

Time

Sessions Overview



CALIFORNIA
NORTHSTATE
UNIVERSITY

CNU Research Day
January 20th, 2017
1st Annual Meeting

Schedule And Abstract Booklet

8:00am - 9:00am	Registration
9:00am - 9:20am	Opening Remarks and Inaugural speech by CNU President, Alvin Cheung, PharmD, MHSA
9:20am - 9:40am	Dr. Cathy Yang (Vice President of Biotechnology & Dean of Graduate Studies, CNU)
9:45am- 9:55am	Dr. Leo Fitzpatrick (Assistant Dean of Research Affairs, Associate Professor, Department of Pharmaceutical & Biomedical Sciences, CNUCOP)
10:00am - 10:45am	Keynote speech – Dr. Toni-Joy Burke, PharmD (Gilead Sciences, Inc.)
10:50am - 11:10am	Student Presentation – COP (Pachai Moua, P3) - " HIC (MDFIC) is a protein that interacts and co-localizes with the RELT family of TNFRs"
11:15am - 11:35am	Student Presentation – COM (Vikas Shahi, M2) – " Use of Serial Hemoglobin in Blunt Trauma Patients to Detect Occult Blood Loss"
11:40am - 12:00pm	Faculty Presentation – CHS (Dr. Heather Brown) – "The goals and structure of Freshmen Research Initiative (FRI) and Capstone Research experiences"
12:00pm - 1:15pm	Poster Presentation – Lunch Break
1:15pm - 1:35pm	Student Presentation – COP (Michael Yadao, P2) – " Trends in Hospitalizations as a Result of Chemotherapy-Induced Adverse Effects"
1:40pm - 2:00pm	Faculty Presentation – COM (Ishwarlal Jialal MD, PH.D) – " Circulating and Cellular Biomarkers of Inflammation in Metabolic Syndrome "
2:05pm - 2:25pm	Faculty Presentation – COP –Dr. Justin Lenhard – " The Combination of Polymyxin B, Ampicillin/Sulbactam, and Meropenem Combats Polymyxin-Resistant Acinetobacter baumannii Over 14 Days"
2:30pm - 2:50pm	Student Presentation – COM (Mohammad Wiese, M2) – " Neurostructural Morphology in CNS-Specific RPGRIP1L Deficient Mice"
2:55pm - 3:35pm	Poster Presentation - Coffee Break
3:40pm - 4:00pm	Student Presentation – COM (Kayla Sheehan, MS1) – " Novel Methods of Medical Education: Clinical Cases as Preparation for the Wards and Beyond"
4:05pm – 4:25pm	Student Presentation – COP (Vinna Nam, P2) – " The Impact Of Telepharmacy Relating to Medication Safety in Rural Areas of California"
4:30pm – 5:00pm	Awards for Students Poster and Oral Presentations & Awards for Grant Winners
5:00pm	Meeting Concludes – Depart or catch up with Poster Presentations

Research Day January 20, 2017 Program at a glance

Abstracts for Oral Presentations

Activation of T cell S1P Receptor 1 Attenuates the Expression of TGF-beta1 from Fibroblasts

Paia Lor¹, Helen Le¹, George Talbott², Zhuqiu Jin²

¹Third-Year Student of Pharm.D. Program, College of Pharmacy, California Northstate University, Elk Grove, CA 95757

²Department of Pharmaceutical & Biomedical Sciences, College of Pharmacy, California Northstate University, Elk Grove, CA 95757

Sphingosine 1-phosphate (S1P) exerts a wide variety of biological functions via G protein-coupled S1P receptors, such as: migration, maturation, proliferation, and survival. Infiltration of T cells in patients with myocardial infarction is associated with increased heart attack and fibrosis. Our previous work demonstrated that conditional knockout of T cell S1P receptor 1 (S1P1) renders mouse hearts vulnerable to fibrosis, and that activation of S1P1 in T cells may attenuate the fibrotic pathway in fibroblasts. The mechanism driving these observations remains unknown. In this study, SEW2871 (1 μ M), a selective S1P1 agonist, was added into the medium of NIH3T3 fibroblasts cultured individually or co-cultured with Jurkat CD4 T cells for 48 hours. Cell viability was determined by trypan blue exclusion and the expression of TGF-beta1 in fibroblasts was determined with Western blotting. After 48 hours, SEW2871 enhanced the expression of TGF-beta1 in fibroblasts cultured individually and, conversely, decreased the expression of TGF-beta1 in fibroblasts co-cultured with CD4 T cells. Pretreatment with W146, a selective antagonist of S1P1, abolished the effects of SEW2871 on the expression of TGF-beta1 in fibroblasts or fibroblasts co-cultured with T cells. To explore the membrane/nuclear localization of S1P1 in T cells, S1P (1 μ M) was added into CD4 T cell-containing RPMI 1640 medium supplemented with charcoal-stripped albumin for 1 hour. Cytoplasmic, membrane, nuclear (soluble and chromatin-bound), and cytoskeleton fractions of T cells were isolated and purified. S1P induced translocation of S1P1 from the membrane to the nuclear fraction. W146 abolished this translocation. These results suggest that activation of fibroblast S1P1 is profibrotic whereas activation of CD4 T cell S1P1 is anti-fibrotic, and that translocation of S1P1 from the plasma membrane to the nucleus in T cells may reduce the expression of TGF-beta1 in fibroblasts.

