CNU TRANSLATIONAL RESEARCH SYMPOSIUM PROGRAM

January 18, 2019

8:45 AM – 5:00 PM

CNU Event Center

9650 W. Taron Drive

Elk Grove, CA 95757

Annual CNU Translational Research Symposium
January 18, 2019 8:00 AM-5:00 PM

Time	Agenda
8:00am-8:45am	Registration
8:45am-9:00am	Opening Remarks **Dr. Alvin Cheung, PharmD, MHSA, CNU President**
9:00am-9:05am	Nobel Prize Lecture Series **Dr. Leo Fitzpatrick, Assistant Dean of Research Affairs, Associate Professor of Pharmaceutical and Biomedical Sciences, CNUCOP**
9:05am-9:50am	Keynote Speaker **Professor Donald Bers, PhD, Joseph Silva Chair for Cardiovascular Research, Distinguished Professor and Chair Department of Pharmacology, UC Davis** Introduction: Professor IshwarlalJialal
9:50am-10:05am	Overview of Clinical Research **Dr. Dinesh Vyas, MD, MS, Surgery Residency Program Director, Associate Professor of Clinical Research and Genetics, San Joaquin General Hospital** Introduction: Dr. Lakshmi Chaturvedi
10:05am-10:25am	Targeting inflammation to reduce ASCVD in type 2 diabetes **Professor IshwarlalJialal, Assistant Dean of Research, Professor of Physiology, Metabolism and Clinical Diagnostics, CNUCOM**
10:25AM-11:05AM	POSTER PRESENTATION-COFFEE BREAK
11:05am-11:25am	*In Silico* Design of Novel Renin Inhibitors **Lillian S. Jundi, 3+ BSMD Student, CNUCHS**
11:25am-11:45am	A Review of Literature for Off-label Indications for 4-factor Prothrombin Complex Concentrate **Dr. Hien Nguyen, PharmD, PGY1 Resident, CNUCOP**
11:45am-12:05pm	Health Outcomes Associated with the Treatment of Mental Illness in Primary Care **Christina Stephenson, P3 student, CNUCOP**
12:05AM-1:00PM	POSTER PRESENTATION-LUNCH BREAK
1:00pm-1:20pm	Treatment Patterns of High-Cost Injectable Medications for the Type II Diabetes **Eric Tang, P2 student, CNUCOP**
1:20pm-1:40pm	Common Indications for Calcitonin and its Utilization Review at Sutter Eden Medical Center Sena Shin, PGY-1 Resident Pharmacist **Dr. Sena Shin, PharmD, PGY1 Resident, CNUCOP**
1:40pm-2:00pm	Increased Mast Cell Abundance in Adipose Tissue of Nascent Metabolic Syndrome: Relevance to the Pro–Inflammatory State and Increased Adipose Tissue Fibrosis **Purnima Gurung, M2 student, CNUCOM**
2:00pm-2:20pm	Identification of Novel Compounds with Anti-carcinogenic Properties **Luis Tolento Cortes, P2 student, CNUCOP**
2:20PM-3:20PM	POSTER PRESENTATION-COFFEE BREAK
3:20pm-3:40pm	Family Promise and CHS, Changing Lives **Dr. Cassandra Perryman, Assistant Professor of Psychology and Sociology, CNUCHS**
3:40pm-4:00pm	Methadone-Induced QT Interval Prolongation in a Narcotic Treatment Center: Identifying Patients at Risk and Simplifying ECG Monitoring **Dr. Erika Titus-Lay, PharmD, BCPP, Assistant Professor of Clinical and Administrative Sciences, CNUCOP**
4:00pm-5:00pm	Awards for Students Poster and Oral Presentations & Awards for Grant Winners
5:00pm	Adjournment

Keynote Speaker

Biography: Donald M. Bers, Ph.D.

Dr. Bers is the Joseph Silva Endowed Chair for Cardiovascular Research, Distinguished Professor and Chair of the Department of Pharmacology at University of California, Davis (UC Davis). Dr. Bers obtained his BA in Biology from the University of Colorado, Boulder, and his Ph.D. in Physiology from UCLA in 1978. He did an AHA-supported postdoctoral fellowship at the University of Edinburgh, Scotland and returned to UCLA to a Research Faculty position. At the University of California, Riverside (1982-92) he rose from Assistant Professor to Professor and Associate Dean of Biomedical Sciences. He joined Loyola University Chicago Stritch School of Medicine as Chair of Physiology in 1992 (through 2008) where he built a strong Physiology Department, and held the James R DePauw endowed Chair. Since 2008 at UC Davis he has rebuilt the Pharmacology Department as an excellent collaborative research environment, and spearheaded a new Cardiovascular Research Institute.

Dr. Bers has been productive in studies of cardiac Ca signaling, with extensive publications (>475 papers, *h-index* = 115), an influential single author book *Excitation-Contraction Coupling and Cardiac Contractile Force,* and had continuous NIH grant funding for >35 years. He has mentored >100 Ph.D. students, postdocs and junior faculty, many of whom have gone on to highly successful independent careers. He has an extensive network of productive collaborations worldwide. His scientific work has focused on Ca and Na transport, signaling and electrophysiology in the heart, including fundamental characterization of ion transporters and channels, electrophysiology, E-C coupling, myofilament activation, mitochondrial Ca/ energetics, GPCR signaling, systolic dysfunction and arrhythmogenesis (e.g. in hypertrophy and heart failure), always with an eye toward both integrative aspects of cardiac function/ clinical relevance and drilling down to more fundamental quantitative mechanistic understanding and the development of computational models.

Dr. Bers has received numerous awards (including AHA Distinguished Scientist Award) and held leadership positions for the AHA, International Society for Heart Research, Biophysical Society, Heart Failure Society of America, American Physiology Society, Association of Chairs of Departments of Physiology. He has served numerous grant review panels, editorial boards and as an associate editor, and as scientific meeting organizer.

Keynote Speaker Abstract: Cardiac Calcium and Calmodulin Signaling in Arrhythmias and Heart Failure

D.M. Bers, Chair Department of Pharmacology, University of California Davis, Davis, CA 95616, USA.

Ca is essential in cardiac electrophysiology, contraction, energetics and nuclear transcription. Calmodulin (CaM) and Ca/CaM-dependent protein kinase (CaMKII) are also important mediators of Ca signaling in myocytes. CaMKII can phosphorylate and modulate function of Na, Ca and K channels, ryanodine receptor (RyR) and IP3 receptor channels, the phospholamban-SERCA complex and myofilaments. Some of these pathways may contribute to decreased cardiac function and enhanced propensity for arrhythmias in hypertrophy and heart failure (HF). Since CaMKII expression and activation state is increased in HF, these pathways may be important in contributing to the development and consequences of HF and may represent important therapeutic targets. CaMKII effects on cardiac Na channels and RyRs may be particularly important in HF and arrhythmias, and these acquired CaMKII-dependent effects can recapitulate genetic channel mutations that are associated with human long QT (LQT) andBrugada syndromes and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). In particular CaMKII can phosphorylate NaV1.5 and cause both enhanced late I_{Na}(as observed in LQT3) and also loss of Na channel availability (as in NaV1.5 mutants linked to Brugada and short QT syndromes). RyR phosphorylation by CaMKII increases diastolic sarcoplasmic reticulum (SR) Ca leak (as in CPVT-linked mutations in RyR2, calsequestrin 2 and CaM). This altered RyR gating can lead to increase delayed afterdepolarizations (DADs) and serve as a source of triggered arrhythmias as well as cause reduced SR Ca content available for release in HF myocytes. Thus, CaMKII activation in HF and arrhythmogenic conditions can mediate acquired forms of cardiac arrhythmias and contractile dysfunction in pathologic conditions. We have used FRET-based methods to identify fundamental changes in RyR conformation associated with pathological arrhythmogenic SR Ca leak, and this involves a loss in CaM affinity for the RyR. Dantrolene and increased CaM concentration can shift this conformational state back to normal and suppress diastolic SR Ca leak and arrhythmias. This raises the possibility of a novel RyR-related therapeutic strategy, namely new molecules that, like dantrolene, can shift the RyR conformational state from pathophysiological to physiological.

Keynote Speaker

Overview of Clinical Research

Dinesh Vyas, M.D. is a world renowned surgery leader with many firsts to his name and more than 20 years of experience in advancing surgery, research, drug discovery, innovation, education, technology integration and global health. He is currently taking responsibilities as program director of on the oldest surgery training program of California and Inaugural Chair of Clinical Surgery Department of new medical school in the US.

Dr. Vyas is deeply engaged in education and has track record of actively involved in successfully turning around three surgery residency training programs and three LCME site visits for three medical schools. He has authored approximately 100 peer reviewed articles and chapters. He is invited by European Research Council, and NIH has invited Dr. Vyas as a grant reviewer. Dr. Vyas is editor-in-chief of multiple Surgery and GI journals, and three textbooks, in addition to his contribution as the editorial boards of more than ten journals, including NATURE group.

He is the pioneer in the advance surgery: imaging guided, robotic and hybrid endoscopic surgery. He is a board member of biomedical startups and helps with direction/funds to their success and integration with the industry. He spreads his vision as he is invited as keynote speaker across the Globe on various surgery and education forums.

Basic science research and Innovation using sensor technology and nanotechnology is Dr. Vyas's forte and he has contributed substantially in the development of smart drugs for cancer and sepsis using nanotechnology. His innovative biomedical products are in various stages of patent process and product development. These biomedical products are a unique type of equipment for mass use, incorporating the AI and Machine Learning in development of smart garments. His first product SMORT, is recently tested for market launch.

Dinesh is most passionate about innovative self-sustaining Global Health programs which have exponentially grown in last 15 years. In 2009, he developed the first MOOC program in medicine and it is highly successful in multiple language and is offered free of cost with millions of online users. The STRONG (Save Trauma and Road Navigators) initiative is in its 16th year now and has successfully launched many products to save millions of lives by 2020. The program centers are focusing on trauma in rural US and globally in fast growing economies. Self-funded projects with an initial million dollar investment are striving for self-sustainability with the launch of infotainment products. Dr. Vyas' deft application of mass media and entertainment for medical causes, will generate a new economic stream.

