid and reliable susceptibility testing methods are critical to deliver effective antimicrobial therapies and minimize the risk of failed treatments resulting in adverse clinical outcomes.

Mass-spectrometry (MS) assays have proven to be an important tool to identify bacterial species. The MS-based identification method (Bruker Biotyper) currently being implemented in clinical labs around Europe (coming to the US) is based on proteomic profiling. Bacterial speciation by proteomics can be highly accurate, but the inability to distinguish antibiotic resistance profiles represents a significant limitation. Lipid profiles, however, especially modifications to lipid A, the membrane anchor of lipopolysaccharide can be directly linked to antimicrobial peptide resistance patterns. Correlation of lipid A modifications and antibiotic susceptibility has been reported in many bacteria and, most importantly, these modifications can be identified using simple mass-spectrometry approaches.

Using a MS approach, MALDI-TOF (Matrix Assisted Laser Desorption-Ionization Time-of-Flight) to analyze modifications to lipid A has enabled us to determine unique diagnostic biomarkers to rapid identify colistin-sensitivity or -resistance profiles in laboratory-adapted A. baumannii, including characterization of heterosensitivity. This work was further extended to analyze lipid A from patient samples to validate the clinical utility of this biomarker. The detection of a novel, modified lipid A with ethanolamine at the 4'position and a novel hexosamine addition. Subsequent LC/MS analysis identified the positively charged hexosamine as galactosamine attached at the 1 position of lipid A.

Modification of lipid A with these positively charged constituents was concordant with antibiotic susceptibility profiles and may be candidate biomarkers to aid clinicians in treatment protocols. Together, these findings clearly demonstrate the feasibility of this type of analysis as a diagnostic test for rapid determination of antimicrobial susceptibility profiles in clinical settings.

### 46. Delirium Subtypes in a Study of Hip Fracture Patients

Emma G. Sheldon, Jennifer Albrecht, Edward Marcantonio, Darren Roffey, Erik Barr, Ann L. Gruber-Baldini

Poster presenation; Room 349

Basic Science G

Objective: Delirium commonly occurs after hip fracture and is associated with poorer functional recovery, increased length of hospital stay, higher healthcare costs, and increased

mortality. Delirium can be divided into three motoric subtypes: hypoactive, hyperactive, and mixed. This study aimed to identify baseline factors associated with motoric subtypes of delirium in patients undergoing surgical repair of hip fracture.

Methods: The Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) Cognitive Ancillary Study assessed delirium in 139 patients pre-randomization (pre- or post-operatively) and up to 3 times over 5 days post-randomization using the Confusion Assessment Method (CAM) and the Memorial Delirium Assessment Scale (MDAS). Motoric subtypes were assessed based on MDAS item 9a.

Results: Prevalence of delirium in this population was 41%, of which 47% (n=27) were pure hypoactive subtype at all assessments, 11% (n=6) were pure hyperactive, 14% (n=8) were mixed, and 14% (n=8) were assessed as having different subtypes at different time points. Additionally, there was a small minority of patients (14%) who met the criteria for delirium but did not satisfy the requirements for a motoric subtype. A pre-randomization diagnosis of dementia was significantly associated with CAM-defined delirium but not with any motoric subtype (p=0.004). Hypoactive subtype was significantly associated with a lower delirium severity score as determined by the MDAS (p=0.01). Patients with the hypoactive subtype were less likely than the other subtypes to have chart documentation of delirium. Only 5 (19%) patients assessed as hypoactive were identified as having delirium in the chart versus 13 (59%) of other motoric subtypes (p=0.003). While not statistically significant, those with pure hypoactive delirium had an increased chance of an inability to walk or death at 60 days (OR 2.72, 95% CI: 0.77, 9.52, p=0.14). Significance was defined as $p<0.05$.

Conclusion: Hypoactive delirium was associated with lower scores on the MDAS delirium severity scale (which has more hyperactive items) and was less likely to be recognized by care providers. This study suggests that increased effort in greater recognition of this subtype may be warranted.

### 47. Education Sessions for Heart Failure Patients: Duration, Cost and Influencing Factors

Eyad Musallam and Johantgen, Meg, PhD, RN

Poster presenation; Room 349

Basic Science G

Research Objective: The American Heart Association's "Get with the Guidelines®- Heart Failure" are designed to ensure that the care hospitals provide to heart failure patients is aligned with the latest scientific guidelines. The guidelines recommend that at least 60 minutes of patient education is needed to ensure that the patient or care provider understands what actions must be taken after discharge. The objectives of the study reported here are: 1) to quantify the minutes of education registered nurses and other providers

spend teaching recommended content for hospitalized patients with heart failure (HF) , 2) to describe factors that cause increment in education sessions length and 3) to quantify the cost of education sessions.

Study Design: This descriptive study was a part of a quasi-experimental study of 40 U.S. Magnet Hospitals designed to evaluate the effect of standardized education on heart failure patient outcomes (knowledge, self-care, and readmission). As part of the fidelity assessment for the Improving Heart Failure Outcomes (IHO) study, nurses with expertise in heart failure management estimated the minutes spent teaching patient within eight domains recommended by the American Heart Association and the Joint Commission. Nurses also estimated the minutes by other providers (e.g., physicians, dieticians, pharmacists). A subset of 25 hospitals was used for the analyses since these represented the preponderance of patient records.

Population Studied: The sample of 439 patients from the 25 hospitals included only patients voluntarily consenting to participate, with a primary diagnosis of HF, speaking English, without an intervention procedure or transfer to another hospital unit, and being discharged to home.

Principal Findings: The study sample was half female, with more than half being 60 or older. The majority of the patients (78 percent) have NYHA class II or III. The average length of stay (LOS) for heart failure patients was 3 days. On average, nurses provided 83 minutes of education with a range of 5 to 685 minutes. Nurses spent the most minutes to cover discharge medications (average 13 minutes), diet (average 13), and what to do if symptoms worsen (average 10 minutes). The length of education sessions found to be affected by patient age and disease stage. A significantly higher number of minutes was required for patients less than 66 years (average 99 minutes) in comparison with patients older than 65 years (average 70 minutes); p LT .001. In addition, higher number of minutes was required for patients with NYHA class III and IV heart failure (M= 86) in comparison with patient with NYHA class III and IV heart failure( M = 78) ; p< 0.26. According to the United State department of labor estimations of nurses' hourly wages, the average education session cost was 80 to 120 $.

Conclusions: This is the first study that quantifies the number of minutes needed to cover the recommended HF patient education domains across multiple hospitals with a large sample size. Nurses and other care providers exceed the recommended minutes of education; medication education requires the most time.

Implications for Policy, Delivery or Practice:

While the average cost of the education sessions is considerably low, the clinical benefit of these session in preventing readmission still questionable. In addition, the condense amount of education within a short length of stay also might affect

the clinical effectiveness of these education sessions. A combination of essential education intervention during hospitalization, reinforcement with a 48-hour follow-up call, and nurses' home visits may be needed to fully address teaching domains, improve patients' self-care confidence, and overall outcomes.

### 48. Cluster Analysis of Uppoer Extremity Fugl-Meyer Assessment Defines Levels of Motor Impairment Severity

Woytowicz, Elizabeth; Rietschel, Jeremy; Goodman, Ron; Sorkin, John; Whitall, Jill; McCombe Waller, Sandy

Poster presentation; Room 349

Basic Science G

Purpose/Hypothesis: Individuals with chronic stroke have a wide range of upper extremity (UE) motor impairments. The Fugl-Meyer (FM) Scale of Motor Impairment is the most commonly used scale for categorizing impairments post stroke. Previously, Woodbury (2007) used factor analysis to demonstrate FM-UE individual scores measured a single unidimensional construct, except for the reflex items. Despite the frequent use of the FM to categorize severity of paresis no quantitative analyses have determined severity ranges. Here, we quantitatively define the levels of severity using cluster analysis with and without the reflex items. This exploratory research had no a priori hypothesis but, based on Woodbury's findings, we expected cluster memberships to differ with and without reflex items. Subjects: 247 subjects with chronic UE hemiparesis (113 female, 134 left paresis), aged 32-89 years (M=58.6±11.75). Materials/Methods: FM scores for individual items were compiled from baseline testing of 5 studies with consistent testing procedures. Two hierarchal cluster analyses were run on the full sample: once with and once without reflex items. A between groups-linkage method was used with a squared Euclidian distance interval. Individual cluster characteristics were then analyzed. Results: The range of FM scores included was 2-63 (M=26.9±15.7) with reflex items and 0-57 (M=22.1 ±15.3) without. Three distinct clusters were found. FM scores with reflex items for cluster 1, 2, and 3 ranged between 2-27, 28-42, and 43-63 with 151, 49, and 47 subjects respectively. FM scores without reflex measures for cluster 1, 2, and 3 ranged between 0-21, 22-38, and 39-57 with 147, 59, and 41 subjects respectively. When reflex items were removed, classification changed to an adjacent cluster for 28/247 subjects (11%). Classification change occurred for 12, 9, and 7 subjects from clusters 1, 2, and 3 respectively. Conclusions: The cluster analysis of the original scale verifies that individuals with UE hemiparesis can be distinctly categorized into 3 levels of severity that can be described as severe (<28), moderate (28 to 43) and mild (>43). The fact that more individuals were in the severe category may reflect the actual distribution of the population or be reflective of the small sample bias caused by, for example, more stroke survivors with severe impairments seeking to be in research studies. The 11% difference in cluster

identification between the two analyses supports the findings of Woodbury et al. that the reflexes represent a different construct. These data suggest the consideration of whether reflexes should be included in the final scoring of the FM. Clinical Relevance: Knowledge of UE motor impairment severity levels of the FM could assist clinicians in interpreting current literature with relevance to the research sample studied. This information could guide therapists in selecting intervention options most appropriate for their individual patients.

### 49. TASK-ORIENTED ARM TRAINING IN STANDING IMPROVES BOTH ANTICIPATORY POSTURAL CONTROL AND UPPER EXTREMITY FUNCTIONAL OUTCOMES IN STROKE PATIENTS.

S McCombe Waller, A Gaeta, C Yang, and M Rogers.

Poster presentation; Room 349

Basic Science E

Objective: Physical disability resulting from stroke is multifaceted, impacting both upper extremity (UE) and postural control, leaving patients at risk for immobility and falls. In current rehabilitation practice, training is often segmented and targets quite narrowly on one area of disability. As a result, carryover of isolated gains in physical abilities to meaningful context-specific functional performance is limited. To function in an upright world, training should prepare individuals to perform tasks in standing. Moving an arm to reach forward in standing involves anticipatory postural adjustments (APAs) of the legs that precede and accompany the goal directed arm movement, and reactive responses that stabilize balance and prevent falling. In previous work we identified delayed and reduced magnitude of APAs preceding a functional reach in standing using a cued reaching task. Hypothesis: Task-orienting arm training in standing without explicit cues for postural adjustments would engage pathways (likely subcortical) that contribute to APAs while also improving UE function. We report in this paper the effects on anticipatory postural control as well as UE functional outcomes after 6 weeks of arm training in standing. Subjects: Nine participants with stroke and four healthy age-matched controls. Methods: UE functional tests included the Fugl-Meyer UE Test (FM), Wolf Motor Function Test (WMFT), Box and Blocks and the University of Maryland Arm Questionnaire for Stroke (UMAQS). Anticipatory postural control and reaching were evaluated with a cued reaching task in standing. APAs were characterized by onset and maximal displacement of the center of pressure (COP), and onset/offset of EMG from tibialis anterior, soleus. Paretic reach onset/offset and duration were measured. Training consisted of 6-weeks task oriented training with the paretic arm, in standing, with no explicit cues for postural weight shift. Results: After training subjects demonstrated significant improvements in APAs as measured by onset and displacement of the COP. EMG timing improved post training to resemble timing characteristics of controls previously collected. Both the onset and timing of

reaching improved significantly. UE functional gains were seen in FM scores and WMFT (time and weight). Gains in UMAQS scores indicated increased daily use of the arm after training .Discussion: Results indicate gains in anticipatory postural responses and paretic reaching in stroke as well as functional UE outcomes. Conclusion: Arm training in the functional context of standing can lead to gains in both postural control and function of the arm after stroke.