Use of Serial Hemoglobin in Blunt Trauma Patients to Detect Occult Blood Loss

Vikas Shahi¹ and Dr. William Mower²

¹California Northstate University College of Medicine

²David Geffen School of Medicine at UCLA: Emergency Department

Serial hemoglobin measurements (ΔHgb) are frequently measured in blunt trauma resuscitations to aid in the early identification of patients with significant blood loss, occult injury, and the need for intervention. However, the utility of ΔHgb has yet to be rigorously studied. To this end, we enrolled 251 blunt trauma patients 18 years of age and older receiving blunt trauma evaluations at a Level I Trauma Center (Ronald Reagan UCLA Medical Center). We measured two hemoglobin levels spaced 5 minutes apart and calculated the difference, ΔHgb , for each patient. We also recorded whether each patient required an intervention to treat their injuries. Interventions included operation or procedure to control hemorrhage, radiographic embolization, administration of blood and blood products, exsanguination, or administration of 3 or more liters of IV fluids. Our population of 192 males and 59 females had a mean age of 40 (Standard deviation: ± 17) years. 56 patients required an intervention and 195 patients did not. The mean ΔHgb was $-0.12 (\pm 1.01)$ for patients requiring an intervention, and $-0.13 (\pm 0.78)$ for patients not requiring an intervention. A ΔHgb of -1.0 showed a sensitivity of 12.5% and a specificity of 87.2%. A ΔHgb of 0.0 showed the most robust combination of sensitivity (71.4%) and specificity (43.6%). A ΔHgb of $+1.0$ showed 98.2% sensitivity and 6.7% specificity. We found the area under the receiver operator curve (ROC) to be 0.53, indicating that ΔHgb is only slightly better than a random coin toss in predicting the need for intervention in blunt trauma patients. The results of our study indicate that the practice of measuring serial hemoglobin levels provides little benefit, is likely to misdirect and confuse, and should be omitted from blunt trauma assessments.

Trends in Hospitalizations as a Result of Chemotherapy-Induced Adverse Effects

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Background: Chemotherapy often causes severe complications that may lead to hospitalizations and negatively affect clinical outcomes. Over time new treatments have been developed and guidelines have been updated to limit the negative impact of these complications. **Objective:** To evaluate the incidence and trends of hospitalizations as a result of certain chemotherapy-induced adverse effects among cancer patients. **Methods:** This was a retrospective cohort study that utilized the National Inpatient Sample database, within the Healthcare Cost and Utilization Project, to evaluate hospitalizations of cancer patients from 1997 to 2010. Hospitalizations were selected using ICD-9 diagnosis codes for aplastic anemia (284), neutropenia (288.00), nausea and vomiting (787.01 – 787.03), and pneumocystis (136.3). Cancer prevalence data, from the Surveillance, Epidemiology, and End Results program, were used to derive the incidence of hospitalizations due to chemotherapy induced adverse effects per 100,000 cancer patients. Linear regression was performed to assess trends in incidence while logistic regression assessed trends in mortality. Multivariable analyses were used to adjust for age, gender, race, and primary source of payment. **Results:** Among the observed chemotherapy-induced adverse effects, the adjusted changes in incidence per year per 100,000 persons with cancer were observed for patients hospitalized due to anemia (4.9 [-24.6 – 34.5]), neutropenia (-23.7 [-45.4 – -2.1]), nausea and vomiting (-4.9 [-9.6 – -0.1]), and pneumocystis (-0.8 [-1.4 – -0.3]). Additionally, the adjusted decreases in the odds of mortality per year were observed for hospitalizations due to anemia (0.947 [0.946 – 0.948]), neutropenia (0.946 [0.944 – 0.948]), nausea and vomiting (0.949 [0.946 – 0.953]), and pneumocystis (0.964 [0.959 – 0.968]). **Conclusion:** Among this national cohort of cancer patients hospitalized due to chemotherapy induced adverse effects, small but statistically significant decreases in hospitalization incidence and mortality may suggest that newer treatment strategies and practices may reduce adverse effects and their impact.

THE ROLE OF INFLAMMATION IN METABOLIC SYNDROME: DYSREGULATION OF CIRCULATING AND CELLULAR BIOMARKERS

ISHWARLAL JIALAL MD, Ph.D FRCPATH

CNSU-COM

Metabolic Syndrome (MetS) is a very common global disorder comprising the cardio-metabolic risk cluster and predisposes to both diabetes and Atherosclerotic Cardiovascular Disease (ASCVD). It affects 35% of American Adults and predisposed to both Diabetes (>5 fold) and CVD (2-4 fold). In this study we investigated the role of inflammation in nascent MetS without the confounding of diabetes or CVD. Circulating biomarkers including pro-inflammatory cytokines, chemokines, adipokines and cellular biomarkers of Inflammation were assayed. Compared to controls there were significant increased levels of hsCRP, IL-6, IL-8, MCP-I, Leptin, RBP-4, HOMA-IR etc. Also there were significant decreases in both total and high molecular weight adiponectin and omentin-1 levels. Using flow cytometry we showed an increase in receptor abundance for both toll like receptor (TLR) 2 and 4, increase in mRNA and their downstream signaling including secreted biomediators and nuclear factor Kappa-B and p38MAPKinase activity. In subcutaneous Adipose tissue we showed increase macrophage density and inflammation. In conclusion inflammation is a pivotal player in the Metabolic syndrome and appears to be due to a conspiracy between macrophages and adipose tissue, and contributes to insulin resistance and the premature risk for CVD.