Title: Targeting inflammation to reduce ASCVD in type 2 diabetes

Authors: IshwarlalJialal[a,b], Ajay Chaudhuri [c]
[a] VA Medical Center, Mather, CA, United States of America
[b] California Northstate University College of Medicine, Elk Grove, CA, United States of America
[c] University at Buffalo, Buffalo, NY, United States of America

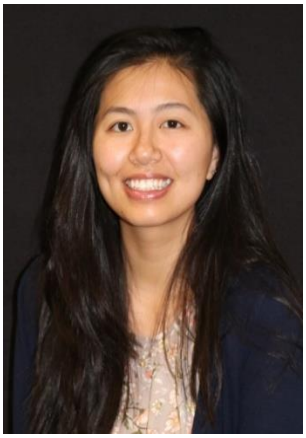
Abstract:ASCVD is the leading cause of mortality in T2DM. Inflammation appears to be pivotal in the genesis of ASCVD. As T2DM is also a pro-inflammatory state, our aim was to determine the benefit of anti-inflammatory strategies on ASCVD in T2DM. PubMed searches were conducted using the keywords of T2DM, ASCVD, Inflammation and clinical trials. Our data review suggests that the Mediterranean diet, GLP1 receptor agonists and a monoclonal antibody against IL-1 reduces ASCVD events in T2DM. The former 2 therapies appear to be safe. Anti-IL-1 therapy resulted in an increase mortality from infections. We conclude that only the Mediterranean diet and GLP1 receptor agonists can be safely incorporated into mainstay therapy for patients with T2DM to reduce ASCVD. Further studies are requiredwith respect to biologics targeting Inflammation to establish benefit to risk ratio.

Title: In Silico Design of Novel Renin Inhibitors

Author: Lillian S. Jundi, 3+ BSMD Student, CNUCHS

Abstract: High blood pressure (hypertension), a condition that affects many American adults, can have many serious consequences when left untreated such as heart disease and stroke. Many medications for treating hypertension target the angiotensin-converting enzyme (ACE), a more downstream effector of the renin-angiotensin-aldosterone system (RAAS), which controls blood pressure. These medications however can have significant side effects. Targeting renin, the initial enzyme involved in the RAAS can help avoid certain interactions and side effects. Inhibitors of renin were designed and tested computationally, creating four main frameworks of inhibitors that were refined. Furthermore, a selection of aromatic oligoamides that have easily synthesizable frameworks were also tested. The binding scores, an indication of the strength of the molecules as inhibitors were determined using UCSF Chimera and AutodockVina. Furthermore, a measure toxicology of the molecules was predicted using the Toxicology Estimation Software Tool (T.E.S.T.). The information gathered was used to further refine the molecules as potential inhibitors of renin.

Title: **A Review of Literature for Off-label Indications for 4-factor Prothrombin Complex Concentrate**



Author: Hien Nguyen, PharmD.[1]
[1]Sutter Health East Bay Region, 350 Hawthorne Ave, Oakland, CA 94609

Abstract: 4 Factor Prothrombin Complex Concentrate (4F-PCC) is FDA approved for warfarin reversal in patients needing immediate reversal for acute major bleeding or urgent surgery or invasive procedure. Warfarin is a vitamin K antagonist used in patients who need anticoagulation therapy for a variety of reasons including atrial fibrillation and deep vein thrombosis treatment. The use of 4F-PCC in off label indications is becoming more frequent. A review of the literature shows use in patients with liver related coagulopathy, factor-Xa acquired coagulopathy, and trauma patients with varying doses, efficacy, and safety.

Title:Health Outcomes Associated with the Treatment of Mental Illness in Primary Care

Author: Christina Stephenson B.S., Erika Titus-Lay Pharm.D., BCPS, BCPP

Abstract: According to the National Alliance on Mental Illness, 1 in 5 adults in the US will experience some form of mental illness, while 1 in 20 adults suffer from a serious form of mental illness. A 2017 report from the US Department of Health and Human Services determined a 6.4% shortage in the psychiatry workforce, indicating a need for 2800 more psychiatrists to join the workforce to meet the current demand. Due to this shortage of psychiatrists, more patients with mental illness are seeking treatment from primary care physicians. While primary care physicians have the capability to prescribe medication for mental illness, there is some concern that they may not have adequate training to feel comfortable providing psychiatric care. However, the current circumstances continue to show greater amount of patients with mental illnesses seeking care from their primary care physician. Current research shows ways in which primary care is attempting to integrate mental health treatment into their daily practice, but there is limited research on the associated health outcomes for patients receiving treatment for their mental illness from primary care physicians. Objective: The purpose of this study is to evaluate care provided to patients with major depressive disorder, bipolar disorder, schizophrenia, substance use disorder, and general anxiety disorder, specifically looking into duplicate therapies, no therapy, or appropriate first line therapy. The study also looked into appropriate monitoring for medications and appropriateness of therapy given comorbid conditions. Methods: This was a retrospective study utilizing data collected from the National Ambulatory Care Survey Database (NAMCS) from the years 2013-2015. IBM SPSS Statistics was utilized to calculate descriptive statistics, bivariate analysis, and logistic regression for variables showing statistical significance ($P< 0.05$) in bivariate analysis. Results: The study pulled 7300 patients from the NAMCS Database from the years 2013-2015 having at least one of the mental health diagnoses of interest. Of these 7300 patients, 2376 patients were 15 years of age and older and treated by primary care physicians. These 2376 patients were used to assess duplicate therapies, lack of therapy, and inappropriate therapies for major depressive disorder, bipolar disorder, schizophrenia, substance use disorder, and general anxiety disorder. The percentage of patients receiving duplicate therapies was 7.5%, 6.3%, 2%, 3.4%, 2%, and 0.9% for major depressive disorder, general anxiety disorder, bipolar disorder, psychosis, opioid use disorder, and alcohol use disorder respectively. The percentage of patients lacking any therapy was 26.4%, 45.8%, 43.4%, 59.3%, 11.9%, and 82.2% for major depressive disorder, general anxiety disorder, bipolar disorder, psychosis, opioid use disorder, and alcohol use disorder respectively. The percentage of patients receiving therapy not considered first line was 27.8%, 46%, 13.9%, and 94.4% for major depressive disorder, generalized anxiety disorder, opioid use disorder, and alcohol use disorder respectively. Further, of patients with major depressive disorder only 0.5% received substance abuse screening and only 8.6% received thyroid screening. Of patients with generalized anxiety disorder, 80% were inappropriately using continued benzodiazepines and only 4.7% were receiving mental health counseling. Of patients with bipolar disorder, 80.5% were prescribed an antidepressant while the majority of patients on Lithium and Valproic Acid were not receiving medication specific lab tests. Of patients with opioid use disorder, 5% were receiving addictive or opioid prescriptions and none of the patients were receiving naloxone. Of the patients with alcohol use disorder, 15% were receiving addictive or opioid prescriptions and only 27% were receiving alcohol abuse counseling. Conclusion: Based on the preliminary analysis, generalized anxiety disorder, psychosis, and alcohol use disorders appear to have the greatest percentage of patients with inappropriate medical therapy. The larger concerns brought about from this study were patients either lacking medication to treat diagnosed mental illnesses or having inappropriate first line medications. This study was limited in that the data pulled from the NAMCS Database used patient visits as the unit of analysis, so each patient's therapy lacked past medical treatment. Further, the data showed minimal use of routine screenings and appropriate lab work. This could suggest the need for changes in how primary care is treating mental illness, like implementation of certain mental illness checklists.

Title: Treatment Patterns of High-Cost Injectable Medications for the Treatment of Type II Diabetes

Authors: Eric Tang and Eugene Kreys, PharmD, PhD, BCPS

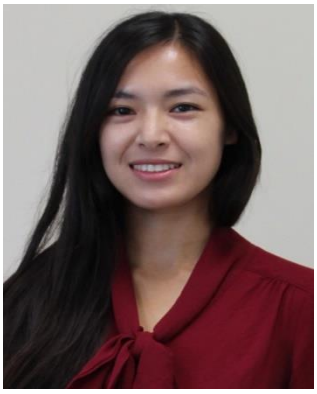
Abstract: The U.S. total annual spending on diabetes soared from $245 billion in 2012 to an alarming $327 billion in 2017. Glucagon-like peptide 1 (GLP-1) agonists, a newer class of medication to treat type II diabetes, are among the most expensive antidiabetic drugs. Medicaid beneficiaries bear less medication cost burden and tend to have better adherence than those without any prescription coverage. States that expanded access to Medicaid in 2014-2015 had an additional 30 diabetes prescriptions filled per 1,000 people, compared to states that didn't expand Medicaid, and the total number of diabetic prescriptions filled also increased significantly over the two years. Studying Medicaid populations may address gaps in treatment patterns of high cost injectable medications for treatment of type II diabetes such as GLP-1 agonists.This research will evaluate treatment patterns, persistence, and adherence of GLP-1 agonists for the treatment of type II diabetes using prescription claims of Medi-Cal beneficiaries asthis is a unique population that has not been extensively studied.

Title: Common Indications for Calcitonin and its Utilization Review at Sutter Eden Medical Center

Authors: Sena Shin, PGY-1 Resident Pharmacist[1]
[1] Sutter Health Systems Pharmacy Department and California Northstate University, 350 Hawthorne Ave., Oakland, CA 94609, United States.