### 50. Extraction of Drug-Gene Relationships from Literature Using Functional Context of Gene Networks

Eduardo Llamas, Emily Doughty, Ye Sol Yun, Maricel G. Kann

Poster presentation; Room 349

Basic Science G

Drug side effects and toxicity are often the result of off-target drug-gene interactions that affect biological processes unrelated to the focus of treatment. Drugs with multiple drug targets often fail in clinical trials due to limited knowledge of their inherent polypharmacology. The biomedical literature is rich in drug-gene relationship data, but much of it remains inaccessible, further hindering comprehensive knowledge of drug-gene interactions. Thus, accessible, high quality drug information databases providing comprehensive drug-gene information are critical for research in pharmacology, toxicology, and pharmacogenomics. Current resources of drug-gene information rely on manual curation that can be inefficient and expensive. Thus, automatic methods aiming to accelerate the identification of drug-gene relationships extracted from biomedical literature have great potential for increasing the coverage and efficiency of drug-gene annotations. We introduce the text-mining method Literature Extraction of Drug-Gene relationships (LEx-DG) that identifies drug-gene relationships in biomedical abstracts when the target genes can be grouped into biological function-relevant clusters. These clusters identify GO terms, pathways, protein domains, sequence motifs, and protein-protein interaction networks that may be affected or targeted by a drug, thereby increasing the precision of the method and leading to new hypotheses about possible functional relationships among a drug's multiple gene targets. In comparison with the PGx pipeline, a well-established drug-gene relationship prediction method, LEx-DG achieves significantly higher precision, F-score, accuracy, and specificity in identifying known drug-gene relationships. Manual curation of LEx-DG results for gemcitabine lead to the identification of 46 relationships that were not previously annotated in PharmGKB or the Comparative Toxicogenomics Database. Our results demonstrate the feasible application of LEx-DG for large-scale annotation of drug-gene relationships to facilitate updates of drug-gene interaction resources.

### 51. Modulation of Inflammation in Mesothelial cells

Sharis Erwin and John McLenithan

Poster presentation; Room 349

Basic Science H

Omentin is a GPI-anchored 38-kDa secreted insulin-sensitizing glycoprotein that has been identified in the mesothelial cells in the stromal vascular fraction (SVF) of adipose tissue. Mesothelial cells expressing omentin are part of the innate immune system and can contribute to the inflammatory state of visceral adipose tissue. Therefore, it is important to determine the role that omentin plays in the regulation of chronic inflammation. Primary cultures of human adipocyte mesothelial cells were isolated by biopsy trypsinization and Immunofluorescence microscopy was used to determine the purity of primary HAMC cultures. To determine if chronic inflammation is the cause of decreased omentin expression, HAMCs were treated with TNF-alpha, a pro-inflammatory cytokine, for 24 hours to simulate chronic exposure. Omentin gene expression was down-regulated by TNF-alpha significantly (41% decrease) in chronic conditions. The protein expression of omentin was also significantly decreased (41%). To demonstrate that omentin acts as an insulin sensitizing adipokine through its anti-inflammatory actions, inflammation-dependent NFκB luciferase reporter assays were performed with 3T3-L1 adipocytes treated with omentin and/or TNFα. It was found that omentin decreases inflammatory transcription in 3T3-L1 adipocytes (85% decrease). In conclusion, omentin plays a role in the anti-inflammatory response, but can become overwhelmed and decreased by excessive and chronic pro-inflammatory cytokines.

## 52. Examining the Accuracy of Optical Coherance Tomography as a Method to Assess Retinal Nerve Fiber Layer Measurements in Alzheimer's Disease

Elizabeth Couser, MSW

Poster presentation; Room 349

Basic Science H

In Alzheimer’s disease research, limited attention has been placed on sensory change research, specifically in the area of vision. Visual dysfunction is a major component of Alzheimer’s disease (AD). As AD progresses, severe visual symptoms, such as a reduction in optic nerve thickness, a decrease in the retinal nerve fiber layer, a decrease in visual acuity, deficits in contrast sensitivity, as well as deficits in color and motion perception, may occur. A popular clinical method to examine ocular changes is optical coherence tomography (OCT). Several studies have used this method to measure the optic nerve and retinal nerve fiber layer (RNFL) width. A previous meta-analysis notes a distinct difference between retinal nerve fiber layer measurements in AD patients in comparison to RNFL width in control patients. This study seeks to shed light on the significance of OCT measurements of AD measurements only, as opposed to previous studies and meta analyses comparing AD to

control measurements, as reported in research articles. A literature search was conducted in the Medline database using the keywords “optical coherence tomography” or “OCT” or “retina*” and “Alzheimer’s”. Only studies that were completed within the last ten years and provided an average RNFL measurement were included. Eleven studies met this criteria. Though suggested as a possible future diagnostic method, OCT studies varied immensely in the measurement of the retinal nerve fiber layer in patients with Alzheimer’s disease, from 59.5µm to 93.18µm. This suggests that though OCT is able to detect differences between AD and control RNFL measurements, it may not be the most accurate or sensitive method to provide a precise range for diagnostic criteria in AD. Other clinical methods should be explored as options in detecting the ocular pathology of Alzheimer’s disease.

### 53. Confused Identity: Cancer Cells as Antigen Presenting Cells and Approaches to Enhance the Immunogenicity of Tumors

Irina Tiper, Wenji Sun, Tonya J. Webb

Poster presentation; Room 349

Basic Science H

Tumors frequently downregulate major histocompatibility (MHC) proteins to evade recognition by the immune system. The MHC class I-like protein, CD1d, activates a unique population of T cells, called Natural killer T (NKT) cells, which have potent anti-tumor effector functions. We hypothesize that tumors employ epigenetic mechanisms to regulate CD1d cell surface expression in order to evade immune detection. To test this hypothesis, we are examining the effects of cytokines and CD1d ligation on CD1d cell surface expression in tumor cells. We have performed time course and dose-response curves to assess the effects of IFNγ treatment on CD1d expression. CD1d expression is assessed by RT-PCR and flow cytometry and T cell assays are used to assess CD1d-specific activation of NKT cells. We found that lymphoma and renal cell carcinoma cells can serve as antigen presenting cells (APCs) to NKT cells. Upon this interaction, NKT cells produced cytokines (such as IFNγ) and lysed the tumor targets. We are currently investigating approaches to enhance the efficacy of this interaction. Collectively, these studies illustrate the potential of tumor cells to serve as APCs and to initiate an anti-tumor response through activation of NKT cells. Lastly, our studies will provide the basis for an NKT cell-based immunotherapy that not only enhances the immune response, but also increases the immunogenicity of the tumor itself.

### 54. Heme induces microglial CXCL2 release - a mechanism of neutrophil-mediated injury after intracerebral hemorrhage

David Kurland, Volodya Gerzanich, J. Marc Simard

Poster presenation; Room 349

Basic Science H

Neutrophils recruited into the CNS after intracerebral hemorrhage (ICH) are an important source of secondary injury. Chemokines are released following ICH, which act as chemoattractants for neutrophils and other inflammatory cells. In the setting of ICH in rodents, the neutrophil-specific chemokine CXCL2 is upregulated and is associated with severity of injury. CXCL2 signals via interaction with CXCR2, the same binding partner of CXCL8/IL-8, the most important neutrophil chemokine in humans. Heme, present in high concentrations locally after ICH, has recently been characterized as an endogenous ligand for Toll-like Receptor 4 (TLR4). TLR4 is well-known as the receptor for LPS and is critical in initiating the innate inflammatory response to bacterial infection. Additionally, TLR4 activation is upstream of CXCL2 production. Here we report results from in vivo experiments showing that physiological concentrations of heme lead to upregulation of CXCL2 by IHC. Furthermore, in cultures of freshly isolated microglia from adult rat hippocampus, application of heme results in significant release of CXCL2 as measured by ELISA. Finally, intrastriatal injection of CXCL2 leads to acute accumulation of neutrophils and produces complex neurobehavioral deficits in rats trained in the 5-Choice Serial Reaction Time task. We conclude that microglial release of CXCL2 may play a role in neutrophil-mediated injury after ICH.

## 55. GLUTEAL MUSCLE COMPOSITION DISCRIMINATES FALLERS FROM NON-FALLERS IN COMMUNITY DWELLING OLDER ADULTS

Mario Inacio, Alice S. Ryan, Woei-Nan Bair, Michelle Prettyman, Brock A. Beamer, and Mark W. Rogers

Poster presentation; Room 349

Basic Science H

Background: Impaired balance, loss of function, and falls are major problems associated with muscle impairments in older adults. However, the extent to which muscle composition and performance measures are associated with risk of falls in the elderly is unclear. This study evaluated lower limb muscle attenuation, intramuscular adipose tissue (IMAT) infiltration and muscle performance in older adults at high and low risk for falls.

Methods: Fifty-eight community dwelling older individuals (>65 yrs.) were classified into high (n=15) or low fall risk (n=43). Computed tomography (CT) was used to determine muscle attenuation and intramuscular adipose tissue (IMAT) of multiple thigh and hip muscles. Muscle performance was assessed with isokinetic dynamometry.

Results: For both groups, Rectus Femoris showed the highest muscle attenuation and lowest IMAT infiltration, and Gluteus maximus and Gluteus Medius/Minimus muscles had the lowest muscle attenuation and highest IMAT infiltration. High fall risk individuals exhibited lower muscle

attenuation and higher IMAT infiltration than Low fall risk subjects in most muscles, where the gluteal muscles were the most affected ($p<0.05$). High fall risk subjects showed a lower peak hip abduction torque ($p<0.05$). There were significant associations ($r=0.31$ to 0.53) between joint torques and muscle composition, with the strongest associations between Gluteus Medius/Minimus and hip abduction strength.

Conclusions: While "fallers" were generally differentiated from "non-fallers" by muscle composition, the most affected muscles were the proximal gluteal muscles of the hip joint accompanied by lower hip abduction strength, which may contribute to impaired balance function and increased risk for falls.

### 56. POSTURE-RELATED MODULATION IN MOTOR CORTICAL EXCITABILITY OF PROXIMAL AND DISTAL UPPER EXTREMITY MUSCLES

Shailesh S. Kantak, Wan-Wen Liao, George F. Wittenberg, and Sandy McCombe Waller

Poster presentation; Room 349

Basic Science H

Objective: Preliminary data from our lab shows increased corticospinal excitability to the proximal muscles of the arm in standing compared to the seated position in healthy adults using noninvasive neurophysiological testing with transcranial magnetic stimulation (TMS). This increased excitability could provide a neural advantage for rehabilitation. The purpose of this study was to determine if postural orientation had similar effects for cortical excitability to distal muscles of the arm.

Design: Within-participant

Setting: University TMS Research laboratory

Participants: 6 healthy adults (age 51.8± 8.1) with no history of seizures or neurological disability

Interventions: Recruitment curves (RC), intracortical inhibition and facilitation (SICI, ICF) were assessed for first dorsal interosseus (FDI) in sitting and standing.

Main Outcome Measure(s): Differences in the MEP amplitude/slope of RC, and percent SICI and ICF were assessed between sitting and standing postures for FDI with comparison to proximal results previously collected with these same subjects.