This study was funded by an ADA Grant to I.Jialal

The Combination of Polymyxin B, Ampicillin/Sulbactam, and Meropenem Combats Polymyxin-Resistant *Acinetobacter baumannii* Over 14 Days

Justin Lenhard, PharmD

California Northstate University, College of Pharmacy, 9700 W Taron Dr, Elk Grove, CA 95757

Background: The emergence of polymyxin-resistant *A. baumannii* has forced clinicians to use empiric, non-optimized triple antibiotic combinations; however, combinatorial pharmacodynamics (PD) of such regimens are poorly defined. Our objective was to characterize the PD of single, double, and triple combinations of polymyxin B (PB), ampicillin/sulbactam (A/S), and meropenem (MERO) against polymyxin-resistant *A. baumannii* in a hollow fiber infection model (HFIM).

Methods: Two extensively-resistant *A. baumannii* isolates resistant to PB (MIC 32 mg/L for 03-149-2, MIC 64 mg/L for N5406), A/S (MIC both strains 32/16 mg/L), and MERO (MIC both strains 64 mg/L) were investigated in a HFIM over 14 days at a 10^8 CFU/mL inoculum. PB (3.33 mg/kg x 1 dose, then 1.43 mg/kg q12h [AUC_{0-24h} 48.2 mg*h/L, AUC_{ss} 35.9 mg*h/L], $t_{1/2}$ 8h), A/S (8/4g q8h, $t_{1/2}$ 1.5h), and MERO (2g q8h, $t_{1/2}$ 1.5h, 3h prolonged infusion) were all administered alone and in double/triple combinations. Viable counts and PB population analysis profiles were conducted.

Results: Against strain 03-149-2, single agents and double combinations were unable to achieve sustained killing. PB + MERO was the only double combination that resulted in early bactericidal activity, with a maximal reduction of $4.2 \log_{10}$ CFU/mL at 6h; however, drastic regrowth occurred by 72h and the percentage of the population capable of growing on 10 mg/L of PB was amplified 55,932 times higher compared to 0h. The triple combination also achieved a $4.2 \log$ reduction at 6h, followed by eradication at 96h. Against strain N5406, PB or MERO alone and the combination of both agents achieved maximal reductions of 0, 0.6, and 1.9 logs, respectively, followed by regrowth. In contrast, A/S alone and in combination eradicated N5406. The triple combination displayed the most rapid killing with a $3.2 \log$ reduction at 6h, while A/S alone, A/S + PB, and A/S + Mero resulted in 0.1, 0.6, and 1.9 log reductions at 6h, respectively, followed by sustained killing.

Conclusions: The triple combination was the most active regimen against both *A. baumannii* strains and may offer a promising countermeasure for combating polymyxin-resistant *A. baumannii*.

Neurostructural morphology in CNS-specific RPGRIP1L deficient mice

Mohammad Masum Wiese¹, George Stratigopolous², Rudolph Leibel³

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Primary cilia are cellular structures important for signal transduction. Perturbation of ciliary components, such as Retinitis Pigmentosa GTPase Regulator-Interacting Protein-1 like (*RPGRIP1L*), a component of the ciliary transition zone, causes obesity. Previous studies have shown that mice hypomorphic for *Rpgrip1l* display increased food intake and, subsequently, obesity. To identify a tissue-specific role for *Rpgrip1l* in the regulation of energy homeostasis (and to bypass any developmental roles of *Rpgrip1l*), our study focuses on the effects of the deletion of *Rpgrip1l* in the CNS of adult mice. We found that *Rpgrip1l* deletion in the adult CNS led to increased food intake and adiposity. Also, while the number of ciliated cells was decreased in the arcuate nucleus, ciliary morphology appeared unchanged. We also noticed a decrease in the total number of cells, suggesting the decrease in the number of arcuate cilia of CNS-specific *Rpgrip1l* deleted mice may be due to a decrease in the total number of cells in the arcuate hypothalamus. Our findings suggest that *Rpgrip1l* may play an important role in the structural integrity of hypothalamic neurocircuitry involved in energy homeostasis. A better understanding of obesity-associated genes, such as *Rpgrip1l*, can lead to new understanding of the underlying biology of obesity, and ultimately, may highlight novel genes and molecules to be targeted for therapeutic intervention.

Novel Methods of Medical Education: Clinical Cases as Preparation for the Wards and Beyond

Kayla Sheehan MS1; Guy DiSibio MD, PhD

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Abstract:

Over the past several decades, evidence-based medicine (EBM) has become the gold standard of clinical practice. The basic elements of EBM involve developing a clinical question, discovering the best available evidence, accurately assessing the strength and legitimacy of that evidence, and finally, applying that evidence in practice. Effectively utilizing EBM relies on a marriage between clinical and research skills, and has been shown to improve patient outcomes (1). Providing medical students with a strong foundation in EBM is a crucial component of assuring its application in their future practices.

The literature surrounding EBM shows that “standalone” approaches (where lectures and seminars are the only methods of instruction) are ineffective in long term behavior and attitude changes. These long-term changes are only seen when teaching EBM is integrated into clinical practice (2).

Our aim is to provide CNU’s students with the opportunity to hone these skills early on in their medical education. Because traditional clinical exposure does not occur until the 3rd and 4th year wards, we have developed clinical cases to emulate patient scenarios. In conjunction with the medical skills course and possible future implementation of technologies such as EMR, our goal is to use the clinical cases as a proxy of the wards, and allow students the opportunity to integrate clinical skills and the practice of EBM earlier than is typically done. By establishing methods of tracking progress, we can tailor the cases to students’ weaknesses, and build a strong foundation to ensure students’ success in the wards and beyond.