Abstract: Calcitonin is an endogenous hormone produced by C-cells of thyroid that regulates calcium levels by reducing bone remodeling and reabsorption of calcium from the kidney. It works to regulate calcium resorption along with activated vitamin D, parathyroid hormone (PTH), and fibroblast growth factor 23.[1,2,3] Calcitonin injection is FDA approved for treatment of symptomatic Paget's disease when alternative treatments are not suitable, for treatment of hypercalcemia, treatment of postmenopausal osteoporosis when alternative treatments are not suitable, and osteoporosis vertebral compression fracture (OVCF) for early mobility and symptom relief. Hypercalcemia affect about 44.2% of specific cancer patients such as lung cancers and myelomas. With continuous high cost of calcitonin injections in the > $2,000 range per 2 mL vial, proper use of first-line therapies and alternatives needs to be reviewed, based on the urgency and severity of hypercalcemia. Through utilization review, we were able to restrict injectable calcitonin for emergent hypercalcemia to restrict use to 48 hours as an adjunctive therapy in addition to first line therapies such as saline, diuretics, and bisphosphonates. It must be used with discretion due to its rising costs, variable responses, and tacyphlexis risks. In reviewing profiles, we were able to pinpoint all other sources of possible causes or causative agents, such as thiazide diuretics or calcium supplements and stopped appropriately. For OVCF indication, treatment can be initiated with nasal spray formulation to improve symptom relief and decrease in narcotic usage. In double-blinded randomized study of 204 patients, randomized to either subcutaneous calcitonin 50 IU/day or intranasal calcitonin 200 IU/day for 30 days, showed that both regimen did not significantly differ in pain scale or average time to pain improvement. Fewer number of patients discontinued due to adverse effects in intranasal group as well.

Title: Increased Mast Cells in Adipose Tissue of Metabolic Syndrome Patients: A Pro-Inflammatory Driver of Angiogenesis and Fibrosis



Authors: Purnima Gurung[1], Karine Moussa[1], Beverley Huet[2], Sridevi Devaraj[3] and Ishwarlal Jialal[1]

[1]California Northstate University, College of Medicine, 9700 West Taron Dr, Elk Grove CA 95757, USA

[2] University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, DallasTX 75390, USA

[3] Endocrinology Department, Baylor College of Medicine, 6621 Fannin St, Houston TX 77030, USA

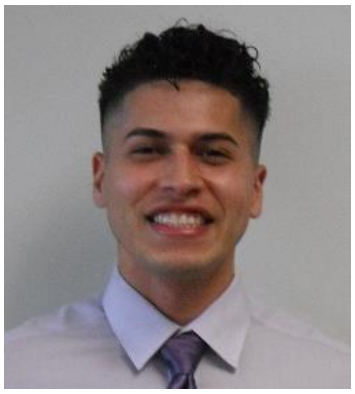
Introduction: Metabolic Syndrome (MetS) affects 35% of American adults > 40 years old and is diagnosed by 3 of the 5 following features: increased waist circumference (WC), hypertriglyceridemia, decreased high-density lipoprotein (HDL)-cholesterol, elevated blood pressure and an elevated blood glucose. The role of mast cells in the pro-inflammatory state of MetS is not well elucidated. We propose that mast cells in subcutaneous adipose tissue (SAT) of MetS subjects contribute to inflammation, fibrosis, and angiogenesis.

Methods: Matched controls (n=15) and nascent MetS (n=19) subjects (aged 24-72) were recruited from Sacramento, California and selected based on Adult Treatment Panel III (ATP III) criteria for MetS. The exclusion criteria for control subjects were the current use of any blood pressure medications, elevated fasting blood glucose levels (>100 mg/dL), elevated triglyceride levels (>200 mg/dL), and 3 or more of the ATP III criteria of MetS. SAT biopsy was performed on all subjects and processed for immunohistochemistry. SAT sections were stained using the Astra Blue stain to visualize mast cells. Fasting blood was obtained for chemistries and biomarkers.

Results: Abundance of mast cells in SAT of MetS subjects compared to controls was increased 2.5 fold ($p = 0.008$).Mast cells correlated positively and significantly ($p<0.01$) with WC, glucose, triglycerides, insulin resistance (HOMA-IR), leptin, Interleukin (IL)-1, IL-6, chemerin, p38 MAP-kinase activity and nuclear factor κB activity in circulating monocytes. Mast cells correlated significantly with markers of fibrosis (collagen and Sirius red staining) and angiogenesis (CD31 and VEGF).

Conclusion: Increased levels of mast cells and relevant biomarkers in SAT of MetS patients indicate a metabolic dysregulation and pro-inflammatory state emanating in SAT. Hence, mast cells contribute to the pro-inflammatory state and promote angiogenesis and fibrosis. Preventing mast cell migration to adipose tissue could be a potential therapeutic target to ameliorate the increased inflammatory burden of MetS.

Title: **Identification of Novel Compounds with Anti-carcinogenic Properties**



Author: Luis Tolento Cortes, P2 student, CNUCOP

Abstract: The use of traditional medicine dates back to ancient civilizations and has led to the development of revolutionizing therapies. With modern science, we are able to analyze potential medicinal plants in an effort to identify therapeutic molecules or templates.*Crinum Latifolium*, also referred to as “the King’s herb,” is a plant of the Amayllidaceace family and has been used as an alternative medicine throughout Asia for hundreds of years.*C. Latifolium* has shown anti-carcinogenic properties against prostatecancer in vitro; however, scientific literature assessing its applicability on other cancers is limited. Here we extracted *C. Latifolium* in aqueous solution and tested its efficacy against prostate cancer, LNCaP, and cervical cancer, C4-II cell lines. Dose-related effects of *C. Latifolium* extract against cell lines were measured through cell viability and cytotoxicity assays. Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) will be used to identify potential mechanistic pathways responsible for the activity of *C. Latifolium.* Once identified, similar bioactive compounds and scaffolds within the *C.Latifolium* extract will be characterized through metabolomics.

Title:Family Promise and CHS, Changing Lives

Authors: Dr. Cassandra Perryman, Assistant Professor of Psychology and Sociology, CNUCHS

Abstract: Homelessness is on the rise nationwide, and that increase can be heavily felt in Sacramento. Although a lot of attention is given to the individuals visible of the streets, there is an entire hidden homeless population of families within the county. It is the focus of this research to understand the structure of those families, the reasons for homelessness, and the markers of success when trying to reintegrate the family in to the community. The psychosocial change of individuals within a 90-day reintegration program are being measured. In order to better understand the community, all program demographics are being recorded. This includes both the families and accepted and not accepted in to the program. This research is in partnership with Family Promise of Sacramento and will be running through 2020. For disclosure, Dr. Perryman sits on the board of directors of Family Promise of Sacramento.

Title:Methadone-Induced QT Interval Prolongation in a Narcotic Treatment Center: Identifying Patients at Risk and Simplifying ECG Monitoring

Authors: Erika Titus-Lay, PharmD, Heather A. Jaynes, MSN, Carol A. Ott, PharmD, Gabriela Dimitrievski, PharmD, Todd A. Walroth, PharmD, Michelle Wilbrandt, RN, Paul R. Moe, MD, James E. Tisdale, PharmD

Background: Corrected QT (QTc) interval prolongation and torsadesdepointes(TdP) are adverse events associated with methadone. Some risk factors for methadone-induced QTc interval prolongation and TdP have been identified; however, the contribution of interacting drugs and concomitant administration of other QTc-prolonging agents to risk remains unknown.One potential contributing factor is genetic polymorphisms,particularly the CYP2B6*6/*6 and CYP2B6*18 allelic variants, leading to higher serum methadone concentrations.Though 12-lead electrocardiograms (ECGs)may assist QTc interval monitoring in methadone-treated patients, they are time-intensive and costly. A simple handheldECG that displayson a smartphone/iPad is available (Kardia/AliveCor®), which could simplify ECG monitoring.

Description of Innovative Service: Our objectives were to identify risk factors associated with QTc interval prolongation in methadone-treated patients, including the contribution of the genetic polymorphisms, and to validate QTc intervals determined using a handheld ECG. Methadone-treated patients at the Eskenazi Health Midtown Narcotic Treatment Center without pretreatment QTc interval prolongation were identified. Those providing written informed consent underwent a follow-up 12-lead ECG and blood draw to determine presence of CYP2B6*6/*6 or CYP2B6*18 allelic variants and serum methadone concentrations. A retrospective medical record review was completed to determine independent risk factors for QTcinterval prolongation, whichwas assessed using bivariate logistic regression analysis. A separate cohort of patientswas enrolled prospectively to validate the handheld ECG for measuring QTc intervals. QTcintervals from simultaneous 12-lead and handheld ECGs werecompared.

Impact on Patient Care: In the risk factors cohort, n=111 patients were enrolled. Aboutone-third of patients(34%) had a follow-up QTc interval> 450 ms, with n=1 > 500 ms. Medical record reviews identified that the only independent risk factor for methadone-associated QTc interval prolongation was concomitant use of one additional QTc interval-prolonging medication. Blood sample analysis is currently ongoing.One-hundred patients were enrolled in thehandheld ECG device validation cohort. The mean of 3 QTc intervals in lead 1 of the 12-lead ECG was compared to the single lead AliveCor® ECG. The 12-Lead ECG had a mean QTc interval of 432 ms (SD 22 ms) compared to 427 ms (SD 27 ms) for the single lead AliveCor® ECG. The bias determined by the Bland-Altman method was 4 ms (SD 18 ms).

Conclusion: This projecthasidentifiedoneindependent risk factor for QTc interval prolongation in methadone maintenance therapy and may simplify ECG monitoring through validation of a simple handheld ECG.

POSTERS

Poster 1 (P1): Basophil and eosinophil contributions in Metabolic syndrome

Authors: Chelsea Hayman, Saif Shaikh, Patrick Bieniek, Mustafa BahramandCOM, CNSU
Mentor/Advisors: Dr. IshwarlalJialal

Objectives: Minor leukocyte populations under study in metabolic syndrome: Basophils and eosinophils. Introduction: Metabolic Syndrome (MetS) represents a low-grade chronic inflammatory state and occurs due to a cluster of conditions which substantially increase risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). MetS is a common disorder that affects 35% of American adults. There are 5 parameters, referred to as cluster factors, that are associated with metabolic syndrome. Those cluster factors are glucose >100 mg/ dL, waist circumference > 89 cm for women and > 102cm for men, blood pressure > 130/85 mmHg, HDL 150 mg/dL. A diagnosis of metabolic syndrome would require three of these five cluster factors. Prior research on the roles of minor leukocyte populations (eosinophils and basophils) indicates that they are involved in inflammation in MetS. Due to the minimal and conflicting research regarding eosinophil and basophil involvement in MetS, this study intends to explore the extent to which these cells participate in the inflammatory processes related to the disease.