Results: FDI testing showed no significant difference between postures for recruitment curve outcome measures or intracortical inhibition or facilitation. Previous testing of the Anterior Deltoid (AD) showed there were significant and consistent increases in RC slope and MEP amplitudes during standing compared to sitting. SICI/ICF testing for AD revealed that in 4/5 subjects decreased inhibition was evident in standing compared to sitting position with little evidence of facilitation in standing.

Conclusions: Our results suggest that motor cortical excitability to proximal arm muscles is enhanced in standing compared to sitting but is not generalized to representation for distal muscles.

### 57. Characterization of the Acinetobacter baumannii heme oxygenase

Bennett Giardina, Angela Wilks

Poster presentation; Room 349

Basic Science E

The gram negative pathogen Acinetobacter baumannii has become an increasing threat for nosocomial infection and infection in combat personnel with trauma and burn wounds. Furthermore, the emergence of multi-drug resistant strains has increased the need for novel therapeutic strategies. One strategy involves targeting virulence factors rather than essential cellular processes for survival. Iron is a virulence factor essential for infection in bacterial pathogens. Many bacterial pathogens have developed mechanisms to use their hosts' heme containing proteins to survive in the iron limiting conditions imposed by the host. Iron uptake mechanisms include siderophores that scavenge iron from iron proteins as well as ABC transporter mediated uptake of iron, siderophores, and free heme. Once heme is inside the cell, iron is released by the oxidative degradation of heme to biliverdin by a heme oxygenase. Iron acquisition mechanisms by A. baumannii are poorly understood however we report the identification and characterization of a Pseudomonas aeruginosa homologue heme oxygenase (hemO). This heme oxygenase has been cloned, expressed, purified, and the primary biliverdin isomer product has been identified by HPLC.

### 58. Clinical candidate galeterone (VN/124-1 or TOK-001) induces the degradation of full-length and splice variant androgen receptors in human prostate cancer cell lines via PI3K-Akt-Mdm2 pathway: implications for prostate cancer therapy

Andrew K. Kwegyir-Afful, Ramalinggam Senthilmurugan, Puranik Purushottamachar, and Vincent C. O. Njar

Poster presentation; Room 349

Basic Science H

Galeterone (VN/124-1; TOK-001; 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene) is a proprietary oral small molecule under clinical development for the treatment of castration resistant prostate cancer (CRPC). Galeterone (hereafter referred to as gal) disrupts androgen receptor (AR) signaling through a unique triple mechanism of actions, including inhibition of CYP17 (androgen synthesis inhibition), AR antagonism and degradation of AR. Although we have previously unraveled the mechanisms of CYP17 inhibition and AR antagonism, the mechanism of AR degradation is still being elucidated. Here, we report for the first time the mechanism of gal - induced AR degradation and also that

gal depletes splice variant AR in human prostate cancer cells. We evaluated the effects of gal on full-length (wild-type and mutant) and truncated (splice variant) AR in LNCaP and CWR22Rv1 cells. Real-time PCR analysis of AR mRNA levels led to the hypothesis that gal's effect on AR occurs through a post-translational mechanism(s). The 26S proteasome inhibitor (MG132) blocked the effect of gal on AR depletion, thus suggesting that gal alters the ubiquitin-proteasome degradation pathway. In addition, gal caused perturbation of the PI3K/Akt pathway by increasing phosphorylation of Akt and Mdm2, and pretreatment with the PI3K inhibitor, wortmannin, robustly inhibited gal-dependent AR depletion. Targeted knockdown of Mdm2 with siRNA also inhibited the depletion of AR. Antibody pull-down data also indicated that gal treatment enhanced the formation of complex between Akt, Mdm2 and AR which promote phosphorylation-depended AR ubiquitination and its degradation by proteasome. The possible involvement of the proteasome-independent pathway (caspase-dependent) was eliminated because AR protein was reduced by gal to similar extents in the presence or absence of the pan caspase inhibitor, z-vad-fmk. Thus, in prostate cancer cells, our data support a model where gal increases phosphorylation of Akt and Mdm2 through the PI3K/Akt pathway. AR then undergoes ubiquitination by Mdm2 E3 ligase followed by AR degradation by proteasome. Using Western blot analyses and MTT cell viability assays, gal exhibited strong correlation between its ability to deplete AR and reduce cell viability. We also show for the first time that gal and some new analogs can degrade both full-length and truncated AR3 in CWR22Rv1. In conclusion, because gal is currently in phase 2 clinical trials as therapy against CRPC, its mechanism of AR degradation is of considerable clinical relevance. These discoveries of gal should generate excitement because it appears to be the only agent currently in clinical trial targeting CRPC progression driven by both full-length and splice variants AR.

### 59. Prevalence and Persistence of Depressive Symptoms and Inflammatory Cytokines in Older Women in the Year after Hip Fracture: Findings from the Baltimore Hip Studies

Matheny, M.E., Shardell, M.D., Lenze, E.J., Miller, R.R., Amr, S., Magaziner, J., Orwig, D.L.

Oral presentation; Room 349

Informatics, Policy, Social Science A

Background- Depressive symptoms have been associated with elevated levels of inflammatory cytokines in older adult populations, though prospective studies are lacking. This association has not been assessed in the hip fracture population, which is at risk for an increase in both depressive symptoms and inflammatory cytokines immediately postfracture. Persistently elevated depressive symptoms are predictors of impaired physical function after

fracture but have not yet been linked with impaired immunologic function.

Methods- Study participants were community-dwelling women age 65 and older with surgical repair of an incident hip fracture (N=136). At baseline and 2 months postfracture, depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS). At 2, 6 and 12 months postfracture, serum was analyzed for levels of IL-6 and sTNF-αR1. Generalized estimating equations were used to model relationships between depressive symptoms and inflammatory cytokines over the year postfracture.

Results- Clinically significant levels of depressive symptoms were present in 12.5% of the study sample at baseline. Baseline GDS scores were associated with higher levels of IL-6 and sTNF-αR1 at 2, 6 and 12 months postfracture, though not statistically significant. Participants with persistently high depressive symptoms had significantly lower sTNF-αR1 levels at 2 months (β=-383 pg/mL; 95% CI: -722,-45; p=0.02) than those without persistently high depressive symptoms, with increasing sTNF-αR1 levels over the year postfracture (p<0.0001).

Conclusions- Persistently high depressive symptoms are associated with altered immunologic function after hip fracture. Elevated cytokine levels in the presence of persistent depressive symptoms may represent a novel antidepressant treatment target in older adults.

## 60. Association between binge drinking and injury occurrence among 18 to 25 years of age student and their working peers: Findings from the national health interview survey 2006-2010

Marie-Claude Lavoie and Gordon Smith

Oral presentation; Room 349

Informatics, Policy, Social Science A

Background: Of all age groups, young adults have the highest annual rates of non-fatal injury. Excessive alcohol consumption is a well-established risk factor for injury. While the majority of young adults are not full-time students, the literature on alcohol consumption among young adults has focused predominantly on college students and seldom includes information on injury. In this study, we assessed the prevalence of injury and binge drinking among US students and working peers aged 18 to 25 and the effect of student/workers status on the association between injury and binge drinking. Methods: Using cross-sectional data from the 2006-10 National Health Interview Survey (N=11,450), we conducted weighted multivariable logistic regression to assess whether student or working status modified the association between binge drinking and medically attended injury. Results: Overall, 3.4% of both students and working peers reported an injury within the past three months. Binge drinkers had 1.5 times the odds of injury (CI=1.17-1.88) compared to non-binge drinkers among both students and working peers after adjusting for covariables.

Student/worker status did not modify the relationship between binge drinking and injury. Prevalence of binge drinking was statistically significantly higher among working peers (44%) compared to students (36%). Conclusion: Among young adults aged 18-25 years, the prevalence of binge drinking was significantly higher in working peers than in full-time students. The association between binge drinking and non-fatal injury was similar in students and working peers. The results support the need for broader population-based interventions

### 61. INDIVIDUAL AND ORGANIZATIONAL IMPACT OF COWORKER CONFLICT AND BULLYING: A PUBLIC SECTOR PERSPECTIVE

Mazen El Ghaziri, MPH, BSN, RN; Carla Storr, MPH, ScD; Matt London, MS; Jane Lipscomb, PhD, RN

Oral presentation; Room 349

Informatics, Policy, Social Science A

Background: Workplace violence is an enormous problem worldwide, one that has received increased attention in the U.S. and elsewhere over the past decade. A widespread and costly segment of this problem includes those actions which are perpetrated by a current or former fellow employee, so-called Type III violence in the U.S. The University of Maryland, with support from NIOSH, undertook a study to measure the impact and predictors of such an impact in relation to coworker conflict in a large public sector workforce through looking at negative acts and bullying. Methods: A cross-sectional web-based survey of coworker conflict was conducted in 2009. We describe the individual and organizational impact of coworker conflict including bullying and predictors of these impact using multinomial logistic regression and multilevel regression models. Individual impact was self-assessed through three impact questions: extent this experience negatively affected your work; influenced your intention to remain in current job; and negatively affected you personally. Organizational impact was assessed through actions like reporting the act or behavior to senior staff member; union or OMCE; police; division of human rights. Seeking counseling or help from EAP; transferring to another position or worksite or shift; completing an incident/accident report; pursing prosecution; charging leave credits; and filing workers compensation claims. Results: A total of 12,546 completed surveys were received, for an overall response rate of 72%. Overall, 44.2% of the participants experienced negative acts and 10% experienced bullying. The model results suggest that being female, job tenure between 2 and 20 years, those who experienced NAQ and bullying within poor work atmosphere and belonging to support/administrative bargaining unit are at a higher risk for high individual impact; While females between the age of 45 and 55, belonging to direct customer related agencies, who experienced NAQ and bullying within poor work atmosphere are at a higher risk for taking more than one action in relation to organizational impact. Conclusions: The impact of co-worker conflict is severe, and it is associated

with several factors where mechanism for intervention should be planned and evaluated.

### 62. Trends in Moderate to Severe Pain and Under-treatment for Pain among Medicare Beneficiaries in Nursing Homes, 2006-2009

Xian Shen, MS, Ilene Zuckerman, PhD, Bruce Stuart, PhD

Oral presentation; Room 349

Informatics, Policy, Social Science A

Research Objective: Pain management in older adults residing in nursing homes (NHs) continues to present challenges to health care practitioners and researchers. An overview of trends in pain and under-treatment for pain in NHs is needed. This study aimed to evaluate the trends in annual prevalence of moderate to severe pain and annual prevalence of under-treatment for pain among Medicare beneficiaries in NHs from 2006 to 2009.

Study Design: An observational study using linked data from 2006-2009 Medicare Current Beneficiary Survey (MCBS) and Minimum Data Set (MDS). MDS assessments are required by federal law to be completed for NH residents in Medicare certified NHs at admission, at significant change in status, quarterly and annually. Pain level was determined by a validated scale based on two items from MDS regarding frequency and intensity of pain. Moderate pain was defined as having daily mild to moderate pain, while severe pain was characterized as having daily pain at times horrible or excruciating. The unit of analysis for under-treatment was a pair of two consecutive MDS assessments with the first assessment indicating moderate or severe pain. An episode of under-treatment was identified if the moderate to severe pain reported at the first assessment was not alleviated at the subsequent assessment. The Cochran-Armitage trend test was performed to detect trends in moderate to severe pain and under-treatment over the 4-year study period.

Population Studied: Medicare beneficiaries residing in NHs who participated in MCBS between 2006 and 2009.