THE IMPACT OF TELEPHARMACY RELATING TO MEDICATION SAFETY IN RURAL AREAS OF CALIFORNIA

Vinna Nam¹, Linh Doan¹, Josephine Wong¹, Kim Cao¹, Warda Nawaz¹, Vu Nguyen¹, Nicole Quang¹, Shirley Zhu¹

Faculty Advisors: Hieu Tran, Pharm. D.¹, Cyndi Porter-Fraser, MBA¹

California Northstate University College of Pharmacy, 9700 West Taron Drive, Elk Grove, CA, 95757,
USA

BACKGROUND: Telepharmacy is the process of providing pharmaceutical care at a distance via information and communication technology. Due to the decline of pharmacies in rural areas, there has been an increased need for telepharmacy. In order to determine the level of need in this highly urbanized state of California, we focused on a region that is mixed rural and suburban. Thus, we focused on Yolo County where 7% of the population is rural.

OBJECTIVE: To evaluate the impact of telepharmacy in rural areas of California, we analyzed database articles regarding (1) the capability of telepharmacy to reach patients in rural California, (2) the potential services provided by telepharmacy, and (3) the quality of care provided by telepharmacy.

METHODOLOGY: This review was conducted through a database literature search (Pubmed, ScienceDirect, Ovid) concerning the implementation of telepharmacy and focusing on medication safety in a rural pharmacy setting. The analysis determined the benefits of telepharmacy and barriers faced by pharmacies of rural areas.

RESULTS:

Quality: A study done by the UC Davis involving 6 rural hospitals across California showed that 19.2% of the patients enrolled in the telepharmacy project experienced one or more medication errors that were successfully prevented.

Cost: A study done in California estimated that it avoided \$15,064 per week by using telepharmacy to prevent medication-related problem. A comprehensive study by UC Davis shows that there is a savings of \$4,662 per use.

Access: Telepharmacy has the potential to be accessed virtually anywhere. As shown in the North Dakota Telepharmacy Project, the increase in the quality of healthcare has the power to expand communities and create new jobs, which in turn will help develop telepharmacy and extend its reach even farther.

Abstracts for Poster Presentations

Differential Antidepressant-like Activity of Positive Allosteric Modulators with Selectivity for $\alpha 7$ Nicotinic Receptors

Matthew Craddock¹, Katarzyna Targowska-Duda^{2,*}, Barbara Budzynska³, Agnieszka Michalak³, Claus J. Løland⁴, Krzysztof Jozwiak², Grazyna Biala³, and Hugo R. Arias^{1,*}

¹*Department of Basic Sciences, California Northstate University College of Medicine, CA, USA*

²*Department of Biopharmacy and ³Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Poland*

⁴*Department of Neuroscience and Pharmacology, University of Copenhagen, Denmark*

$\alpha 7$ Nicotinic acetylcholine receptors (AChRs) are widespread in the brain and involved in sensory response, memory, cognition, and mood regulation. The enhancement in activity of these receptors by positive allosteric mediators (PAMs) is of therapeutic importance in a number of cognitive deficits. Until recently, no research had considered the potential of $\alpha 7$ -PAMs as treatments for depression. Recent results demonstrated that one of these compounds, PAM-2, has antidepressant-like activity in mice (Targowska-Duda et al., 2014, *Neurosci. Lett.* 569:126). To demonstrate whether other $\alpha 7$ -PAMs have similar antidepressant-like activity, type I (NS-1738) and type II (PNU-120596 and PAM-2) PAMs were assessed using both the forced swim test (FST) and tail suspension test (TST). The FST results showed antidepressant-like activity in all $\alpha 7$ -PAMs after subchronic treatment, and particularly in PAM-2 after chronic treatment. In general, the TST results confirmed the FST results, except for NS1738. Methyllycaconitine, an $\alpha 7$ -antagonist, inhibited the observed antidepressant-like activity, demonstrating that $\alpha 7$ AChRs are involved in this activity. PAM-2, -3, -and -4 do not inhibit the human serotonin (hSERT), dopamine (hDAT), and norepinephrine (hNET) transporters at clinical concentrations, ruling out involvement of these neurotransmitter systems in the observed activity. Synergistic effects were shown when PAM-2 was co-administrated with the antidepressant bupropion, but not with the $\alpha 7$ -agonist DMXBA. This enhancement elicited by $\alpha 7$ -PAMs could pave the way for new adjunctive therapies in existing antidepressants since the clinical activity of many antidepressants is only around 10% better than the placebo effect. The results show that PAM-induced $\alpha 7$ AChR potentiation produces antidepressant-like activity, which opens the door to a new area of therapeutic possibilities for PAMs in mood disorders.