Patients and Methods: This was an exploratory study of patients with nascent MetS (n=59) and matched controls (n=45). The patients were screened and recruited from the UC Davis academic center where the study took place. MetS was defined according to the Adult Treatment Panel III criteria. Fasting blood was collected to obtain complete blood count, insulin, glucose, high-sensitivity C-reactive protein (hsCRP), and HOMA-IR. Eosinophil count and percentage and Basophil count and percentage were correlated with measures of inflammation. Data was analyzed by Wilcoxon rank sum test Spearman rank test. Significance was defined as a $p<0.05$.

Results: Our analysis showed that eosinophil count and eosinophil percent were elevated in metabolic patients vs healthy controls, and basophil percent was significantly decreased in MetS patients vs healthy controls (p=. 0003, p=.0065, p=.0046 respectively) after adjusting for BMI, sex, and age. Spearman statistical analysis found an inverse correlation between basophil percent and hSCRP and HOMA-IR (p=.0212, p=.0287). Spearman analysis did not find any significant correlations between the anti-inflammatory parameters (hsCRP& HOMA-IR) and eosinophil count and percent (hsCRP: p=.0808, p=.5591; HOMA-IR: p=.1358, p=.2588).

Conclusion: Eosinophil count and percent are significantly elevated in patients with metabolic syndrome compared with matched controls. This finding presents evidence against eosinophils having antiinflammatory action in patients with MetS and controls. Basophil percent is significantly decreased in patients with metabolic syndrome compared with controls. Our results show an inverse relationship between basophil percent and inflammatory markers. This is a novel finding which suggests that basophils in MetS have anti-inflammatory properties and may ameliorate insulin resistance in MetS patients.

Poster 2 (P2):Evaluation of Spinal Analgesic Protocol

Authors: Juliette Gerardo, Daniel Sessler, Sanchit Ahuja
Department of Outcomes Research, The Cleveland Clinic Foundation Main Campus
General Anesthesiology, Cleveland Clinic Main Campus
9500 Euclid Avenue
Cleveland, OH 44195

Introduction:Post-operative pain management is a serious consideration with the current opioid crisis. Acute and chronic pain management in complex spinal surgery influence patient satisfaction, aid in reducing complication, improving patient comfort, and long-term health-related quality of life. Complex spinal surgery is multilevel, instrumentation, fusion, and/or scoliosis procedures. Gabapentin, lidocaine, ketamine, acetaminophen, and NSAIDs all improve acute pain management.

Objectives:There are currently insufficient preventative and therapeutic protocol approaches for complex spinal surgery pain management. Spinal surgery analgesic pathways are being studied for patients at high risk for post-operative pain to improve quality of recovery (QOR).

Methods: This is a randomized controlled trial comparing spine surgery analgesic pathway (SSAP) with usual care pathway in improving QOR and pain management. A maximum of 440 complex spinal surgery patients will be enrolled at Cleveland Clinic Main Campus. Data is collected preoperatively with Amsterdam Preoperative Anxiety and Information Scale, Opioid-Related Symptom Distress Scale, and Pain and Disability Questionnaire. Postoperatively data is collected at 24hrs, 36hrs, and 48hrs for QOR, pain score, and opioid utilization and opioid-related side effects via questionnaire. Patients randomized into SSAP receive gabapentin and acetaminophen pre-operatively, lidocaine and ketamine infusions intraoperatively, and gabapentin and acetaminophen post-operatively. Those assigned current level of care pathway are assigned placebo for all phases. All administrations of analgesia are blinded.

Analysis:A linear regression model will be used to assess the relationship between third day postoperative QOR scores. Cumulative opioid consumption and pain intensity within 48hrs will be analyzed using joint hypothesis testing framework. SSAP will be considered superior if both outcomes are non-inferior, and at least one SSAP outcomes is superior. It is believed SSAP patients will have a superior QOR compared to usual care. Additionally, SSAP patients will have lower opioid consumption, pains scores, and opioid-related side effects compared to usual care.

Poster 3 (P3): Developing a Pharmacy Primer to Enhance P1 Academic Preparedness, Team Building Skills and Career Awareness

Authors: Ashim Malhotra, Tiffany Kreys, Jonathan Ballard, Eman Atef, Erika Titus Lay, Justin Lenhard, Peter Tenerelli, Suzanne Clark, Hieu Tran
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Objective: To promote learning, review prerequisite content, adequately prepare students for the rigors of pharmacy school, and encourage academic success, the California Northstate College of Pharmacy developed and implemented the Pharmacy Primer Program (PPP) in the summer of 2018.

Methods: The PPP was offered to all incoming first-year pharmacy students joining the Class of 2022. This non-mandatory, voluntary, tuition-free, four-day long program offered select topical coverage in key areas of pharmacy and pharmaceutical sciences to review important material from prerequisite courses and to better prepare students.The PPP was delivered the week before New Student Orientation Week. Each day was 6 hours long, with 3 hours in the morning and the afternoon, interspersed with an hour-long lunch break. The PPP included foundational and pharmaceutical sciences, pharmaceutical calculations, information about career paths and postgraduate opportunities in pharmacy, professionalism, and peer-led discussions of strategies for success in pharmacy school.

Results: Student perception surveys showed that 98% of respondents felt that the PPP positively impacted their professional commitment and knowledge of pharmacy; 98% felt that it provided a strong orientation to pharmacy school work; 97% agreed that the PPP provided team- building activities and enhanced professionalism; while 91% felt that the program provided adequate preparation for pharmacy school. Student performance also increased in post-PPP assessments.

Impact: In response to the gap in the development of holistic orientation programs offered by colleges and schools of pharmacy, the Pharmacy Primer Program was established to ease the transition of first-year pharmacy students into the professional degree program. AC.A.P.E.-based survey instrument was also developed to collect student perception data of the Primer Program and evaluate its effectiveness.

Poster 4 (P4): Interprofessional Education Collaborative at the California Northstate University

Authors: Ashim Malhotra[1], Rudolph Holguin[2], Welly Mente[1], Joseph Rogers[2], Claire Baranov[2], Thura AlKhayat[2], Nila Din[2], Forshing Lui[2], Linda Buckley[1], Catherine Yang[2], Hieu Tran[1], Joseph Silva[2]

[1]College of Pharmacy; **[2]**College of Medicine, California Northstate University, 9700 W Taron Drive, Elk Grove, California

CNU IPE. The mission of Interprofessional Education (IPE) at the California Northstate University is to prepare students to be practice ready by seamlessly integrating with interprofessional healthcare teams for the provision of patient-centered care. Our vision is to educate students in the appropriate choice of pharmacotherapy thereby improving patient outcomes by engaging interdisciplinaryexpertise and working as an integrated member of the healthcare team.

Structure.CNUCOMand CNUCOP have IPE programs coordinated by a Chair. The IPE Chair interfaces with faculty, students, staff, committees, directors and Chairs of the Departments within their own programs, continually assessing and evaluating the IPE-related curriculum. In AY 2018-2019, recognizing the collaborative nature of IPE, IPE chairs became Co-Chairs of the CNU IPE Committee. To further centralize IPE operationalization and enhance the development and implementation of an IPE program, the University established the Institute of Teaching and Learning Excellence (ITLE).

The CNU IPE Curriculum. The CNU IPE program includes multiple modalities for IPE instruction such as 1) simulation manikin-based patient case scenarios addressed by teams of pharmacy, medical, and nursing students for hands-on learning, 2) IPE Case Conferences with patient cases co-developed and led by Pharmacy and Nursing faculty, 3) hospital simulation to introduce learners to the flow of work and team-based effort of patient care in a hospital, and 4) participation in complex-care IPE through a nationally-offered elective that engages our students in home visit based long-term patient care. The IPE program is vertically and horizontally integrated through required courses. IPE events vary and may include diabetes (Sim and ICC), acute pancreatitis (Sim), acute kidney injury (Sim), congestive heart failure (Sim), medication error (ICC), and End-of-life Hospice care (Sim).

Summary. The CNU IPE curriculum offers an advanced, horizontally and vertically integrated, immersive hands-on experience for learning interprofessional work ethics, team dynamics and communication.

Poster 5 (P5): Enhancing Team-based Learning of Pharmacology Using Technology-assisted Prerequisite Content Preparation

Author: Ashim Malhotra
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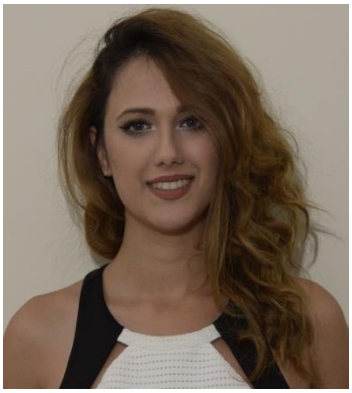
Abstract: Team-based learning engages students in a pedagogy that begins with pre-class self-directed preparation, leading up to an in-class individual Readiness Assurance Test (iRAT). Although TBL encourages active participation, team dynamics and other factors may lead to grade inflation. The California Northstate University College of Pharmacy employs a hybrid-TBL approach in the first, second and third professional years (P1, P2, P3) of the Doctor of Pharmacy program. To enhance TBL delivery in our pharmacology courses, we prepared a series of video lectures using online technology to help students prepare for their iRATs and tRATs. These short “Info-Blast” video lectures were typically 30-40 minutes in length, posted to YouTube, and emphasized the salient learning objectives, goals, terminology, and concepts included in prerequisite content required for upcoming pharmacology course lectures. Lectures included Pharmacogenomics, Biotechnology and An Introduction to Viruses in the Cell and Molecular Biology course (P1), and the pathophysiology of arrhythmia, the pharmacology of antiarrhythmic drugs, dyslipidemia, and dyslipidemia drugs in the Pathophysiology and Pharmacology II, Cardiovascular Sciences course (P2). The YouTube videos were accompanied by documents detailing self-directed Learning Objectives and a Practice Question Workbook, all of which were posted at least two weeks ahead of the class. Students provided comments and suggestions verbally and via email which were strongly positive. Student iRAT scores and exam performance scores were captured using TurningPoint and ExamSoft and showed a positive correlation with the number of hours spent watching the video lectures. Among the advantages mentioned by students was the ease of access, the ability to repeat the lecture and detailed clarity added to expectations regarding outcomes and performance. One disadvantage mentioned was the extra time needed to prepare using the enhanced content, which we hope to address by using online technology such as InsertLearning to incorporate textual sources with the posted video lectures.