Principal Findings: The annual prevalence of moderate to severe pain among Medicare beneficiaries in NHs was 29.3% in 2006, 28.5% in 2007, 25.9% in 2008 and 22.2% in 2009. The decline was statistically significant (trend test, $p=0.0001$). For the analysis on under-treatment, 1307 pairs of assessments from 685 unique individuals were included. The mean time interval between assessments was 32.9 days. The annual prevalence of under-treatment for pain was 67.3% in 2006, 61.3% in 2007, 60.1% in 2008 and 65.1% in 2009 (trend test, $p=0.5047$) among the residents with moderate to severe pain at their first assessment. The probability of an episode of moderate to severe pain being undertreated significantly declined with increasing time interval between MDS assessments from 69.3% for 7 days, 64.8% for 14 days, 61.8% for 30 days, 59.4% for 90 days to 53.4% for more than 90 days (trend test, $p=0.0005$).

Conclusion: The annual prevalence of moderate to severe pain among Medicare beneficiaries in NHs consistently declined from 2006 to 2009. However, the annual prevalence of under-treatment for pain remained high over the study period with more than 60% of the 685 residents with moderate to severe pain being under-treated. The probability of an episode of moderate to severe pain being undertreated was inversely associated with time between MDS assessments.

Implications for Policy, Delivery or Practice: The study findings suggest that pain management in NHs gradually improved between 2006 and 2009 with fewer NH residents reporting moderate to severe pain. However, timely resolution of identified pain among Medicare beneficiaries in nursing homes remains problematic.

### 63. Proxy Response Bias in Assessing Health and Functional Status among Medicare Beneficiaries

Minghui Li; Bruce Stuart; Ilene H Zuckerman

Oral presentation; Room 349

Informatics, Policy, Social Science A

Research Objective: The objectives of the current study were (1) to examine the presence, direction, and magnitude of proxy response bias in health and functional status measures among Medicare beneficiaries participating in the Medicare Current Beneficiary Survey (MCBS), and (2) to assess whether the extent of proxy response bias varies by the relationship between the subject and the proxy (spouse, relative, and non-relative).

Study Design: This study used a pooled cross-section of data from the MCBS surveys in 2007, 2008, and 2009. Health and functional status was assessed across five domains: physical, affective, cognitive, social, and sensory status. A propensity score was used to create matched cohorts with and without proxy using a greedy matching technique. Variables included in the propensity score were age, gender, race, education, marital status, household size, income, Medicare status, and cognitive impairments. Subject self-reports and proxy-reports were compared on the five domains of health and functional status.

Population Studied: Community-dwelling Medicare beneficiaries.

Principal Findings: After applying the propensity score method, proxy response bias was not found in the sensory status domain (seeing [95% CI=0.92-1.12] and hearing [95% CI=1.00-1.20]). Proxy response bias was present in the other four domains. Two domains had moderate proxy response biases: affective status (OR: 1.19-1.25) and social status (OR: 1.52). The cognitive status domains (OR: 2.35-3.71) had large proxy response bias. Within the physical status domain, moderate proxy response bias was found in mobility (OR: 0.91-1.52) and large proxy response biases were found in activities of daily living (ADL) (OR: 1.31-4.05) and instrumental activities of daily living (IADL) (OR: 1.69-6.95).

A question regarding subjects' difficulties in managing money was associated with the largest proxy response bias (OR=6.95). In subgroup analyses, the magnitude of proxy response bias was almost twice as high for relative or non-relative proxies versus spouse proxies in the physical and cognitive status domains.

Conclusions: Proxy response bias was present in the physical, affective, cognitive, and social status domains but not in the sensory status domain. Specifically, proxies tend to over-report health and functional limitations in comparison to subjects themselves. For questions involving private information, unobservable factors, or complex answers, the magnitude of proxy response bias was large. When assessing the impact of different relationships on proxy response bias, the presence and direction remained the same, but the magnitude varied.

Implications for Policy, Delivery or Practice: The current study provides useful findings for survey organizations that wish to minimize proxy response bias. At the questionnaire development stage, objective, observable, or easy questions that do not call for judgments by proxies are preferred. At the survey execution stage, when the subject is unable to respond, interviewers should identify a proxy who has a close relationship with the subject and is familiar with the questions being asked. The results of this study will also help researchers better use survey data. When using survey data obtained from proxies, researchers should describe possible effects of proxy response bias on study results.

## 65. The Need to Conduct Future Research on the Benefit of the Prostate Specific Antigen Screen Test Using the Value of Information Framework

Emily S. Reese, Susan dosReis, Arif Hussain, Ebere Onukwugha, Ming Tan, C. Daniel Mullins

Oral presentation; Room 349

Informatics, Policy, Social Science A

Background: Prostate cancer (PC) is the second most common cancer in men worldwide and the second leading cause of cancer deaths in men in the United States. Recently, the prostate specific antigen (PSA) test used to screen and diagnosis PC has been questioned due to concerns regarding clinical utility and its inability to accurately identify men with PC. This research aims to estimate the Value of Information (VoI) of the PSA screening research and to determine whether future PSA screening research should be focused on specific populations.

Methods: This research uses the Minimal Modeling Approach (MMA) in order to determine the expected value of information for PSA research. The population expected value of information (pEVI) for racial (African Americans and non-African Americans) and age (65-75 years, 76-85 years, >85 years) subgroups will be determined. Investigators will model survival based on published randomized controlled trials of PSA

screening and will use data from the Surveillance Epidemiology and End-Result (SEER)-Medicare dataset for both survival and costs. Investigators will structure analyses by modeling the net benefit of men who received a prostate specific antigen screening exam between 2000 and 2007.

Resuts: VoI is recognized for providing a framework for estimating the expected benefits of clinical research. Due to the controversy surrounding the PSA screening test, patients and clinicians are challenged when trying to make informed decisions regarding diagnosis and treatment of PC.

Conclusions: This research seeks to determine where the greatest return on research investment would provide a more accurate evidence base for PSA screening for PC.

### 66. Impact of Heterogeneity of Treatment Effects on Survival, Cost Effectiveness, and Coverage of Androgen Deprivation Therapy in Metastatic Prostate Cancer Patients

Abdulla M. Abdulhalim, C. Daniel Mullins, Eberechukwu Onukwugha, Arif Hussain, David Yoder and Francoise Pradel

Oral presentation; Room 349

Informatics, Policy, Social Science A

For many oncology treatments, uncertainty in clinical decision making at the physician level and drug coverage decision making at the payer level is ubiquitous due to large evidence gaps and the lack of reliable patient-centered research. Despite the availability of a dearth of comparative effectiveness and cost effectiveness studies, most of that evidence is based on population averages and very little address patient heterogeneity using sound statistical methodology. Decision-makers, like physicians and payers who use that evidence, use their judgment to make individualized decisions that affect individual patients. For example, physicians deal with individual patients at their clinics and more often than not rely on their experience with patients whom they have seen in the past to make tailored treatment decisions for patients they see in the future. Similarly, payers look at the overall effectiveness and value of drugs to make coverage decisions and implement strategies to restrict access only for certain subpopulations. Therefore, it is important to establish an evidence base that appropriately assesses patient heterogeneity in response to treatments, or what is known as heterogeneity of treatment effects (HTE), and disseminate that evidence in a manner that is usable by decision makers to inform individualized treatment and coverage policy. HTE refers to the non-random variability in the response to a specific treatment between different individuals given their characteristics. Accounting for that heterogeneity in response to treatment allows physicians to practice personalized medicine by targeting treatments to those patients who will benefit most from it, while avoiding treatments in patients for whom there is expected harm or no expected benefit. Physicians are primarily interested in selecting the best treatment the first time (at

diagnosis) based on readily available clinical information for each patient. Further, failing to account for HTE could mean that health care payers may initially be paying for treatments that are ineffective and, in the long run, payers may be paying for additional downstream costs attributed to initially ineffective or harmful therapies. Health care payers are therefore requesting pharmacoeconomic evidence that is representative of their beneficiaries to tailor coverage decisions for their subpopulations. Using metastatic prostate cancer (mPC) as a case study, this dissertation proposal aims to examine how patient heterogeneity affects response to primary androgen deprivation therapy (PADT) among incident mPC patients, how patient heterogeneity affects the value (i.e. cost effectiveness) of PADT among incident mPC patients, and how HTE evidence and variations in cost effectiveness impacts payer's coverage and reimbursement decisions. This will be accomplished by using the Surveillance Epidemiology and End Results (SEER) – Medicare linked datasets and conducting qualitative semi-structured interviews with payers. Specifically, the aims are: 1) To estimate the HTE associated with PADT receipt in elderly Medicare beneficiaries with mPC across levels of Gleason score and age at diagnosis. Treatment effect will be defined as a) the overall and prostate cancer specific survival benefit and b) time to chemotherapy initiation; 2) To estimate the variation in cost and incremental cost effectiveness ratio (ICER) of PADT for mPC Medicare beneficiaries across subgroups defined by Gleason score and age at diagnosis; and 3) To explore how payers use HTE evidence in making coverage and reimbursement decisions in the metastatic PC setting

### 67. Patterns of Bone Active Medication Utilization Before and After Hip Fracture

Rasheeda Johnson, Emma G. Sheldon, Mark Jones, William G. Hawkes Ph.D. , Jay Magaziner Ph.D., and Denise Orwig Ph.D.

Poster presentation; Room 349

Informatics, Policy, Social Science B

Bone-active medications (BAMs), including prescription (RxBAM), calcium and vitamin D, increase bone mineral density (BMD) and reduce the risk of fracture, yet, it is unclear who is likely taking these medications prior to and after hip fracture. This study sought to examine the prevalence of BAM use at time of hip fracture, over the year post fracture and identify baseline factors that predict BAM use following hip fracture. Participants were 180 community-dwelling women age 65+ with incident hip fracture from the fourth cohort of the Baltimore Hip Studies (BHS-4) testing an in-home exercise intervention. Study assessments were conducted within 15 days of hip fracture and at 2, 6, and 12 months post fracture. Prior to the fracture, 85 (47%) took calcium/vitamin D only, 5 (3%) took RxBAM only, 50 (28%) took both calcium/vitamin D and RxBAM, and 39 (22%) took neither. Over 12 months post fracture, only 29 (16%)

participants took RxBAM during the entire study period. Of those who were using RxBAMs at any timepoint post fracture (81) only 26 (32%) were new users while many participants started and stopped treatment or never started. RxBAM use at baseline ($p<0.0001$) and history of osteoporosis ($p<0.001$) predicted future RxBAM use at 2, 6 and 12 months. Despite known benefits, few people at risk for hip fracture are taking BAMs at the time of fracture, and more importantly, new user rates after hip fracture are very low indicating a large proportion at risk for further BMD loss and future fractures.

### 68. Optimizing Independent Eating for Institutionalized Older Adults with Dementia: A Systematic Review

Wen Liu, Mmed, Bmed; Elizabeth Galik, PhD, CRNP; Barbara Resnick, PhD, RN, CRNP, FAAN, FAANP

Poster presenation; Room 349

Informatics, Policy, Social Science B

Background The ability to eat or feed by oneself is crucial to maintain good physical and psychosocial quality of life for older adults with dementia. Effective interventions can alleviate eating or feeding dependence and enhance mealtime pleasure. None of current reviews on relevant intervention studies provided any evidence on optimizing oral eating independence among this population comprehensively. The purpose of this review is to evaluate the benefits of currently retrievable interventions on optimizing independent eating for older adults with dementia.

Design A systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement.

Data sources Pubmed, Medline (OVID), EBM Reviews (OVID), PsychINFO (OVID), and CINAHL (EBSCOHost) were searched between January 1980 and December 2012 by using keywords as dementia, Alzheimer, feeding, eating, mealtime(s), oral intake, autonomy, nutrition, intervention and any matched terms. Other sources included Google Scholar and relevant bibliographies.

Review Methods Eligibility criteria were established by defining the population, intervention, comparator, outcomes, timing and setting of interest. Studies were reviewed by screening title and abstract, and assessing full-text for eligibility. Data of eligible studies were extracted with a self-developed structured tool. Eligible studies were classified by intervention, accessed for quality using the Quality Assessment Tool for Quantitative Studies, and graded for evidence using the Grading of Recommendations, Assessment, Development and Evaluation Working Group criteria.