Activation of T cell S1P Receptor 1 Attenuates the Expression of TGF-beta1 from Fibroblasts

Paia Lor¹, Helen Le¹, George Talbott², Zhuqiu Jin²

¹Third-Year Student of Pharm.D. Program, College of Pharmacy, California Northstate University, Elk Grove, CA 95757

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Anxiolytic Activity of 3-Furan-2-yl-N-p-tolyl-acrylamide, a Positive Allosteric Modulator of α 7 Nicotinic Receptors

Nayson L. Fernandes¹, Katarzyna Targowska-Duda², Dirk Montag³, Barbara Budzynska⁴, Krzysztof Jozwiak², Grazyna Biala⁴, and Hugo R. Arias¹

¹*California Northstate University College of Medicine, Elk Grove, CA 95757, USA*

²*Department of Biopharmacy and ⁴Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Lublin, Poland*

³*Neurogenetics Laboratory, Leibniz Institute for Neurobiology, Magdeburg, Germany*

Alpha-7 nicotinic acetylcholine receptors (AChR) belong to a superfamily of ligand-gated ion channels that are implicated in different mood-related disorders, including anxiety. In this regard, to determine whether 3-furan-2-yl-N-p-tolyl-acrylamide (PAM-2), a selective positive allosteric modulator of α 7 AChRs, has anxiolytic activity, elevated plus maze (EPM) and elevated zero maze (EZM) tests were conducted on mice after acute and chronic treatments. After acute treatments, 0.5, but not 1.0-2.0, mg/Kg PAM-2 exhibits anxiolytic-like activity on only male mice, whereas 0.1 mg/Kg PAM-2 is also effective after chronic treatments (determined by EPM and EZM). The observed anxiolytic-like activity is readily reversed by the α 7 selective antagonist, methyllycaconitine (MLA), thereby confirming that the effect is mediated by α 7 AChRs. To determine the effect of PAM-2 on agonist-induced anxiety, the activity of PAM-2 was determined after treatment with 0.1 mg/Kg nicotine or 10.0 mg/Kg PNU-282987. The results indicate that PAM-2 reverses the anxiogenic activity elicited by nicotine, but not by PNU-282987, a selective α 7 agonist. In addition, the combination of inactive doses of PAM-2 and DXMBA, an α 7-agonist, shows synergistic effects. This confirms the cooperative interaction between both drugs on the α 7 AChR. These results suggest that low doses of PAM-2 holds promise as an anxiolytic therapeutic agent, especially for smokers. Our results warrant further research to determine the precise neuronal and neurochemical mechanisms underlying the anxiolytic activity of PAM-2.

The Effects of Anterior Pelvic Tilt on Walking Kinematics in Pregnant Females and Non Pregnant Adults

Katherine K Whitcome ¹

¹ College of Health Sciences, California Northstate University, 2910 Prospect Park Drive, Rancho Cordova, CA 95670, USA

Pelvic function has long been a focus of researchers interested in the evolution of bipedality and human obstetrics. Walking kinematics in modern bipeds change during pregnancy widening the base of gait (Foti et al 2001). Although a broad base of support may maximize locomotor safety (Forzek and Staszkiewicz 2012), increased ankle separation conflicts with our functional understanding of human knee valgosity. We hypothesized that the wide base of gait observed in pregnancy may be linked to intrinsic constraints of the adult hip and lower limb. We tested for the effects of natural pelvic tilt in 15 gravid females and experimentally induced pelvic tilt in 15 non-gravid females and 15 males on the variables of base of gait, limb rotation and foot abduction. Analyses of 3D positional data show that base of gait diameter and foot abduction angle significantly increased with anterior pelvic tilt ($p = 0.006$ and $p = 0.01$, respectively). Subjects who achieved anterior tilting greater than 40% of the baseline angle experienced significant external limb rotation ($p = 0.02$). There was a significant but weak relationship between pelvic tilt and valgus angle ($p = 0.01$, $R^2 = 0.22$). Although human pregnancy is associated with a widening of base of gait and external rotations of the lower limb, the similar effects of anterior pelvic tilting in non gravid females and males suggests that structural constraints of the human hip limit gait performance in gravid females and may be a factor in alternative forms of ventral load carrying.

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Vinna Nam¹, Linh Doan¹, Josephine Wong¹, Kim Cao¹, Warda Nawaz¹, Vu Nguyen¹, Nicole Quang¹, Shirley Zhu¹

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Neurostructural morphology in CNS-specific RPGRIP1L deficient mice

Mohammad Masum Wiese¹, George Stratigopolous², Rudolph Leibel³

4. California Northstate University, College of Medicine, 9700 West Taron Drive, Elk Grove, CA 95757
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Use of Serial Hemoglobin in Blunt Trauma Patients to Detect Occult Blood Loss

Vikas Shahi¹ and Dr. William Mower²

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Serial hemoglobin measurements (ΔHgb) are frequently measured in blunt trauma resuscitations to aid in the early identification of patients with significant blood loss, occult injury, and the need for intervention. However, the utility of ΔHgb has yet to be rigorously studied. To this end, we enrolled 251 blunt trauma patients 18 years of age and older receiving blunt trauma evaluations at a Level I Trauma Center (Ronald Reagan UCLA Medical Center). We measured two hemoglobin levels spaced 5 minutes apart and calculated the difference, ΔHgb , for each patient. We also recorded whether each patient required an intervention to treat their injuries. Interventions included operation or procedure to control hemorrhage, radiographic embolization, administration of blood and blood products, exsanguination, or administration of 3 or more liters of IV fluids. Our population of 192 males and 59 females had a mean age of 40 (Standard deviation: ± 17) years. 56 patients required an intervention and 195 patients did not. The mean ΔHgb was -0.12 (± 1.01) for patients requiring an intervention, and -0.13 (± 0.78) for patients not requiring an intervention. A ΔHgb of -1.0 showed a sensitivity of 12.5% and a specificity of 87.2%. A ΔHgb of 0.0 showed the most robust combination of sensitivity (71.4%) and specificity (43.6%). A ΔHgb of +1.0 showed 98.2% sensitivity and 6.7% specificity. We found the area under the receiver operator curve (ROC) to be 0.53, indicating that ΔHgb is only slightly better than a random coin toss in predicting the need for intervention in blunt trauma patients. The results of our study indicate that the practice of measuring serial hemoglobin levels provides little benefit, is likely to misdirect and confuse, and should be omitted from blunt trauma assessments.