Poster 6 (P6): Effects of Red Clover Fractions on Cell Viability and Pro-Inflammatory Cytokine Secretion



Authors: PanizJenabzadeh, George Talbott, TibebeWoldermariam, Leo R. Fitzpatrick
Department of Pharmaceutical & Biomedical Sciences, California Northstate University College of Pharmacy, Elk Grove, CA

Abstract: Recent results from our laboratory have identified plant extracts with anti-colitis activity [1]. Red Clover derived extracts have received recent attention due to its anti-inflammatory effects. Therefore, we were highly interested in examining the pharmacological actions of red clover in macrophage and colonic epithelial cell lines, which have some applicability to human Inflammatory Bowel Disease (IBD).

Methods: The obtained residue from the red clover extract methanol mixture was chromatographed, which yielded five fractions containing different concentrations of red clover components. Then, the anti-inflammatory effect of the red clover crude extract and fractions were examined by pre-treating colonic epithelial (HT-29) and murine macrophage (RAW 264.7) cell lines with these derivatives (10, 30, and 300 µg/mL concentration ranges). In these studies, LPS (1µg/mL) was used to stimulate RAW-264 cells and TNF-α (10 ng/mL) to stimulate HT-29 cells. Commercially derived Diadzein and Genistein were used as positive control drugs with the macrophage cell line. In conjunction with these studies, wequantitatively measured the amount of secreted TNF-α (macrophage cell line)and IL-8 (colonic epithelial cell line) with commercially available ELISA kits. We also performedMTT assays to determine the viability of HT-29 cells after red clover treatment.

Result: Significant reductions in IL-8 and TNF-α secretion were obtained with crude Red Clover extract and tested fractions, but only at a concentration of 300 µg/ml. Diadzein and Genistein (1 µM) also blocked TNF-α secretion by macrophages. Red Clover derivatives (300 µg/ml) had no effect on colonic epithelial cell viability.

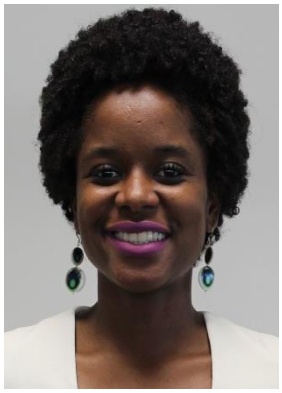
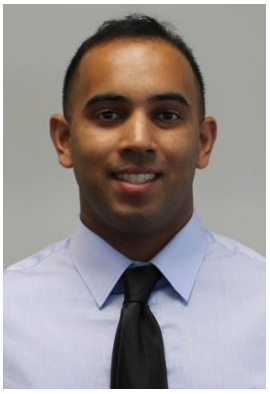
Conclusion: Red Clover crude extract, and its fractions with high concentration, reduced pro-inflammatory cytokine secretion in cell lines applicable to IBD.Future studies, will expand upon these results, including possible testing in other pertinent *in vitro*, *ex vivo* or *in vivo* models of IBD and possibly increasing the number of testing to acquire more significant results.

Poster 7 (P7):Proteomic Analysis by Mass Spectroscopy of Cryoprecipitates from Patients with HCV Associated Cryoglobulinemic Vasculitis Undergoing Direct Acting Antiviral Treatment Compared to Patients with Persistent Cryoglobulinemia after Sustained Viral Response

Authors: Ahmed El-Shamy[1,2], Francis Eng[1], Erin H Doyle[1], Thomas Schiano[1], Andrea Branch[1] and Peter Gorevic[3].
[1]Division of Liver Diseases Icahn School of Medicine at Mount Sinai, New York, New York;
[2] Department of Pharmaceutical and Biomedical Sciences Collage of Pharmacy California Northstate University and
[3] Division of Rheumatology Icahn School of Medicine at Mount Sinai, New York, New York

Background and Aim: Mixed cryoglobulinemia (MC) is strongly associated with HCV infection, but also occurs in autoimmune diseases. HCV cure decreases cryoprecipitates (CPs). We aimed to determine the impact of HCV cure on the composition of CPs and on cryoglobulinemic vasculitis (CryoVas) in patients treated with antiviral drugs.
Methods: CPs were isolated from sera of a) 10 HCV patients enrolled in a prospective trial (NTC0282512) of antiviral treatment (Harvoni/Epclusa) with 24-wk follow-up of CPs and extrahepatic symptoms; b) 5 patients with persistent MC and Cry/Vas 2-15 yr after HCV cure; and c) 4 HCV-negative patients with MC and Sjogrens syndrome or lupus. CPs were analyzed by qRT/PCR for HCV RNA and by Western blotting, mass spectroscopy, and immunofixation. Immunoglobulin (Ig), Ig free light chain (FLC), and components of complement pathways (C') were quantified in serum. The relationships between concentrations of C4 and concentrations of C1q, C4-binding protein (C4-bp), C1 esterase inhibitor, and C4a were analyzed. CP and C' components were analyzed by mass spectroscopy.
Results: At baseline, extrahepatic symptoms of the 10 DAA-treated patients included arthropathy (n=8), cutaneous manifestations (n=6) and neuropathy (n=5). All had C4a elevation, an indicator of C4 cleavage. C4a concentration was directly related to CRP concentration and inversely related C4 and C1q concentrations. Total hemolytic complement activity (CH50) was depressed in 7/10, indicating FLC was elevated in all 10 and in other κactivation of the classical complement pathway. Serum restriction in CPs. Among HCV+ patients, CPsκFLC was associated with κpatients with persistent MC. had 5-20% of the HCV RNA in the sample. The 10 DAA-treated patients cleared HCV by wk 2-3. CryoVas improved in 7/10 and stayed the same in three. CH50 decreased during HCV treatment. CPs of patients -IgG. Western blots showed that CPs containedκwith persistent MC after HCV cure were all Type 2 IgM IgM, IgG, C1q and C4-bp. Mass spectroscopy analysis showed that the immunoglobulin and complement-related proteins are the prominent components of CP. Conclusions: We conducted serial measurements of C' measurements in serum and performing proteomic analysis of peptides from isolated CPs by mass spectroscopy and obtained new details about restriction, and C4 activation. The findings support published data showing that CPsκCP composition, and Cryovas may persist for long periods of time following clearance of HCV, which may indicate a pathogenic similarity to the MC/Cryovas/C4/C1q depletion reported in other autoimmune diseases.

Poster 8 (P8): Elucidation of the mechanisms which regulate Nrdp1 localization and function in prostate cancer cells, and their contribution to prostate cancer health disparities

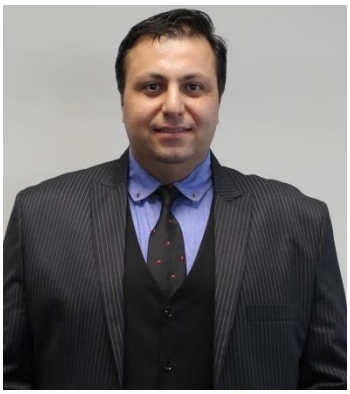

Authors*:* Shawna Evans*[1], Adarsh Konda*[1], Anhao Sam*[1], Sheryl Krig[1], Neelu Batra[1], Thomas Steele[2,3],Salma Siddiqui[2], Paramita M Ghosh[2,3], and Ruth L Vinall[1]
[1]California Northstate University, Elk Grove, CA, [2]VA Northern California Health Care System (VANCHCS), Mather, CA;[3]University of California Davis (UCD), School of Medicine, Sacramento, CA.

Abstract: In 2015, the last year for which SEER data has been released, African American (AA) men were 2.12 times more likely to die from prostate cancer (CaP) compared to their Caucasian American (CA) counterparts[1]. Higher rates of biochemical recurrence (BCR) and worse response to the standard of care treatment for BCR, androgen deprivation therapy (ADT), likely contribute to this disparity; recent evidence indicates that AA CaP patients are more likely than CA CaP patients to experience BCR, and ADT use has been shown to shorten survival in AA men with favorable-risk CaP[2-4]. The goals of the current study were to determine whether dysregulation of Nrdp1 contributes to these worse outcomes and to elucidate the mechanisms involved.

We previously demonstrated that Nrdp1, an E3 ubiquitin ligase, is a transcriptional target of the androgen receptor (AR) and that Nrdp1 levels are reduced by ADT in CA CaP cell lines[5, 6]. Nrdp1 regulates levels of multiple targets including ErbB3, a molecule that is associated with ADT resistance. We now show that racial differences in Nrdp1 expression and localization exist. Immunohistochemistry (IHC) in prostate tissue determined that nuclear Nrdp1 levels are significantly lower in AA CaP patients (n=19) versus CA CaP patients (n=121) with localized disease (p=0.008), and that nuclear Nrdp1 expression levels correlate with rates of BCR (p=0.0324). Subcellular fractionation experiments using AA and CA CaP cell lines followed by western blot confirmed that Nrdp1 can be located in the nucleus as well as the cytoplasm of CaP cells (this has not previously been reported), and that AA CaP cells express dramatically lower levels of nuclear Nrdp1. Our data indicate AR plays a role in determining Nrdp1 localization;knockdown of AR or treatment with enzalutamide reduced levels of nuclear Nrdp1, while treatment with synthetic androgen increased Nrdp1 levels. Immunoprecipitation experiments verified Nrdp1 can bind to AR,and demonstrated it can bind to several other nuclear proteins which may play a role in CaPprogression.In patients, a strong negative correlation exists between nuclear Nrdp1 and cytoplasmic (inactive) AR ($R=-0.64$, $p<0.001$) in AA tumors, but a weak negative correlation between cytoplasmic (inactive) AR and nuclear Nrdp1 in CA ($R=-0.37$, $p<0.001$). Lastly, forced overexpression of Nrdp1 in CaP cell lines resulted in increased levels of ubiquitination in both the nucleus and cytoplasm, indicating Nrdp1 retains its function as a ubiquitin ligase in both locations.