Results Seventeen intervention studies (8 RCTs), including a total of 1918 older adults with dementia and 318 caregivers from more than 47 institutions, were identified, and classified into five types: training/education program,

environment/routine modification, feeding assistance, nutritional supplement, and mixed interventions. Five studies were strong, 9 moderate and 3 weak in quality. Weaknesses of current literature included lack of randomization and/or control group, small sample size without power analysis, single setting, high withdrawal rate, lack of theory-based interventions, lack of measurement reliability and/or validity evidence, lack of blinding during data collection, inadequate statistical analysis and plausible confounding bias. "Training program" demonstrated moderate evidence to decrease feeding difficulty. "Environment/routine modification" with or without "feeding assistance" were insufficient to improve mealtime communication and participation. Evidence was low in "education program" and high in "nutritional supplement" not to improve eating ability.

Conclusions This review provides some evidence for clinical practice and points out priorities for nursing research regarding optimizing eating independence in older adults with dementia. Current evidence is based on a body of research with moderate quality and existing weaknesses, and needs to be further explored with more rigorous studies.

### 71. ANTIPSYCHOTIC DURATION OF USE AMONG MEDICAID-INSURED PRESCHOOLERS, YOUNG CHILDREN AND ADOLESCENTS

Mehmet Burcu, Julie Zito, Daniel Safer

Poster presentation; Room 349

Informatics, Policy, Social Science B

Research Objective: Over the last two decades, the increased use of psychotropic medications singly or in combination, often for unlabeled indications, has been profound. In particular, antipsychotic medications to treat behavioral disorders in youth are growing concern due to limited data on antipsychotic effectiveness for attention deficit hyperactivity disorder (ADHD), as well as increasing awareness of serious treatment-emergent adverse events. However, patterns of antipsychotic use in relation to their duration of by age group and psychiatric diagnosis among youth populations are lacking. The main objectives of this study were to characterize antipsychotic medicated youth, and to assess total days of exposure to these agents, specifically by age group and psychiatric diagnoses among Medicaid-insured youth.

Study Design: Using a one-year cross-sectional design, bivariate analyses and multivariable quantile regression modeling were employed to assess characteristics of antipsychotic medicated youth and to assess differences in median duration of exposure to these agents across age groups [preschoolers (2-5 years); young children (6-12 years); adolescents (13-17 years)] mainly by clinician-reported psychiatric diagnoses and additional study covariates. Other covariates included Medicaid-eligibility groups (SSI [Social Security Income], foster care, TANF [Temporary Assistance for Needy Families], CHIP [the State Children's Health Insurance Program]), gender,

race/ethnicity, U.S. region, and other psychotropic medication classes. A hierarchical approach to diagnoses was adopted from Olfson et al.(2006) for youth with diagnoses in more than one psychiatric category to create mutually exclusive groups, beginning with schizophrenia/other psychoses and followed by pervasive developmental disorders and mental retardation, bipolar disorder, disruptive disorders, ADHD, depressive disorders, anxiety disorders, adjustment disorder, and any other psychiatric diagnosis.

Population Studied: In a mid-Atlantic state Medicaid program, computerized administrative claims for youth aged 2-17 years with 12 months of enrollment in 2006 were assessed.

Principal Findings: Among 266,590 continuously enrolled Medicaid-insured youth, the majority (56.0%) were Medicaid-eligible through TANF program followed by CHIP (36.2%). The study population was predominantly African American (56%) and aged 6-12 years (42.8%). The prevalence of antipsychotic use was 3.4%. Youth with ADHD or disruptive behavior disorders, and youth who were Medicaid-eligible through TANF or CHIP constituted the largest group of antipsychotic users, in particular for youth aged 12 years or younger. Compared to SSI-eligible youth (with disability), youth in foster care had longer median durations of antipsychotic use across the age groups (preschoolers: 180 vs. 150 days; young children: 261 vs. 225 days; adolescents 245 vs. 221 days). Among antipsychotic users, clinician-reported bipolar disorder increased with increasing age. However, among preschoolers, the longest duration of antipsychotic use occurred diagnosed with pediatric bipolar disorder (203 median days) in the study year.

Conclusions: Overall, in an annual cohort of continuously enrolled Medicaid-insured youth, the exposure to antipsychotic agents was 6 or more months in a year. Long durations of use were particularly notable in youth with clinician-reported diagnosis of pediatric bipolar disorder, ADHD, and disruptive behavior disorder.

Implications for Policy, Delivery or Practice:

Long term effectiveness, safety, and monitoring of antipsychotic medications in youth, particularly those diagnosed with externalizing behavior disorders and off-label (FDA-unapproved) conditions are needed. In addition, state Medicaid program oversight is warranted.

### 72. A Multilevel Modeling Analysis of Depressive Symptoms among Older Adults Living Alone

Kyeongmo Kim, MSW

Poster presentation; Room 349

Informatics, Policy, Social Science B

Limited empirical evidence is known regarding neighborhood effects on depressive symptoms among Korean older adults living alone. Understanding of the neighborhood effects on depressive symptoms could help to reach the larger number of

older adults by using environmental intervention strategies. To fill the existing gap, this study, guided by Andersen's behavioral model of health service utilization, examines whether individual characteristics are associated with depressive symptoms, and identifies whether neighborhood characteristics are predictors of depressive symptoms among Korean older adults living alone, controlling for individual characteristics.

Data using a cross-sectional design and stratified probability samplings were collected from 1,023 Korean older adults living alone in the Busan Metropolitan area in South Korea. A multilevel modeling analysis was conducted to test the hypothesis that neighborhood characteristics are predictive of depressive symptoms. The results revealed that male gender, lower income, lower level of functional abilities, higher number of chronic diseases, and lack of social networks were related to higher risk of depressive symptoms. There was no relationship between age and depressive symptoms. Neighborhood poverty, elderly concentration, and the ratio of senior centers to older adults were not associated with depressive symptoms.

On the basis of this study's findings, these results can be used for practice and policy to target and provide educational outreach programs and supportive services to people in high risk populations. This study suggests that future research may examine more applicable neighborhood characteristics by means of a longitudinal design.

## 73. Influences on Interdisciplinary Collaboration Experience among Health Sciences

Sang Jung Lee

Poster presentation; Room 349

Informatics, Policy, Social Science B

Objective: Interdisciplinary education can improve the skills and behaviors that are needed for effective interdisciplinary collaboration, and consequently, it will positively influence healthcare outcomes and quality. (Barr, 2002; Meads & Ashcroft, 2005; Curran, Sharpe, Forristall, & Flynn, 2008). It is important for healthcare professionals to learn their roles and to understand other professions' values in learning their process before they actually enter interprofessional teamwork settings. Therefore, this study examines factors that influence health sciences students' positive experiences of interdisciplinary collaboration, which can contribute to future interprofessional collaboration.

Methods: A cross-sectional study design with a non-probability convenience sample was used. Interprofessional Students Interdisciplinary Survey was conducted in a Mid-Atlantic public school. The online survey method used Qualtrics software (www.qualtrics.com) to gather data from study participants. Responses of 202 from health sciences students (Nursing, Medicine, Pharmacy, and Social Work) were used for statistical analyses.

Findings: A binominal logistic regression analysis yielded significant results of the model (X2(9) = 32.66; p <.001). Pseudo-R2 values indicate that the model is useful in explaining group membership (Cox & Snell =.17, Nagelkerke =.25). The Hosmer & Lemeshow goodness-of-fit test also indicates a good fit between the observed data and the predictive model (X2(8) = 4.60; p =.80). Students who were currently working in an interdisciplinary setting (Exp(B) = 2.75, p <.05, 95% CI:.16, .83), students who had positive attitudes toward interdisciplinary healthcare teams (Exp(B) = 1.12, p <.01, 95% CI: 1.04, 1.20), and students who were male were more likely to have positive experience with interdisciplinary collaboration (Exp(B) = .30, p <.05, 95% CI:1.18, 9.42). The overall success rate (79.8%) of predicting students with positive experience improved compared to the baseline model (75.8%), with sensitivity 30.2% and specificity 95.6%.

Conclusion: Health sciences students who were working in an interdisciplinary setting as a form of field placement, internships, or part/full-time job were more likely to belong to the positive experience group. Headrick and Khaleel (2008) suggested creation of interprofessional experiences by involving students in interprofessional teams and by involving trainees from one profession working with other health professionals as their mentors or teachers. Health sciences students and professionals generally reported positive attitudes toward interprofessional teamwork or education (Curran et al., 2008; Curran et al., 2010). However, stereotyped impression of other professions, maturity, higher education, and affiliation in medical school have been identified as barriers to positive attitudes toward interprofessional teamwork or collaboration (Pollard, Miers, & Gilchrist, 2004; Tanaka & Yokode, 2005; Rudland & Mires, 2005; Curran et al., 2010). Therefore, educators and students in health sciences professional disciplines need to put effort into preventing the barriers. Male students were more likely to have a positive experience with interdisciplinary collaboration than those who were female. Considering that female professionals more appreciated the process of collaboration and more engage in interdisciplinary collaboration (Carr, Pololi, Knight & Conard, 2009; Rijnsoever & Hessels, 2011), future repetitive studies are necessary to confirm gender effect on interdisciplinary collaboration.

Health sciences schools and educators should offer opportunities for interdisciplinary collaboration practices. Educators and students in health sciences disciplines should put effort into promoting positive attitudes toward interdisciplinary teamwork. When students have positive experience with interdisciplinary collaboration, they will be more open to collaborating with other professionals and the collaboration will contribute to better healthcare outcomes and quality.

### 74. VALIDATION OF DYNAMIC WEIGHT BEARING APPARATUS AS A MEASUREMENT TOOL FOR INFLAMMATORY PAIN IN MICE

Griffioen, M. A., Dernetz, V. H., Yang, G. S., Griffith, K. A., and Renn, C. L.

Poster presenation; Room 349

Informatics, Policy, Social Science C

Background: Preclinical pain assessment contributes to the investigation of novel and therapeutic treatments for attenuating symptoms in pain research. Weight bearing and gait evaluation is often used to examine a variety of pain etiologies. However, traditional behavioral tests such as the von Frey test are limited as they can cause stress and restrain movement in the mouse. The use of dynamic weight bearing (DWB) apparatus can be a novel end-point for the assessment of non-evoked pain in the mouse model. Purpose: The aim of this study was to evaluate a new dynamic weight bearing apparatus based on pressure captors in the Complete Freund's Adjuvant (CFA) model of inflammatory pain in mice. Methods and sample: To assess the effect of CFA in the DWB test, 30 male C57BL/6J mice weighing 20-25g data were randomized to a case group (N=15) and a control group (N=15). The case group received an intra-plantar injection of 25µl of CFA at a concentration of 1mg/ml and the control group received saline as vehicle in the left hind paw. Data were collected at baseline, 3 hours, 1, 3 and 7 days after the injection. To verify inflammation, volume and thickness were measured with plethysmometer and caliper. Results: Inflammation occurred at 3 hours post CFA injection and persisted for the experimental duration (7 days). A significant weight shift measured by DWB was noted as a reduction in the left paw load in comparison to right paw in terms of mean over time at 3 hours, 1 day and 3 days after injection ($p<.05$), A significant difference in the surface distribution was noted at 3 hours and 1 day following injection in the left paw compared to the right paw in terms of mean over time ($p<.05$). Conclusions: DWB could provide a new approach to assess non-evoked mechanical hypersensitivity in the mouse intra-plantar CFA model of inflammatory pain.