Title: Implementation of Self and Peer Evaluation Process in Didactic Pharmacy Curriculum to Improve Self and Teammate Accountability

Presenter: Sukhvir Kaur¹

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Abstract: Training professionals including pharmacy students on providing effective feedback to reflect on their own behaviors as well as behaviors of their peers can aid in raising self-awareness. Providing effective and constructive feedback is a skill that can aid in making a person an effective teammate which can lead to personal and professional growth. The purpose of this session is to sample a successful self and peer evaluation process in didactic pharmacy curriculum that allows pharmacy students an opportunity to reflect and improve on their behaviors to increase self-awareness. At CNUCOP, we have successfully implemented the self and peer evaluation program in the didactic pharmacy curriculum and utilize Comprehensive Assessment of Team Member Effectiveness (CATME), behaviorally anchored rating scale, to conduct self and peer evaluations and rating team processes in Fall of 2015. Five behaviors the tool asks the participants to reflect upon include contributing to the team's work, interactive with teammates, keeping the team on track, expecting quality, and having relevant knowledge, skills and abilities.

The process of self and peer evaluation involves comprehensive student training during orientation on providing effective feedback, opportunities for students to work in teams for a semester including utilization of team contracts, administering mid-semester formative CATME self and peer evaluations followed by end of the semester summative CATME self and peer evaluations. The formative non-punitive evaluations are run during mid-semester and results are disseminated to the students in a timely fashion so they can reflect on their behaviors and give them an opportunity to both keep the positive behaviors as well as improve on the behaviors that they were rated low on. It also allows students to visualize their behaviors in relationship to the aggregate peer's results utilizing a Likert-scale. At the end of the semester, students complete the same summative evaluation which is a graded exercise in an attempt to hold students accountable for being either an effective or non-effective team member.

Cancer Biosimilars: Regulation Challenges and Clinical Impact

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A biosimilar is a biological product designed to imitate a reference biologic with high similarities in structure, efficacy, and safety. Unlike generics, which are bioequivalent to the reference drug, most biosimilars are not approved as interchangeable products. The potential benefits of biosimilars are substantial, including immense savings in public health spending. As first-generation cancer biologics experience loss of patent protection, it can be expected that more biosimilars will be in the pipeline over the next several years. There are currently four FDA-approved biosimilars available in the United States, but only one (Zarxio) has cancer indications. Several other cancer biosimilars are also in the FDA approval process. There is an urgent need for clinicians to become increasingly aware of the regulation challenges and clinical impact of biosimilars.

HIC (MDFIC) is a protein that interacts and co-localizes with the RELT family of TNFRs

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Receptor Expressed in Lymphoid Tissues (RELT) is a human Tumor Necrosis Factor Receptor (TNFR) that is expressed most prominently in cells and tissues of the hematopoietic system. RELT has two identified homologous binding partners RELL1 and RELL2. This study sought to further elucidate the function of RELT by identifying novel protein interactions with RELT family members. Human I-mfa domain-containing protein (HIC), also known as MDFIC, was identified in a yeast two-hybrid genetic screen using RELL1 as bait. HIC is a transcription factor encoded by a gene located adjacent to regions of chromosome 7 (7q31.1) frequently lost in Acute Myeloid Leukemia (AML) patients. HIC physically interacts with both RELT and RELL1, as determined by in vitro co-immunoprecipitations. HIC co-localizes with RELL1 at the plasma membrane and co-localizes with RELT in intracellular compartments. A series of deletion mutants of RELT were created that could be used to identify the regions of RELT required to bind to HIC. Co-immunoprecipitation experiments indicate that regions of RELT proximal to the plasma membrane are sufficient for physical interaction with HIC. Deletion mutants of RELT were also utilized to determine regions of RELT required for the activation of p38 and induction of apoptosis in HEK-293 cells, two previously described functions of RELT. Overexpression of RELT induces cleavage of PARP and Caspase-3 as determined by western blotting. Interestingly, induction of apoptotic morphology by RELT overexpression was not prevented if signaling by FADD or Caspase-8 was blocked, indicating RELT induces apoptosis by a pathway distinct from death-domain containing TNFRs such as TNFR1. Finally, the actin-binding protein Filamin was also identified as a RELL1 binding partner in the genetic screen. RELL1 was shown to physically interact with Filamin by in vitro co-immunoprecipitation. Filamin was shown to co-localize with RELT in intracellular compartments and co-localize with RELL1 at the plasma membrane.

Epidemiology and Characteristics of Mental Health Related Ambulance Calls in 2013/14 in the United States

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Objective: To elucidate the burden of illness of mental health related pre-hospital care to drive further research to alleviate the strain on emergency departments (EDs) nationwide, as well as serve as a model for data mining methodology.

Background: Due to the large gaps in outpatient care for psychiatry/neurologic, EDs have become the de facto point of care for psychiatric/neurologic emergencies and acute care. The increasing EMS demand, ED closures, and overcrowding leads to increasing number of ambulance diversions, longer transport times, and ultimately, a worsening prognosis for patients.