In summary, our patient and in vitro datademonstrate that AA cells express significantly lower levels of nuclear Nrdp1 compared to CA CaPcells and that a consequence of lower levels of nuclear Nrdp1is reduced ubiquitination of nuclear proteins.The involvement of AR in mediating nuclear translocation of Nrdp1 indicates ADT may further lower nuclear Nrdp1 levels in AA CaP patients and thereby contribute to worse outcomes. Next steps will be tofurther elucidate thefunction of nuclear Nrdp1 and to determine the contribution of Nrdp1 and its downstream effectors to driving CaP health disparities.

Poster 9 (P9): Evaluating Polyphenolic Dietary Compounds in Cellular Models of Pancreatic Cancer



Authors: Mohammad Amin Asadirad, Britney Satow, James Lugtu, George Talbott, TibebeWoldemariam, Ashim Malhotra
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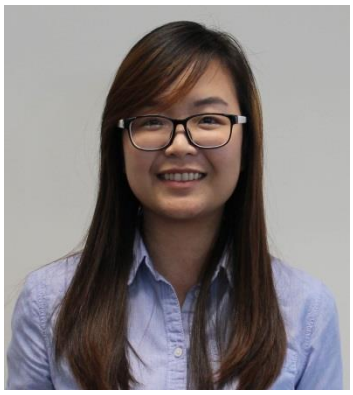
Abstract: Pancreatic cancer (PCa) hasa poor 5-year survival rate of 6-8% following diagnosis. Although PCaincidenceis lower than carcinomas like those of the breast and prostate, lack of targeted therapy, paucity of early detection, and a sparse biomarker profile outline the gap in our understanding of its etiology and pathophysiology. Pancreatic ductal adenocarcinoma begins as a dysplasia driven by mutations in a variety of genes such as the human homologue of the Kirsten Rat Sarcoma viral oncogene (*KRAS*). Although *KRAS* mutations occur in 90 percent of PCa patients, little is known about its downstream signal transduction. There is also a gap in our knowledge about how xenobiotics such as drugs and food affect the regulation of the aberrant K-ras signaling system in PCa cells. To address this and to identify protein regulators of K-ras signaling that orchestrate mitochondrial responses, we prepared aqueous extracts of Middle Eastern (sumac, dill, artichoke, noni, rose) and Indian (curry leaves) dietary components and treated human PCa cells in culture. We employed two PCa cell lines, one with the well-established (MIA PaCa-2) and another with a less common *KRAS*mutation (PANC-1) to elucidate whether there was a genetic selectivity in response. We identified that aqueous extracts of sumac and artichoke (AESA) precipitated cytotoxicity in both the PCacell lines, while sparing the non-tumor mouse fibroblast cell line NIH 3T3, suggesting specificity. To further explore AESA, we used preparative reverse phase HPLC, isolating 3 peaks and retested the bioactivity of the fractions. The fraction with maximum cytotoxicity was analyzed by mass spectrometry to identify pentagalloyl glucose as the active ingredient. We hypothesize that AESA induce apoptosis in *KRAS*-mutant PCa cells and are elucidating the effect of AESA on mitochondrial membrane potential and ROS production to identify the cause of AESA-mediated cell death.

Poster 10 (P10): Role of Sirt3 in Lipid Generation



Authors: Oanh Ma and Truc Le, George Talbott, Sarah James, Dimple Vallabh, Linh Ho
California Northstate University College of Pharmacy, Elk Grove, CA 95757, USA

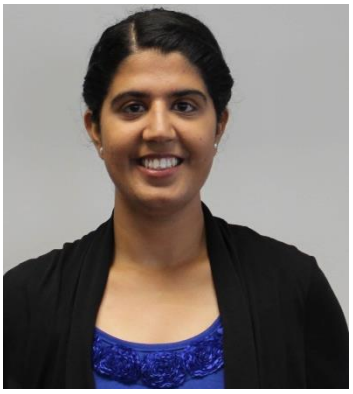
Abstract: Sirt3 is a major mitochondrial deacetylase which has important roles in regulation of metabolic homeostasis and metabolic diseases. ST2 cells are mesenchymal stem cells taken from bone marrow.The purpose of this research is to identify if Sirt3 plays a role in marrow adipogenesis to regulate insulin sensitivity through adipokines, especially adiponectin using ST2 cell models.

Particularly, we used the gain-function of Sirt3 in ST2 cells to assess the role of Sirt3 in adipogenesis. We were able to successfully overexpress Sirt3 and differentiate ST2 cells into adipocytes. We found that the induction of Sirt3 leads to increased adipogenesis compared to controls. The increase in adipogenesis was in line with elevated triglyceride levels in Sirt3 overexpression compared to controls ($P < 0.01$ in day 5 and $P < 0.05$ in day 7 after differentiation). This data is consistent with the increase in percentage area of adipocytes, which was highly significant in Sirt3 overexpression than that in the controls using Oil Red O staining ($P< 0.01$). The induction of adipogenesis by Sirt3 is associated with increased gene expression of adipocyte markers as well as adiponectin/adipokines.

In addition, we inhibit Sirt3 function in ST2 cells using an inhibitor of Sirt3 called 3-TYP. We treated cells with 50µM and 100M of 3-TYP, versus control. Our results show that ST2 cells treated with Sirt3 inhibitor decreased adipogenesis by reduced area of adipocytes compared to controls especially at 100µM of 3-TYP($P<0.05$). Triglyceride measurements of 3-TYP treated cells versus controls showed consistent results with reduced adipogenesis, especially at 100µM on day 5 (p-value <0.001).The expression levels of adipocyte markers and adiponectin/adipokines were statistically significantly reduced compared to the controls.

These statistically significant consistent data suggest that Sirt3 gene plays an important role in modulating adipogenesis and adiponectin/adipokines expression. We hope our study contributes to the efforts of revealing Sirt3 functions in metabolic homeostasis and diseases. The ultimate goal is to use Sirt3 as a potential target in treating insulin resistance and other metabolic abnormalities.

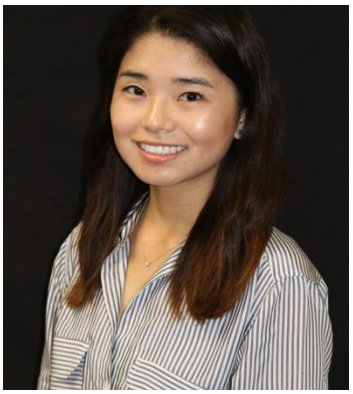
Poster 11 (P11):The Use of Flipped Classroom Pedagogy and Other Active Learning Strategies in US Pharmacy Schools



Authors: Christina Stephenson B.S., Janie Yu B.A., Tiffannie Nguyen B.S., Shawna Evans B.S., Luis Tolento B.S., Harpreet Kaur B.S., Tiffany Wong B.S., Ravneet Kaur B.S., Eugene Kreys Pharm.D., Ph.D., BCPS, Tiffany Jade-Kreys Pharm.D., BCPP

Rational: A flipped classroom is a learning method that encourages active-learning by reversing the traditional learning environment and delivering instructional content outside of the classroom, while bringing the application of the content into the classroom. Flipped classroom can be implemented in a variety of methods including through team based learning (TBL) and problem based learning (PBL). Team-based learning is a structured method that revolves around a three-step process: preparation, in-class readiness assurance testing, and team-based application exercises. Problem-based learning is a teaching method where students learn about a topic by working in teams to solve open-ended real-world problems. A 2010 survey evaluating the extent of active-learning techniques used in schools of pharmacy found that 87% of pharmacy faculty use some type active-learning strategy, with problem based learning (PBL) reported as the most common at 71%. Since the study was conducted; twenty-three new schools of pharmacy were established. Beyond simply including these schools in our survey, our study also focuses on the use of active-learning strategies, but with the emphasis in flipped classroom pedagogy, in the overall curricula of pharmacy schools rather than individual use by faculty members. Objective: The purpose of this study is to evaluate the use of flipped classroom method of teaching and other active learning strategies in U.S. colleges/schools of pharmacy. Methods: This was a cross-sectional study conducted using an eight-item multiple choice survey. The survey was administered to the deans of academic affairs of all 138 active pharmacy schools in the US. The study was IRB approved and collection of the survey responses was conducted on an anonymous basis. The survey items included questions asking information on the characteristics of pharmacy schools, the type of teaching pedagogy used within the curriculum, and to what extent these methods are used based on the general type of courses. The primary analysis was limited to descriptive statistics. Using non-parametric statistical tests, secondary analysis was used determine association between college's general characteristics and their utilization of flipped classroom pedagogy and other active-learning strategies. Results: The study has been completed and a total of 74 (54%) of the subjects contacted completed the survey. Of the 74 pharmacy schools that participated in the survey, 97% utilize some form of active learning strategies and 81% percent employed a flipped classroom pedagogy. Of these, only 27% exclusively employ TBL, 2% exclusively employ PBL, while 72% employ either a combination or some other form of flipped classroom pedagogy. Exactly half of the colleges were established after 1995, 53% maintain an average class size of less than 100, and 51% are public institutions. Thirty-nine percent of the schools completing the survey are located in the South, followed by the Midwest (23%), Northeast (19%), and the West (19%). Older schools (established on or before 1995) were less like to be smaller (average class size < 100) (Odds Ratio = 0.04 [95% Confidence Interval: 0.01 – 0.15]) and less likely to be private (OR = 0.09 [95% CI: 0.03 – 0.26]). Likewise smaller schools were more likely to be private (OR = 3.73 [95% CI: 1.4 – 9.90]). No statistically significant association was observed between the location of the college and any of the other general characteristics. Conclusion: Based on the preliminary analysis, some use of flipped classroom is common; however, the frequency at which this pedagogy is used varies greatly based on the course type. Such that Clinical/Pharmacy Practice courses demonstrated the most frequent use, followed by Social and Administrative Science courses, and Basic Science courses demonstrating the least frequent use. Similar findings were observed in schools exclusively employing TBL. Larger schools were more likely than smaller schools to employ flipped classroom. Of the schools that employ flipped classroom pedagogy, the smaller schools were more likely to use TBL exclusively compared to the larger schools.