### 75. RELIGIOSITY, DEPRESSIVE SYMPTOMS, AND HEALTH-PROMOTING BEHAVIORS AMONG KOREANS IN THE UNITED ARAB EMIRATES (UAE)

Hee Jun Kim, MSN, RN; Michelle Pearce, PhD

Poster presentation; Room 349

Informatics, Policy, Social Science C

Aim: To explore the relationship between religiosity, depressive symptoms, and health promoting behaviors among Korean expatriates living in the UAE.

Background: Expatriates face numerous challenges that can impact their health and well being because of different environment and culture of the new country. Many studies have demonstrated a positive associations between religiosity and health; however, the role religiosity might play among Koreans living in the Middle East area has not been explored.

Methods: A cross-sectional, descriptive design was used. A total of 117 Koreans in Dubai were recruited through a private clinic, and data were collected between November, 2010 and March, 2011. Questionnaires included frequency of religious attendance, depression items from the depression, anxiety, and stress scale (DASS), and health-promoting lifestyle behaviors (HPLP). General linear model was used to test mean differences of depression and HPLP according to religious attendance. Mediating effect of depression between religious attendance and HPLP was tested using Baron and Kenny steps.

Results: Means of depression and total HPLP score were significantly different by religious attendance ($F=5.476$, $p=.021$; $F=6.494$, $p=.012$, respectively). Attendance for religion was a significant predictor for self-actualization ($\beta=.256$, $p=.006$) and stress management ($\beta=.245$, $p=.008$), controlling for gender and education status. Depression showed partial mediating effects between religious attendance and interpersonal support, and stress management.

Conclusion: Religiosity is an important factor for health-promoting behaviors for Korean expatriates residing in the Middle East. Participating in religious activities may reduce depressive symptoms by facilitating positive support and resources, resulting in greater interpersonal relationships and stress management. Addressing depression among this population should also be considered to improve health behaviors.

## 76. INCREMENTAL COST ANALYSIS OF SKELETAL RELATED EVENTS (SREs) AMONG ELDERLY MEN WITH STAGE IV METASTATIC (M1) PROSTATE CANCER (PCA) IN SEER-MEDICARE

Jayasekera J, Onukwugha E, Mullins CD, Seal B, Bikov K, Hussain A

Poster presenation; Room 349

Informatics, Policy, Social Science C

Objective:Patients diagnosed with metastatic PCa are predisposed to SREs, such as bone surgery (BS), pathologic fracture (PF) and spinal cord compression (SCC). There is limited information in the literature regarding the incremental costs associated with SREs among stage IV M1 PCa patients.

Methods:We analyzed patients aged 66 or older with an incident SRE, following a PCa diagnosis with (AJCC) M1 disease. Cases diagnosed between 2000 and 2007 were identified from the linked Surveillance, Epidemiology, and End Results (SEER) - Medicare dataset. Patients were followed until death, Medicare disenrollment or end of the study (December 31, 2007). The total costs for each patient were calculated for the 12-month pre-period and the 12-month post-period relative to first SRE after PCa diagnosis. Incremental costs were assessed and reported as average percent change in pre-post period costs. Subgroup analysis was carried out separately for individuals who survived and died within the 12-month post-period. A sensitivity analysis was carried out for a 6-month pre-post interval. The analysis was

conducted from a US Medicare system perspective.

Results:Application of inclusion criteria resulted in 1,234 stage IV M1, PCa patients with SREs. The average age was 78 years and 11% were African American. Five, mutually exclusive SRE groups were evaluated: PF-only (n = 180), SCC-only (n = 634), BS-only (n = 200), PF with BS (n = 163), SCC with BS (n = 57). The average percent increase in the total SRE costs in the post-period compared to the pre-period was 67%. The average percent increases in costs for each of the subgroups were as follows: PF-only; 53%, PF with BS; 71%, SCC-only; 64%, SCC with BS; 88%, and BS-only; 70%. Sub group analysis showed a 77% increase in costs among individuals who were alive and a 60% increase in costs among those who died within the 12 month post-period. The average percent increase in SRE costs for a pre-post period of 6 months was 75%.

Conclusions:The percentage increase in costs post-SRE varies by type of SRE and survival post-SRE.

### 77. Exploring Preferences for Evidence-Based Treatments for Attention Deficit Hyperactivity Disorder (ADHD) from a Patient-Centered Perspective

Xinyi Ng, John F P Bridges, Emily Frosch, Gloria Reeves, Susan dosReis

Poster presenation; Room 349

Informatics, Policy, Social Science C

Research Objective: Attention-deficit/hyperactivity disorder (ADHD) is a chronic condition that affects over 5 million U.S. children aged 4-17 years old. It is a child mental health disorder for which there are a number of well-established evidence-based medication and behavioral treatments, yet adherence has been problematic with as many as 50% of children who discontinue treatment within 60 days. Untreated ADHD can have life-long consequences resulting from academic and social difficulties. A body of evidence has shown that caregivers have great concerns with using medication for their child's ADHD, however, they often reluctantly use it when all other options have been exhausted. To date, there has been little patient-centered research to explore treatments matter most to caregivers of children with ADHD. The objective of this research was to identify which types and combinations of evidence-based treatments for ADHD that caregivers most prefer.

Study Design: The study was designed to test a discrete choice experiment survey of caregiver preferences for evidence-based components of treatment for ADHD. Treatment components included frequency of medication use, location of child therapy, coordination with the school, parent behavior management training, communication with the provider, care management professional, and monthly cost of care. There were three variations of options in how each treatment type could be delivered. One delivery option per treatment type was presented in a profile and caregivers selected the

best and worst option from the profile. The survey included 18 questions, each with a slightly different profile. Utilities were estimated for each variant of a treatment options. This was a proportion of the number of times an option was selected as best minus the number of times it was selected as worst divided by the total number of times the option was shown to participants. The maximum difference between the highest and lowest utility within a treatment component was used to assess the relative importance of that component to participants.

Population Studied: Thirty-seven caregivers who had a child currently receiving mental health services were recruited across four family support groups between December 2012 and January 2013.

Principal Findings: In considering treatment options for their child, caregivers ranked type of parent behavior management training and frequency of medication use as the two most important treatment components. The least important component was the location of child therapy. Treatment options that were associated with positive utilities for caregivers were: location of child therapy (range: 0.108 – 0.288), coordination with school (range: 0.090 – 0.284), and care management professional (range: 0.032 – 0.211). Out-of-pocket cost was consistently associated with a negative utility (range: -0.405 – -0.613) across all levels. Parent behavior management training (23%) followed by medication frequency (19%) accounted for the treatment options with the maximum difference in utility, and thus were among the most important components of ADHD treatment. Specifically, participants placed a greater value on medication use 7 days a week all year round and on learning behavior management techniques one-on-one with a therapist.

Conclusion: This preliminary research suggests that the way medication is used and how caregivers learn behavior management techniques are important to caregivers. The findings carry important implications for delivering patient-centered care to caregivers who are the surrogate decision-makers for a child.

Implications for Policy, Delivery or Practice: A patient-centered approach to care must incorporate individual preferences of which type of treatment and in which way it is delivered to patients. This work holds great promise for developing patient-centered care management approaches in delivering evidence-based treatments that caregivers will adhere to. The implication for clinical practice is the advancement of personalized treatment.

### 78. Post-Marketing Surveillance of Insomnia-related Adverse Events

Xing Chen, Minghui Li, Sarah Tom, Sheila Weiss

Poster presentation; Room 349

Informatics, Policy, Social Science C

Objectives: In 2011, nearly one fifth of the adults in the U.S. suffered from chronic insomnia, defined as difficulty initiating or maintaining sleep. Insomnia is associated with the development of certain chronic diseases, including diabetes, cardiovascular disease, obesity, and depression. People with insomnia are also at high risk for substance abuse and involving in accidents and disasters. Insomnia may be caused by disease, other sleep disorders, medicines, or substances. The objective of this study is to investigate what medications are likely to be associated with insomnia.

Methods: All insomnia-related adverse events reported in the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database during 1997 and 2011 were included. Qscan-FDA (DrugLogic, Inc., Reston, Virginia) was used to get access to the AERS data and conduct the analysis. The insomnia related adverse events were ranked separately by suspected drugs and by primary suspected indications. We then tested whether the reporting trends and patterns differed by the date of report, sex, and age group for 2005 - 2011.

Results: The number of insomnia-related adverse events reports tended to rise since 1997. Between 2005 and 2011, AERS collected 2,428,580 total medication-related adverse event reports. Among them, 49,731 (2.05%) were insomnia-related. The reporting trends and patterns were very similar in both sexes and across age groups in adults from 2005 to 2011. Within this period, the top ten medications most frequently associated with insomnia-related adverse events were eszopiclone (N=5,069), varenicline (N=4,635), acetaminophen (N=3,524), acetylsalicylic acid (N=3,024), levothyroxine (N=2,766), quatiapine (N=2,621), zolpidem (N=2,375), alprazolam (N=2,282), atorvastatin (N=2,053), and paroxetine (N=2,051). The top ten indications associated with insomnia-related adverse events were insomnia (N=3,920), smoking cessation therapy (N=3,504), depression (N=2,873), multiple sclerosis (N=1,626), drug use for unknown indication (N=1,309), bipolar disorder (N=1,000), blood cholesterol increased (N=764), attention deficit/hyperactivity disorder (N=762), pain (N=723), and osteoporosis (N=682). The top ten suspected drugs and primary suspected indications varied by different sex and age groups.

Conclusions: The public awareness of the importance of sleep quality has increased over time. The current study provides useful findings for prescribers that wish to minimize insomnia-related adverse events. Prescribers should recognize medications associated with insomnia, prescribe them with caution, and provide patient counseling if necessary. Prescribers should also screen for drugs using without indication, properly prescribing these drugs can contribute to the avoidance of unwanted side effects and improve the sleep quality among patients. Some diseases may be undertreated, which resulted in insomnia. Prescribers should recognize them and manage them appropriately to

minimize patient suffering from insomnia.

### 79. The Reciprocal Causation Between Cyber-delinquency and Depression During Adolescence: Autoregressive Cross-Lagged Modeling

Jeongseok Kong

Poster presenation; Room 349

Informatics, Policy, Social Science C

Overview: This study compared the reciprocal longitudinal, causal relations between cyber-delinquency and depression of 2,844 adolescents. Autoregressive cross-lagged modeling was used to explore the relationship between cyber-delinquency and depression. Results indicated that cyber-delinquency impacted adolescents' depression for all youth with no gender differentiation and vice versa.

Learning Objectives:
(1)Participants will understand the concept of cyber-delinquency and the prevalence of cyber-delinquency in Korea.

(2)Participants will learn the basics of the theoretical connection between cyber-delinquency and depression through a discussion of the recent literature.

(3)Participants will be introduced to the reciprocal relationship between depression and cyber-delinquency.

Purpose: In accordance with the rapid development of information and communication technology, there are many serious issues of adolescents' delinquent behaviors on cyberspace by using anonymity. For exploring these cyberspace issues, investigating the reciprocal relations between cyber-delinquency and depression is clinically meaningful because the comorbidity of depression and conduct problems are the most common disorders during adolescence (Borelli & Prinstein, 2006; Wolff & Ollendick, 2006). Therefore, the purpose of this study is to verify the relationship between cyber-delinquency and depression, a gender difference with regard to this relationship, and longitudinal changes in this relationship over time.