Design/Methods: The study included 49,732,940 ambulance calls from 33 states in the years 2013 and 2014. Calls were gathered by the National EMS Information System. Using Shannon's machine learning algorithm "Gain Ratio" and "Information Gain" we were able to determine that provider's primary impression is the most reliable factor to categorize calls as either mental health related or not. These calls were further analyzed using R.

Results: MHRAC calls peaked on Tuesday while total calls peaked on Fridays. Both MHRAC and non-MHRAC troughed on weekends, especially Sundays. Days with the highest number of MHRAC calls included September 12, May 14, and June 4, and the lowest number of MHRAC calls included Thanksgiving, Christmas, and Easter. MHRAC peak in the evening, 20:00, whereas non-MHRAC peak in the afternoon, 15:00. Seasonal variation did not affect volume of MHRAC. Volume of MHRAC as a correlate to lunar variation was not significant.

Conclusions: The weekly and daily temporal variations elucidate a gap in outpatient psychiatric/neurologic care that can alleviate the burden on ED facilities. Contrary to popular belief Thanksgiving, Christmas and Easter saw the lowest amount of both MHRAC and non-MHRAC. A common myth surrounds the effects of lunar variation on mental health, and there does not appear to be a statistical difference.

Title: The effects of low testosterone and high-fat diet on neuroinflammation in the central and peripheral nervous systems

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Abstract: Inflammatory pathways contribute to the pathogenesis of several diseases, including Type 2 Diabetes Mellitus (T2D) and Alzheimer's disease (AD). Inflammation is regulated by many factors. For example, testosterone can attenuate inflammation in part by decreasing the expression of pro-inflammatory cytokines such as TNF α and IL-1 β . On the other hand, high-fat diet is associated with activation of pro-inflammatory pathways. High-fat diet also induces obesity, promotes T2D, and is associated with decreased testosterone levels. In this study, we hypothesize that interactions between low testosterone and high-fat diet-induced metabolic changes both independently and cooperatively regulate inflammatory pathways. We investigate the effects of experimental manipulation of testosterone levels combined with high-fat diet on neuroinflammation in male WT mice cortex. In particular, we determine the effects of low testosterone levels in the presence and absence of a high-fat diet on expressions of pro-inflammatory pathways, metabolic markers of T2D, and levels of activated microglia. Our results indicate that low testosterone levels and high-fat diet significantly elevate blood glucose levels, reduce insulin sensitivity, and increase expression levels of TNF α and IL-1 β . In addition, we show that neurons exhibit reduced survival and poorer neurite outgrowth when co-cultured with glial cultures generated from high-fat fed animals in comparison to glial cultures from animals on a normal diet. We also noticed changes in the inflammatory pathways in the peripheral nervous system under manipulated testosterone levels and high-fat diet conditions. These results demonstrate neuroinflammatory effects of high-fat diet and its association with testosterone levels. Together, our findings suggest that low testosterone and obesity are interactive regulators of neuroinflammation that may result in an increased risk for downstream disorders such as T2D and Alzheimer's disease.

Title: Exploring Neuronal Functions for the Endosomal Regulators VPS-39 and SAND-1 With Potential Ties to Neurodegenerative Disease

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Neurons are highly specialized cells that form the fundamental building blocks of neurological systems in metazoans. Using a combination of behavioral assays, genetics, and fluorescence microscopy, we aim to more fully understand two major cellular processes of critical importance to neurons: long-range axonal transport and local membrane trafficking at synapses. Dysregulation of both processes has been linked to neurological disease states and neurodegeneration in humans, yet many of the individual molecular pathways remain poorly understood due to the difficulties associated with studying neurons *in vivo*. Here, we present novel findings regarding the neuronal functions of two endosomal regulators, VPS-39 and SAND-1, using the nematode *Caenorhabditis elegans* as a model system. These proteins have known human orthologues, and have been best characterized in yeast (*Saccharomyces cerevisiae*) as functioning within the endosomal system as regulators of the Rab GTPase protein family. Rabs are monomeric peripheral membrane G proteins that are involved in various membrane trafficking-related processes such as vesicle formation and membrane fusion. Recent data from our group demonstrates critical roles for both VPS-39 and RAB-5 in neuronal membrane trafficking events, with mouse models of Down Syndrome (Ts65Dn) displaying marked decreases in VPS-39 levels at synapses and enlarged RAB-5 positive compartments, commonly identified as early endosomes. Aldicarb sensitivity assays in *C. elegans* also reveal strikingly similar phenotypes between VPS-39 and SAND-1 mutant animals, supporting neuronal roles for both regulatory molecules. VPS-39 and SAND-1 are thought to operate in close temporal proximity during the endosome maturation process. We hypothesize that VPS-39 and SAND-1 are required for synaptic endosomal trafficking and membrane fusion events, and therefore sustained synaptic transmission. We aim to further explore this system in *C. elegans* by generating transgenic animals carrying the *sand-1* loss of function mutation and fluorescently tagged endosomal markers.

Title: Horizontal EMR Integration Into Medical Education – A Novel Approach

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Abstract

Since 2010 Electronic Medical Records (EMR) have been increasingly adopted by health systems and individual practitioners due to benefits to quality of patient care, improve care coordination, improve patient participation, and federal subsidies and penalties. While EMR proficiency is widely expected from physicians our literature search returned little documentation of formal training by medical schools and no utilization of EMR as an educational tool beyond familiarization.