Poster 12 (P12):Efficacy and Tolerability of Non-Daily Statin Administration: A Systematic Review of Literature



Authors: So Young (Christina) An, PharmD
California Northstate University College of Pharmacy/Adventist Health Lodi Memorial
9700 West Taron Drive, Elk Grove, CA 95757

Abstract: Amongst many different medication classes of dyslipidemia, statins are best known for lowering LDL and reducing cardiovascular events in majority of patients. Statins are generally well tolerated by the patient population, however, there are a small percentage of patients who end up discontinuing statin therapy due to undesired side effects. Finding different strategies to maintain statin use and adherence is important to continue using statin therapy. To maximize the advantages statins has to offer, it is beneficial to find different strategies to maintain its use. The primary objective of this study was to summarize the efficacy, tolerability, and cost effectiveness of non-daily statin administration from the past 11 years. Cochrane, PubMed, Embase and Web of Science was searched to collect relevant literatures dated between 2007 to 2018 to complete this study. After eliminating thousands of studies based off inclusion and exclusion criterias, a total of 15 studies were eligible for study. Despite various study methods, all studies shared a common result of supporting the use of intermittent statin regimen to lower lipid levels in patients with dyslipidemia. Thus the administration of non-daily statin regimen was proven to be an effective and safe alternative for patients who are intolerable to daily statin regimen.

Poster 13 (P13): Effect of Therapeutic Hypothermia on Drug Metabolism

Authors: Author: Andes Wong
Purpose: Understand the effect of therapeutic hypothermia on drug metabolism
Introduction: Therapeutic hypothermia protocol has been used for the treatment of cardiac arrest and traumatic brain injury since 1940. At that time, we assume its effects only limited to reduction in metabolism, which lead to decrease oxygen and glucose's demand to the brain. However, the true pathophysiology behind it is much more complex than we thought. The poster will help us understand the pathophysiology and learn the process of therapeutic hypothermia protocol. Additionally, it will also demonstrate the change in drug metabolism and electrolytes shifting under the body temperature modification.

Poster 14 (P14):Comparing the impact driven by the Transitions of Care Pharmacy Team

Authors: Tiffany Chu, Pharm.D. PGY1 Resident
Adventist Health White Memorial Pharmacy
1720 East Cesar E. Chavez Avenue
Los Angeles, CA 90033

Introduction: Hospital admissions are a significant concern for not only patient safety, but also for payers, providers, and policymakers who seek to improve health care and lower health care cost. Readmissions may be due to poor communication between physicians and patients during transitions, patients' lack of understanding of medications, lack of resources, or incomplete medication histories.

Purpose: The primary objective of this study is to evaluate the impact of a Transitions of Care on readmission. The secondary objective is to evaluate which intervention is commonly made to impact readmission.

Methods: The Transitions of Care (TOC) services included collaboration between physicians, pharmacists, pharmacy residents, pharmacy students, pharmacy technicians, and nurses. Once patients were admitted to the hospital, pharmacy technicians or pharmacy students updated the patient's medication list. The pharmacist then made recommendations to the medication profile upon admission and discharge. TOC clinic follow-up appointments were scheduled within 48-72 hours post-dischargethrough referrals from physicians. Services provided included: medication education, Medi-Safe set-up for medication adherence, contacting physicians to resolve medication issues, providing medical devices, monitoring the patient's vitals and labs, and referrals to the Community Information Center (CIC).A retrospective chart review was completed by manually extracting data from high-risk lists for patients referred to the TOC services from October through December 2018 and comparing interventions made by the pharmacy team.

Results:A total of 1282patients were examined from October through December 2018 with 499 patients intervened on (38.9%). 382 interventions were made which included: 151 initiated medication to regimen, 126 labs ordered, 67 discontinued medication, and 38 discontinued medications. 276 medication histories were also adjusted.

Conclusion: The two common services included medication history adjustments followed by initiation of medications to current regimens.TOC program driven by a pharmacy team pharmacists have the potential to make a significant impact on reducing hospital readmission rates.

Poster 15 (P15): miR-155; a negative regulator of acute oscillatory shear stress-induced AT1R/ETS-1 pathway and downstream vascular inflammation and barrier dysfunction

Authors: Islam Mohamed[1], Sheena Thomas[2] BS, Kim Rooney[2] BS, Nick Willet[3] PhD, W. Robert Taylor[2] MD, PhD and Charles D. Searles[2] MD.

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Rationale: Atherosclerotic lesions preferencially localize to areas that are exposed to low magnitude oscillatory shear stress (OSS) forces. MicroRNA-155 (miR-155) and Angiotensin II Receptor Type 1 (AT1R) expression are known to be shear-responsive and can potentially modulate vascular inflammation through the E26 transformation-specific sequence factor-1 (ETS-1) pathway. Nevertheless, little is known about the interplay between miR-155 and AT1R/ETS-1 pathwayin response to OSS in vivo and whether targeting miR-155 can prevent OSS-induced vascular inflammation.

Objective: To test the hypothesis that acute induction of OSS in vivo increases vascular inflammation and barrier dysfunction through activation of AT1R/ETS-1 and determine whether this pathway is modulated by shear responsive miR-155.

Methods: C57B/6J wild type (WT), miR-155 knockout mice (KO) and AT1Ra-KO were subjected to abdominal aortic coarctation (AAC), a unique model of acute induction of OSS in mouse abdominal aorta, for 3-7 days. miR-155 expression was enhanced by tail vein injections of lentivirus particles and Candesartan treatment was used to block AT1R in WT mice. Downstream acute OSS segments were compared to upstream unidirectional shear stress (USS) segments using RT-PCR, western blot and two-way ANOVA.

Results: In WT mice, acute OSS resulted in differential expression of AT1Rb versus AT1Ra isoform, along with increased miR-155, ETS-1 and downstream inflammatory mediators and vascular permeability in OSS compared with USS aortic segments. miR-155-KO mice showed enhanced ETS-1 pathway in OSS versus USS segments, while ETS-1 pathway was suppressed upon exogenous delivery of miR-155 in WT mice. OSS-induced vascular inflammation was enhanced in AT1Ra-KO mice along with decreased miR-155 levels, whereas, EST1 proinflammatory pathway was partially attenuated by Candesartan treatment in WT mice.

Conclusion: These data support a negative feedback relationship between miR-155 and pro-inflammatory AT1R/ETS-1 pathway in response to OSS in vivo. Our findingssuggest miR-155 as a novel potential therapeutic target for vascular inflammation.

Poster 16 (P16): Novel method for hemivisual field restriction under naturalistic conditions, for clinical applications.

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Abstract:Hemivisual field restriction is a challenging task that holds promise for simulating, measuring and monitoring psychological, neurological, and ophthalmological conditions. I describe a novel way to restrict visual information to corresponding left or right hemivisual fields of both eyes simultaneously, during free ocular scanning, using a combination of polarized contact and spectacle lenses. This apparatus improves upon existing visuospatial lateralization techniques by correcting for refraction errors, lens slippage, and individual differences in orbit, eye, and retina morphology. This combination of parts and improvements will also allow for cheaper, easier, and more accurate psychological and neurological testing of basic and higher cognitive properties in both normal and clinical populations. Furthermore, the apparatus may contribute to a more detailed understanding of the human visual system and the dual hemispheric design that defines the mammalian brain, for existential, as well as for commercial applications.

Poster 17 (P17): Second Generation Irreversible Proteasome Inhibitor (SGIPI), Betulinic Acid (BA), Lemongrass Essential Oil (LEO) and Bitter Melon extract (BM) differentially modulate hepatic steatosis in HepG2-C3A cells

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Abstract: Hepatic steatosis (Nonalcoholic fatty liver disease, NAFLD) is one of the most common form of chronic liver disease around the world, especially in the Western nations. Nonalcoholic steatohepatitis (NASH) is present in one-third of the adult population in the United Statesand free fatty acid (FFA) uptake is a major contributor to these processes.Therefore, understanding fat accumulation in hepatocytes is key to the pathophysiology of the hepatic steatosis metabolic disease. In the current study investigated whether increased concentrations of commercially available Lipid Mixture-1 (LM-1) in solution lead to increased levels of FFA and its modulation with Second Generation Irreversible Proteasome Inhibitor (SGIPI), Betulinic Acid (BA), Lemongrass Essential Oil (LEO), and Bitter Melon (BM) extract in C3A cells. Hepatoma cells (HepG2-C3A) were cultured in EMEM containing 10% heat-inactivated fetal bovine serum and 1% penicillin-streptomycin mixture at 37^0C, 5% CO_2. Cells were treated or untreated with LM-1 as well as various concentration of potential modulators namely;Second Generation Irreversible Proteasome Inhibitor (SGIPI), Betulinic Acid (BA), Lemongrass Essential Oil (LEO), and Bitter Melon (BM) extract to assess the cell-viability. Cells were treated or untreated with Lipid Mixture 1 (LM1) for six-days followed by non-toxic concentration of each modulator for an additional 2 days before assessing for FFA uptake and accumulation byOil Red O (ORO) neutral lipid staining and triglyceride (TG) content measurement by spectrophotometer. We observed that LM-1 significantly increased FFA uptake and accumulation in comparison to vehicle control. Furthermore, Second Generation Irreversible Proteasome Inhibitor (SGIPI), Betulinic Acid (BA), Lemongrass Essential Oil (LEO), and Bitter Melon extract (BM) differentially modulate FFA uptake and accumulation in C3A cells. These results suggest that an increase in FA uptake can be mitigated by various modulators used in the study that could be utilized to reverse the course of the fatty liver disease. Further studies will delineate the molecular mechanism of modulators in the modulation of hepatic steatosis.