Methods: The present study used 2,844 student (1,320 girls and 1,524 boys) surveys the Korean Youth Panel Survey (KYPS), which was a 5-year (2004 to 2008) longitudinal study, provided by the National Youth Policy Institute. Cyber-delinquency of adolescents in this study refers to general crimes and delinquent acts committed by adolescents mainly in cyberspace. To measure adolescents' cyber-delinquency, six dichotomous items (where "1" represented yes and "0" represented "no") were used: hacking, spreading false information, downloading illegal software, using other people's Internet ID or social security number, obscene and violent chatting. Depression of adolescents in this study refers to loneliness, sadness, anxiety and suicidal ideation. To measure depression of adolescents, six Likert-type items that are included in the DSM-IV-TR diagnostic criteria for major depression diseases were used. To study the longitudinal

relation between cyber-delinquency and depression, we used autoregressive cross-lagged modeling (ACLM). In addition, we performed multigroup autoregressive cross-lagged modeling to explore gender differences in the relationship between cyber-delinquency and depression. The present study used AMOS 18.0 software and used the Full Information Maximum Likelihood (FIML).

Results: The cross-lagged coefficients for cyber-delinquency predicting later depression were significant ($\beta$=.020 ~ .028, $p<.05$), as were the cross-lagged coefficients for depression predicting later cyber-delinquency ($\beta$=.040 ~ .043, $p<.001$). Concerning the autoregressive coefficients, moderate relationships ($\beta$=.30 ~ .38, $p<.001$) between adjacent time points in cyber-delinquency and also moderate relationships ($\beta$=.43 ~ .45, $p<.001$) between adjacent time points in depression were found. Results from multi-group analysis revealed that there was no gender difference in the reciprocal relationship between cyber-delinquency and depression, but there was significant gender difference in depression only from grades 4 to 6.

Conclusions and Implications: Results, based on multivariate autoregressive cross-lagged modeling, indicated that cyber-delinquency had effect on adolescents' depression and vice versa. Having two or more comorbid disorders simultaneously can cause more serious symptoms than having only one disorder (Rockhill, Vander Stoep, McCauley, & Katon, 2009). In order to prevent this increased severity of symptoms, finding of this study through the understanding of reciprocal relationship can be used to develop a program to prevent the comorbidity of depressive symptoms and cyber-delinquency.

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## 80. UP-TO-DATE LONG-TERM SURVIVAL OF OLDER ADULT PATIENTS WITH LUNG CANCER: PERIOD ANALYSIS

TANG,YING and SMITH, GORDON

Poster presenation; Room 349

Informatics, Policy, Social Science D

Introduction:Lung cancer remains to be the leading cause of cancer-related deaths among older adults in the United States. While treatment and care for lung cancer patients have evolved over the years, it is not known whether long-term survival rate has improved for the older population.

Objective: To estimate up-to-date long-term survival proportion and relative survival ratio of older adults with lung cancer the perid of 2000-

2008 and to compare the proportion with those of the other age groups.

Methods: SEER were used to abstract lung cancer patients diagnosed between 1973 and 2008. All the patients were followed up since their cancer diagnosis until December 31, 2008. Patient's vital status, either dead or alive, and follow-up time between cancer diagnosis and death or the censor date of December 31, 2008, were recorded. Period analysis was employed to calculate observed long-term survival proportion for three 3-year intervals between 2000 and 2008. Population mortality data for the period of 2000-2008 in the United States was applied to the cancer population to calculate the expected number of death. Relative survival ratio was then calculated as the ratio of the observed survival proportion to the expected survival proportion.

Results: 5-year RSRs during 2000-2008 by age groups are: 22.2% in 40-44 year-old, 20.4% in 45-54, 20.0% in 55-64, 17.7% in 65-74, and 14.0% in 75+. During 2000-2008, among older patients aged 65 or over, 5-year RSRs were 18.7% and 13.6% among females and males, 16.3%, 11.5%, and 17.2% among whites, blacks, and other races, respectively. 5-year RSR of older patients was 50.2%, 22.2%, 3.2%, and 9.1% for localized, regional, distant, and un-staged lung cancers.

Conclusion: Long-term survival of cancer patients has improved during the period of 2000-2008. However, the enhanced survival varies greatly among different age groups. Patients 45 years of age at the time of diagnosis showed the most improved long-term survival while older adults appeared to show much less improved survival.

### 81. LONGITUDINAL RELATIONSHIP BETWEEN OBESITY AND MUSCULOSKELETAL DISORDERS AMONG REGISTERED NURSES

Kihye Han, Alison M. Trinkoff, Carla L. Storr, and Kyungsook Kim

Poster presentation; Room 349

Informatics, Policy, Social Science D

Research Objective: Nurses, the largest group of health care workers, are at greater risk of work related musculoskeletal disorders (MSD) than other workers. There is a lack of knowledge about the relationship between obesity and MSD in nurses. In addition to the physically demanding nature of nursing work and work-related sleep problems attributed to scheduling, some hypothesize that obese employees are more likely to have poor ergonomic fit and lack of alertness at work due to sleep difficulties thus resulting in injury or disorder of the joints or other tissues in the back or the upper/lower limbs. This study examined the impact of obesity on reported MSD of back, neck and shoulder among registered nurses.

Study Design: This study utilized data from the longitudinal Nurses Worklife and Health Study that had collected information on self-reported weight and height at baseline and MSD symptoms six and 15 months in subsequent waves. Overweight/obesity was defined as 25

or more body mass index. MSD cases were defined as those with relevant symptoms in the back, neck, and/or shoulder lasting one or more weeks, or at least monthly, with moderate or more pain, on average. Using binomial regression models, we related baseline obesity to the new occurrence of three types of MSD (back, neck, shoulder). Other potential risk factors were also included in models: physical and psychological demands, restless and/or inadequate sleep, age, race/ethnicity, caring for dependents, and lack of exercise.

Population Studied: Out of the 4,229 eligible actively licensed nurses sampled randomly from two US states, a cohort of 2,273 nurses working in nursing within the past year of the baseline survey participated in all three waves. Study nurses had similar characteristics to US nurses in terms of age (47 years old on average), race (87% White), gender (95% female), education (48% diploma/associate's degree) and work setting (54% working in hospitals).

Principal Findings: The estimated proportion of overweight/obese nurses was 55%. Cumulative incidence of MSD was 21% for back, 14% for neck, and 17% for shoulder problems. When compared to underweight/normal weight nurses, overweight/obese nurses were significantly more likely to have an incident MSD: back (OR=2.17, 95% CI=1.70-2.78), neck (OR=1.72, 95% CI=1.31-2.25) and shoulder (OR=1.97, 95% CI=1.51-2.58). These associations were attenuated slightly after including other potential risk factors: back (OR=1.97, 95% CI=1.48-2.63), neck (OR=1.61, 95% CI=1.17-2.22) and shoulder (OR=1.71, 95% CI=1.24-2.37). Nurses with incident MSD were also significantly more likely to report high physical and psychological demands, restless and inadequate sleep than asymptomatic nurses.

Conclusions: Obesity was significantly associated with nurse MSD. Findings suggest that efforts to reduce obesity, as well as job demands and impaired sleep, among nurses could be beneficial to minimize risks of MSD.

Implications for Policy, Delivery or Practice: To prevent MSD in nurses, collective actions for reducing obesity would be helpful. A favorable organizational climate that offers healthier food choices and meal breaks for sufficient time to have a proper meal can decrease obesity risk and future health problems such as MSD. Additionally, ergonomic re-design of workplace to decrease demands and efforts to improve quality and quantity of sleep by providing healthful work schedules may also be beneficial to protect nurse MSD.

### 84. Quality of Pharmacotherapeutic Management of Atrial Fibrilation for Nursing Home Residents

Sarah K. Dutcher, Ilene H. Zuckerman

Poster presentation; Room 349

Informatics, Policy, Social Science D

Objective: Stroke prevention is a cornerstone of pharmacotherapeutic management of individuals with atrial

fibrillation (AF). Older nursing home (NH) residents are at especially high risk for stroke based on their age and poorer health status. This study describes the quality of stroke prevention in AF NH residents.

Methods: Using a retrospective cohort design with Medicare administrative claims linked to the Minimum Data Set, older (≥65 years), long-stay NH residents with AF and Medicare Parts A, B, and D coverage were identified. The index month was an individual's first month in a NH following the first observed AF diagnosis between 1/1/2007-12/31/2009. Quality measures were based on ACC/AHA guidelines for AFIB management and were defined as monthly use of antithrombotic medications and receipt of recommended laboratory monitoring (i.e., INR). Average monthly prevalence is reported.

Results: The cohort (n=23,935) was predominantly female (76.9%), white (87.7%), and aged ≥80 (74.3%). Individuals were followed for a median of 12 months (range 1-36) and 53.8% died during the study period. The average monthly prevalence of any antithrombotic use was 44.8%, of which warfarin comprised 76.4%. Among those receiving warfarin, 84.8% had evidence of laboratory monitoring test during the month. Age was negatively associated with antithrombotic use ($p<0.001$) but there was no difference in antithrombotic use between males and females. Caucasians had the highest prevalence of use while Asians were least likely to receive an antithrombotic ($p<0.001$).

Conclusion: Use of antithrombotic medications is low among long-stay NH residents with AF despite guidelines that recommend their use, although monitoring is adequate. Better understanding of the individual- and facility-level factors influencing management decisions may assist in developing interventions to improve care for NH residents with AFIB.

### 85. MULTIDISCIPLINARY PHYSICIAN CARE AND MORTALITY IN HEPATOCELLULAR CARCINOMA

Chirikov VV, Mullins CD, Hanna NN, Breunig IM, Seal B, Shaya FT

Poster presentation; Room 349

Informatics, Policy, Social Science D

OBJECTIVES: Multidisciplinary physician care has increased for many cancers yet little evidence exists for hepatocellular carcinoma (HCC). The study objective was to evaluate the association between multidisciplinary care and mortality in HCC. METHODS: Non-transplant treated patients with an HCC primary diagnosis in 2000-07 were followed-up in SEER-Medicare data. Multidisciplinary care was operationalized as the number of distinct specialists seen pre-treatment, including surgeons, radiology oncologists, intervention radiologists, hematologists/medical oncologists, gastroenterologists, and generalists. We built survival analysis models controlling for treatment, demographics, and clinical characteristics, and adjusted for selection/survival bias using inverse probability weighting and time-

dependent covariates. RESULTS: Of 3320 treated HCC patients, 1323 (40%) saw one, 1250 (38%) saw two, and 747 (23%) saw three or more disciplines. Liver directed therapy and radiation was administered to a greater proportion of patients who encountered multiple specialists compared to those who saw a single discipline, who received more resection and chemotherapy. Multidisciplinary care was associated with stage 3 HCC and hepatitis C presence. In contrast, patients from rural areas and those diagnosed with stage 4 HCC saw fewer specialists prior to treatment. In time-dependent, propensity score adjusted survival analysis, patients who saw three or more disciplines had 10% (P=0.05) reduced mortality, compared to those who saw one discipline. When stratified by treatment received, patients on chemotherapy who saw three or more disciplines had 28% (P=0.002) reduced mortality. CONCLUSIONS: Multidisciplinary care for non-transplant HCC patients was associated with reduced mortality, particularly among chemotherapy recipients. While adjusting for selection and survival bias, our study may not fully capture the confounding effects of referral patterns among specialists on treatment and survival. Our findings provide evidence that may further support the development of models for coordinated health care delivery such as accountable care organizations (ACOs).

### 86. ACCULTURATION AND DEPRESSION AMONG OLDER IMMIGRANTS

Seokho Hong

Poster presentation; Room 349

Informatics, Policy, Social Science D

Acculturation research has been growing for a couple of decades, but empirical systematic research has rarely evaluated the relationship between acculturation and depression among ethnic minority elderly. The objective of this systematic review is to provide empirical evidence concerning the relationship between the experience of linguistic and cultural adaptation and depression for immigrant elderly. For the systematic review, the sources were based on the electronic databases with full texts. The base search string using Boolean format was (depression or mental health) AND (elderly or older adult or senior) AND (acculturation or culture change) AND (immigration). Selected articles were: (1) peer-reviewed studies that are available through the Health Science and Human Services Library at the University of Maryland; (2) studies written in English or Korean; (3) quantitative studies; (4) studies related to four kinds of key terms. Out of 311 articles, 13 derived through screening and eligibility assessment. Relatively, participants in included studies had the high prevalence of depression. Also, even though the studies used a different analysis and different scale to measure acculturation, almost all the studies found association between acculturation and depression in common. The importance of acculturation as a factor of immigrant elderly's depression was found. Multidimensional acculturation approaches should be used among practitioners, and standardized sub-

domains of acculturation measure should be developed for future research.