Of the publications on EMR training we found two schools that have documented their EMR education and its effects. OHSU has students train on EMR before rotations on simulated records to identify gaps, correct errors, interpret lab results, and adding/correcting patient records. Emory Health has asked students to reconcile pharmacy and practice ordering labs for simulated patients. Both studies have reported that students valued the experience on simulated EMR (Likert scale).

At California Northstate University College of Medicine we have a clinical case program that is integrated into our clinical skills program and general medical education. We are currently preparing to create a model EMR with built in assessment capabilities in order to track and assess development of student critical thinking and organizational skills required for the real practice of medicine. Upon completion, we will import our clinical cases (which are aligned to material students are studying that week for MS1 and additionally integrated with clinical skills for MS2) into the program for dissemination to students.

The goals of our program are to: 1) Mirror EMR layout and function to familiarize students with the software and 2) Enable individual evaluation and tracking of clinical skills, critical thinking (e.g., lab ordering), and ability to extract important data (e.g., pertinent positives and negatives).

Title: In Vitro and Ex Vivo Effects of Silymarin Fractions on Pro-Inflammatory Chemokine Secretion

Presenter: Ella T. Mokrushin, **Authors:** George Talbott, Tibebe Woldermariam, Leo R. Fitzpatrick.

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Silymarin is comprised of four major classes of anti-inflammatory flavonoligands including silybinin, silychristin, silydianin and isosilybinin. Our prior studies determined that specific silymarin-derived fractions decreased the secretion of pro-inflammatory cytokines (TNF- α and IL-8) from macrophage and colonic epithelial cell lines. **Methods:** Crude silymarin was extracted from milk thistle seeds and separated into fractions. The compositions of silymarin fractions were confirmed by LC/MS analysis. Colitis was induced in male C57BL/6 mice ($n=16$) by giving 2 % Dextran Sulfate Sodium (DSS) drinking water for a six-day period. Control mice ($n=8$) were given untreated water. Employing a 24 hour colonic culture system, the *ex vivo* effects of crude silymarin extract, two different silymarin fractions, as well as commercially derived silybinin and isosilybinin (20 to 200 μ g/ml) were examined. Colonic strips obtained from mice with/without DSS-induced colitis were used; and the secretion of MIP-2 in cell culture media was determined by ELISA. Further, the effects of silymarin fractions/compounds on IL-8 chemokine secretion induced by TNF-alpha (10 ng/mL) were characterized with a HT-29 colonic epithelial cell line. **Results:** With colonic strips from DSS treated mice, the mean percent inhibition of basal MIP-2 secretion (relative to vehicle treatment) was: Fraction 2 (96%) = Isosilybinin (96%) > Silybinin (92%) > crude fraction (75%) > fraction 5 (69%). Using colonic strips from water treated mice, silymarin fractions (as well as isosilybinin, silybinin) effectively inhibited IL-1 β plus IL-23 stimulated MIP-2 secretion. For inhibiting the secretion of IL-8 by HT-29 cells, the potency order (IC_{50} values) for tested fractions was: Fraction 2 (19.9 μ g/ml) > fraction 5 (32.8 μ g/ml) > crude extract (36.1 μ g/ml). **Summary:** Prominent inhibition of basal and stimulated secretion of MIP-2 from colonic strips of mice with/without DSS- induced colitis, and IL-8 from TNF- α -stimulated HT-29 colonic epithelial cell line, was observed for a sylmarin fraction (#2) containing mainly isosilybinin and silybinin, or commercially derived isosilybinin and silybinin. **Conclusion:** These results additionally contribute to the identification of silymarin-derived flavonoligands with optimal anti-inflammatory properties, which can be employed for future *in vivo* testing in murine models of colitis.

Delivering Vancomycin to Bone Tissues Using Alendronate Surface Modified Liposomes for Osteomyelitis Treatment

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Purpose:

To develop a targeting system that targets vancomycin directly to bone tissue by using liposomes as a carrier and alendronate as a targeting moiety in attempt to reduce the side effects associated with treating osteomyelitis with high dose of vancomycin.

Method:

Liposomes were prepared using thin film hydration method followed by a dehydration-rehydration technique to maximize vancomycin encapsulation efficiency. Alendronate, a molecule with high bone affinity, was successfully conjugated with distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE) -PEG using Dicyclohexylcarbodiimide as a linker. The conjugation was confirmed using IR spectroscopy. The conjugated DSPE-PEG-alendronate was then used to prepare bone targeting vancomycin-loaded liposomes. An *in vitro* test was performed using hydroxyapatite, a common bone ingredient to measure the binding of the formulation. In addition, the binding of the formulation to sliced mice tibia was investigated.

Results:

The modified dehydration-rehydration method increased the encapsulation efficiency to 21.9%. The mean particle size of the liposomes was 243.9 nm. The formation of amide bond between the carboxyl group of DSPE-PEG-COOH and the amine group of the alendronate was confirmed by observing a sharp amide I and amide II peaks at 1575 and 1625 cm⁻¹. These results confirmed an amide bond formation and a successful conjugation of DSPE-PEG-COOH and sodium alendronate. The hydroxyapatite binding study showed significantly higher binding affinity of the surface modified liposomes compared to the control. Additionally, the surface modified liposomes showed higher fluorescence intensity to the bone tissue compared to the control group after 5 hours incubation.

Conclusion:

The encapsulation efficiency of vancomycin was successfully maximized using modified dehydration-rehydration method. The prepared surface modified liposomes had a significant binding to hydroxyapatite and bone tissue compared to the unmodified liposomes.