### 87. LONGITUDINAL ASSOCIATION OF RESTLESS AND INADEQUATE SLEEP TO WORK RELATED MUSCULOSKELETAL DISORDERS AMONG REGISTERED NURSES

Kyungsook Kim, Alison M. Trinkoff, Carla L. Storr, Kihye Han

Poster presentation; Room 349

Informatics, Policy, Social Science E

Research Purpose: Previous studies have shown that reduced sleep increases risk of work-related injury. It is unclear whether restless sleep (RS) and/or inadequate sleep (IS) together impact musculoskeletal disorders (MSD) injury. The purpose was to explore the relation of self-reported RS and IS to work-related MSD among registered nurses.

Methods: This study used secondary survey data from the longitudinal Nurses Worklife and Health Study on self-reported RS and IS and work-related MSD. Three wave surveys of 2,273 registered nurses were analyzed. Using binomial regression models, the relationship between wave 1 (baseline) RS and/or IS and risk of incident MSD in waves 2 or 3 (6 and 15 months after baseline respectively) was examined. Other potential risk factors were: age, caring for children, caring for dependents, exercise, smoking, obesity, and work schedules.

Findings: RS (compared to no RS) increased the risk of having a MSD of all three body regions by 2.6 times. IS (compared to no IS) was associated with a doubling of MSD risk in all body regions.

Compared to nurses without any RS and IS disturbance, nurses with only RS had more than 3.6 times the risk of MSD (back OR=3.57, 95% CI=2.14-6.15; neck OR=3.67, 95% CI=2.06-6.66; shoulder OR=3.62, 95% CI=2.06-6.47). For nurses with only IS the risk was 2.3 (back OR=2.25, 95% CI=1.62-3.15; neck OR=2.67, 95% CI=1.84-3.88; shoulder OR=2.42, 95% CI=1.68-3.49). Nurses with both RS and IS showed an additive interaction on MSD (back OR=4.84, 95% CI=3.48-6.82; neck OR=6.47, 95% CI=4.52-9.37; shoulder OR=5.84, 95% CI=4.10-8.40). However, the additive interaction exists only for neck area after adjustment for confounders (neck OR=5.53, 95% CI=3.69-8.39).

Conclusions: RS and IS by themselves are associated with a doubled risk of developing an MSD. When combined, the risk ranges from 4.8-6.5 times the risk for those without these sleep difficulties, suggesting the importance of getting adequate sleep to avoid work related injuries.

Implications for Public Health: Educational intervention for sleep improvement strategies may help prevent nurse MSD. Screening for undiagnosed sleep disorders may be beneficial as well.

### 88. A REVIEW OF EFFECT OF EDUCATION ON INFORMATION LITERACY IN NURSING STUDENTS

SeonYoon Chung and Amy Daniels

Poster presenation; Room 349

Informatics, Policy, Social Science E

The objective of this paper was to conduct a systematic review to evaluate the effects of education on information literacy in graduate nursing students. Published, peer-reviewed, English-language, studies were identified in a search of Medline, CINAHL, Web of Science, ERIC, and LISTA from 1987 to 2012. Eligible studies included graduate and non-graduate nursing students including RN-BSN students; Information Literacy including information search, evaluation, processing, communication, or dissemination; Education including program, courses, or trainings. Ineligible studies were qualitative studies, conference proceedings, dissertations, case studies, and "Grey" or "Fugitive" literatures. A PRISMA flow chart and table of final articles were presented.

### 89. PATIENT-CENTEREDNESS IN THE DESIGN OF CLINICAL TRIALS

C. Daniel Mullins, PhD, Joseph Vandigo, MBA, Jason Zheng, PhD and Paul Wicks, PhD

Poster presenation; Room 349

Informatics, Policy, Social Science E

Evidence from clinical trials should contribute to informed patient decision making and a learning healthcare system. However, patients frequently find participating in clinical trials meaningless or disempowering. Moreover, patients often do not incorporate trial results directly into their decision making. The lack of patient centeredness in clinical trials may be partially addressed through innovative trial designs. For example, designing trials to adapt in a pre-specified manner to changes in clinical practice would motivate patients and their healthcare providers to view clinical trials as more applicable to real-world clinical decisions. Incorporating new information from outside the trial could help to generate and synthesize relevant evidence to maximize benefit, minimize risk, and offer flexibility to support the learning process and medical decision making. Innovation in clinical trial design would transform the evidence generation process to be more patient centered, providing patients with an incentive to participate or continue participating in the clinical trial process. However, in order to achieve the transformation to patient-centeredness in clinical trial decisions, there is a need for transparent and reliable methods and education of trial investigators and site personnel.

### 90. HOSPITALIZATIONS, EMERGENCY DEPARTMENT VISITS AND PLACEMENT STABILITY OUTCOMES ASSOCIATED WITH ANTIPSYCHOTIC USE AMONG YOUTH IN FOSTER CARE

Tai MH, dosReis S, Desai, B, Reeves G, Shaw T

Poster presenation; Room 349

Informatics, Policy, Social Science E

Research Objective: The increase in use of antipsychotic medications among youth in foster care, despite

the mounting evidence of adverse metabolic effects, is a critical national concern that has resulted in federal mandates for better monitoring of utilization to ensure clinical appropriateness. The goal of antipsychotic treatment is to minimize symptoms, which in youth are typically aggression and severe mood dysregulation, so that youth are able to be maintained successfully in outpatient treatment settings. However, few studies have examined the impact of treatment with second generation antipsychotics (SGA) on improved mental health-related and child welfare-related outcomes among youth treated in community settings. The objectives of this study were to 1) examine the prevalence of antipsychotic treatment among youth in foster care; 2) determine if antipsychotic use is associated with hospitalization and emergency department (ED) visits; and 3) assess the association of antipsychotic use with stability of placement in child welfare.

Study Design: This was a retrospective, cross-sectional study that used data from the 2010-2011 child welfare administrative records and the Medicaid claims for all mental health and pharmacy services during the study period. Antipsychotic exposure was categorized as treatment with a single versus concomitant use. Concomitant use was defined as 30 days or more of overlap with two or more antipsychotics. The dependent variables, measured over the 24-month study period, were: a) number hospitalizations, overall and psychiatric-related; b) number of ED visits; c) number of transitions in foster care placement. Poisson regression models were used to examine the association between single versus concomitant antipsychotic use with a) number of hospitalizations (overall and psychiatric); b) the number of ED visits; and c) the number of transitions in foster care placement. The regression models were adjusted for age, gender, and race.

Population Studied: The focus of this study was the 2,463 youth who were entered the child welfare system on or before January 1, 2010 and remained in child welfare through December 31, 2011.

Principal Findings: Of the 2,463 youth in this study, 511 (21%) received at least one antipsychotic medication during the study period and 119 of the 511 (23%) received concomitant antipsychotic treatment. Compared to youth who received treatment with a single antipsychotic, those who received antipsychotics concomitantly had significantly more hospitalizations (mean: 2.9 vs 0.7, $p<0.05$), ED visits (mean: 2.7 vs 1.8, $p<0.05$) and transitions in foster care placement (mean: 3.5 vs. 2.4, $p<0.05$). Youth who received antipsychotics concomitantly had a 3.9 and 1.5 higher rate of hospitalizations and ED visits, respectively, compared to youth who received a single antipsychotic, even after adjusting for age, race/ethnicity, and gender. In terms of foster care placement, 129 (32.9%) of youth with single antipsychotic use had no transition in foster placement compared with 17 (14.3%) of youth with concomitant antipsychotic use.

Concomitant antipsychotic use remained a statistically significant determinant of foster care placement stability, after adjusting for age, race/ethnicity, and gender. Compared to single antipsychotic users, concomitant users had a 1.4 higher rate of transitions in foster care placement, adjusting for age, race/ethnicity, and gender.

Conclusions: Nearly one-quarter of youth with any antipsychotic received more than one agent concomitantly. The findings suggest that youth who receive antipsychotics concomitantly may have more severe impairment that resulted in more hospitalization and ED visits and a greater number of transitions in foster care placement. Thus, a considerable number of youth have less than optimal mental health and child welfare outcomes and are difficult to maintain in a stable outpatient setting.

Implications for Policy, Delivery or Practice: The findings carry important implications for cross-agency collaboration in the monitoring and oversight of antipsychotic treatment for youth in foster care. This potentially could result in less complex medication therapy, less use of costly inpatient and ED care, better family unification, and ultimately better child outcomes.

### 91. PATHWAYS TO CARE FOR EARLY PSYCHOSIS SPECIALTY CLINICS

Karen McNamara, Sapna Mendon, Lisa Dixon

Poster presenation; Room 349

Informatics, Policy, Social Science E

Increased duration of untreated psychosis (DUP) has been implicated in increased illness severity and reduced treatment response for early psychosis. As part of efforts to reduce DUP and improve outcomes, clinics specializing in early interventions in psychosis have emerged around the world. However, the low incidence rate of schizophrenia, coupled with complex differential diagnosis make this population particularly difficult to identify. Few studies have explored pathways to care to clinics specializing in early psychosis in the US.

The Recovery After an Initial Schizophrenia Episode Implementation and Evaluation Study (RAISE-IES) engaged in a wide variety of outreach efforts to identify potential clients and connect them with program services. We refer to individuals seeking services who made contact with the program as “Service Seekers”. "Disposition" describes the admission status of each service seeker. The findings will

• Describe the types of initial contacts, outreach methods and referral sources used to connect service seekers with a specialty treatment program

• Compare the frequency that different types of initial contacts, outreach methods and referral sources are used by service seekers

• Compare whether service seeker dispositions vary based on the types

of initial contacts, outreach methods or referral sources

• Describe reasons why service seekers contacting a specialty clinic are not admitted

• Compare the frequency of reasons why service seekers are not admitted based on initial contacts, outreach methods or referral sources.

### 92. AN INTEGRATED HELP-SEEKING THEORY AND POTENTIAL APPLICATIONS FOR EARLY PSYCHOSIS

Karen McNamara

Poster presenation; Room 349

Informatics, Policy, Social Science E

An extensive body of literature exists describing theories for help-seeking behavior for health and mental health services; however, most current literature on pathways to care for early psychosis is atheoretical. Two mental health help-seeking theories were reviewed for potential relevance in pathways to care in early psychosis: The Network Episode Model (NEM; Pescosolido,1992) and Unified Health Theory (UHT; Jaccard, Dodge, & Dittus, 2002). The UHT emphasizes individual decision making which impacted during early psychosis. The NEM describes the influence of environmental and social factors on an individual's pathway to mental health services; however, it may discount the individual decision-making process. An emphasis on external influences for help-seeking may minimize the important agency of individuals when choosing or refusing healthcare services.

Neither theory sufficiently described the process that occurs as an individual understands the need for and seeks treatment. Individuals experiencing psychosis may struggle to articulate the nature of their problem, and social supports and the treatment system may be essential in helping individuals to construct an understanding of their illness and seek help. However, in order to fully engage in treatment, individuals must perceive a benefit in receiving treatment services.

A proposed Unified Health-Behavior Network Model(UHNM)integrates these two help seeking models and expands them by adding information seeking behaviors applying a symbolic interactionist approach to the relationships among individuals, their environment, and their supports. Pathway to care data for specialty early psychosis programs are used to support the proposed theory.

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