Poster 18 (P18): Serum Free Differentiation of Adipocytes from the 3T3 L1 Pre-adipocyte Fibroblast Cell Line

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Abstract: Obesity is a global public health concern. The prevalence of this disease is increasing at an alarming rate, especially in developing countries leading to designation by the world health organization as an epidemic. Obesity is caused by an overabundance of calorie intake, however more research is needed into the molecular mechanism for adipose accumulation. Investigations into lipid accumulation commonly involve the adipocyte model derived from the NIH-3T3-L1 pre-adipocyte cell line. Commonly, induction of differentiation is achieved using Fetal Bovine Serum. Tight control of compounds available in medium necessitates a method for differentiation in absence of poorly defined serum. Our project investigates whether a serum-free differentiation can be achieved using BSA, fatty acids, and growth factors in absence of fetal calf serum to increase levels of free fatty acid (FFA) uptake and adipogenesis in 3T3-L1 pre-adipocyte cells in a static culture.NIH-3T3-L1 pre-adipocyte cells were maintained in DMEM containing 10% fetal calf serum and 1% penicillin-streptomycin mixture at 37^0C, 5% CO_2 in a humidified atmosphere. Differentiation was induced using Dexamethasone-0.25 µM, 3-isobutyl-1-methylxanthine (IBMX-0.5 mM), Insulin-10 µg/mL or ITS-1%. Cells were cultured in media containing DMEM with bovine serum albumin (BSA-2.5%) and Lipid mixture 1 (LM1-1%).We observed that serum-free differentiation shows increased fatty acid accumulation relative to controls using Oil Red O neutral lipid staining and spectrophotometry. However, differentiation with fetal calf serum outperformed the experimental media. This experiment suggests that serum-free differentiation can lead to fat accumulation in NIH-3T3-L1 pre-adipocyte into mature adipocyte. Further studies are required to better understand the cellular process of adipocyte differentiation and use of potential modulators that may be utilized to reverse the course of the adipocyte differentiation in serum-free conditions.

Poster 19 (P19): Serum-free Condition Induces Both Adipogenic and Lipogenic Gene Expression During Differentiation of 3T3 L1 Pre-adipocyte Mouse Fibroblast into Mature Adipocyte

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Abstract: Obesity is a global epidemic implicated in rising rates of heart disease, type II diabetes, stroke, and overall mortality. Addressing this epidemic requires models for investigating adipose accumulation. One such model utilizes adipocytes differentiated from 3T3 L1 preadipocytes using fetal bovine serum and induction media. Due to concerns regarding the scarcity, consistency, and contamination of serum, a means of achieving differentiation in absence of serum is needed. We have previously observed that serum-free differentiation increases fatty acid accumulation with Oil Red O neutral lipid staining and spectrophotometry. In this study, a serum-free differentiation using BSA and growth factors supplemented with fatty acids in lieu of fetal bovineserum was utilized and the levels of expression of adipogenic/lipogenic including peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT/enhancer binding protein alpha (C/EBPα) key transcription factors, fatty acid binding protein 4 (FABP4/aP2), fatty acid translocase (FAT, also known as CD36) and Peripilin genes were quantified. Mouse fibroblast (3T3-L1 pre-adipocyte) cells were maintained in DMEM containing 10% Fetal Calf Serum and 1% penicillin-streptomycin mixture at 37^0C, 5% CO_2 in a humidified atmosphere. Cells were cultured for 6 days in media containing either DMEM or F12 with bovine serum albumin (BSA-3%) and Lipid mixture 1 (LM1-0.1%). Differentiation was induced on day 0 using Dexamethasone-0.25 µM, 3-isobutyl-1-methylxanthine (IBMX-0.5 mM), Insulin-10 µg/mL with half the wells receiving treatment on day 4 with Rosiglidazone-0.2µM. Total RNA was extracted and performed quantitative-RT-PCR of adipogenic and lipogenic genes.We observed significantly increased expression of adipogenic/lipogenic *PPAR-γ, C/EBP-α*, FABP4/*aP2*, FAT/CD36 and Peripilin genes in comparison to both untreated control and standard adipogenic differentiation protocol. Our observations suggest that serum-free differentiation can lead adipocyte maturation by increasing adipogenic and lipogenic gene expression. Further studies are required to better understand the cellular process of adipocyte differentiation and use of potential modulators which can be utilized to reverse the course of the adipocyte differentiation in serum-free conditions.

Poster 20 (P20): Real-world Experience with Ledipasvir/sofosbuvir Combination and velpatasvir/sofosbuvir Combination in Patients with Chronic Hepatitis C Genotype 6 Patients in the United States

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Background and Aims: Genotype 6 (GT6) is a rare sub-type of hepatitis C virus (HCV). As such, GT 6 has been underrepresented in clinical trials that use the new interferon- and ribavirin-free all oral acting agents (DAA's) to treat and cure HCV, limiting the generalization of the results. A newer DAA combination of sofosbuvir (SOF) and velpatasvir (VEL) was recently approved for treatment of HCV GT 6. The study's aim was to compare sustained virologic response (SVR12) rates between the first approved DAA ledipasvir (LDV)/SOF and SOF/VEL for treatment naive, cirrhotic, and non-cirrhotic GT6 patients.

Method: This was a retrospective study of adult patients with HCV GT6 (n=148) who were treated with either LDV/SOF (n=99) or SOF/VEL (n=49) for 8-24 weeks from 2014-2017 at 2 community clinics in the United States. All patients in the SOF/VEL group were treated for 12 weeks. Of the patients in the LDV/SOF group, 5 patients were treated for 8 weeks, 91 patients for 12 weeks and 3 patients for 24 weeks. These patients were not in any previous clinical trials. After excluding patients who did not yet have SVR data(n=17), patients with hepatocellular carcinoma (HCC) (n=7) and/or prior treatment (n=12), the LDV/SOF group had 73 patients and the SOF/VEL group had 33 patients. Of the 7 HCC patients, all except 1 were in the LDV/SOF group and all had cirrhosis, except 1, who was in the LDV/SOF group.

Results: The mean age was 63.3±10.2 years, with 67% male, 94% Vietnamese and 97.3% GT6 and 2.7% GT 6c (all in the LDV/SOF group). There was a higher percentage of cirrhotic patients (47.5%) in the LDV/SOF cohort than the SOF/VEL cohort (16.3%, p<.001). Overall, 94.5% of LDV/SOF cohort achieved SVR12 compared to 100% of the SOF/VEL cohort. Among the non-cirrhotic patients, 94.9% of LDV/SOF cohort achieved SVR12 compared to 100% of the SOF/VEL cohort. Among patients with cirrhosis, 94.1% of the LDV/SOF achieved SVR-12 compared to 100% of the SOF/VEL cohort (Table).

Conclusion: Treatment-naïve non-cirrhotic HCV-6 patients had 100% SVR12 rate with 12 weeks of SOF/VEL therapy. The few treatment-experienced and cirrhotic SOF/VEL patients also had 100% SVR. For the LDV/SOF group, SVR12 was about 95% for treatment-naïve patients regardless of cirrhosis status but was only 88% in the few treatment-experienced patients. Additional real-world data is needed for SOF/VEL for cirrhotic and/or treatment experienced patients, but overall, SOF/VEL was superior to LDV/SOF.

Poster 21 (P21): Buproprion Associated Seizures Following Acute Overdose

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Background: Patients with bupropion overdose are routinelyobserved for prolonged periods due to concerns for delayed seizures. The study sought to evaluate characteristics of bupropion ingestions and attempt to determine an appropriate observation period.
Hypothesis: Patients with bupropion toxicity will have antecedent altered mental status (AMS) and/or tachycardia before their seizure.
Methods: This multicenter,retrospective study, utilized standardized data abstraction methods, included all patients who presented with a bupropion ingestion to one health system (20 hospitals), one toxicology practice (5 hospitals), and toxicology referral center. Data collected included demographics, ingestion history (time, dose, preparation), clinical characteristics (vital signs, seizures, AMS)length of stay, and treatment. Medians (IQR) were utilized for descriptive statistics, *Chi* square and/or Fisher's exact for categorical variables. Logistic regression was performed to assess for confounders.The following definitions were used: delayed seizure (1st seizure > 8 hours post arrival); persistent tachycardia (tachycardia lasting > 2 hours).
Results: 437 encounters were identified. The median (IQR) age was 28 (18-43) years; 275 (63%) were female. 78% of cases involved intentional exposures. Accidental double-dose ingestions accounted for 39 (8.9%) cases. Seizures occurred in 122 (27.9%) subjects (68 pre-hospital seizures, in-hospital seizures).The median (IQR) length of stay was 36 (12-72) hours. Using logistic regression, the tachycardia or AMS at arrival were each associated with an increased oddsof seizure (OR 3.98 [95% CI 2.2-7.3] for tachycardia; OR 2.65, [95% CI 2.18-7.26] for altered mental status). Only 1 of 143 subjects who arrived without tachycardia or AMS had a delayed seizure (0.7%; 95% CI 0.02-3.9%).Of 8 cases with delayed seizures, all had persistent tachycardia prior to the seizure.
Conclusion: Seizures are common following bupropion overdose and are predicted by tachycardia or AMS. Seizures beyond 8 hours of observation are unusual and were accompanied by antecedent tachycardia and/or AMS.

Poster 22 (P22):*Ex Vivo* Effects of ROR-gamma t Inhibitors on Pro-Inflammatory Cytokine Secretion from Colonic Strips of Mice with DSS-Induced Colitis

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Abstract: ROR gamma t (RORγt) inhibitors (e.g., GSK 805, VPR 254) have shown efficacy in murine models of colitis. To determine an optimal compound(s) for further in vivo testing, we utilized an ex vivo colonic strip model from mice with DSS-induced colitis. This colitis has been proposed by some investigators to involve IL-17, IL-21 and CCL20, which are under transcriptional control by RORγt. Therefore, we hypothesized that secretion of these cytokines by colonic strips would be attenuated by RORγt inhibitors. Methods: Five RORγt inhibitors were obtained from Visionary Pharmaceuticals (San Diego, CA). Dextran Sulfate Sodium (DSS) was given to male C57BL/6 mice (n = 16) in the drinking water (2% concentration), for a six-day period, to induce colitis. Control mice (n = 8) received water. The ex vivo effects of the RORγt inhibitors (0.05 to 5 μM concentration range) were tested in our 24 hour colonic culture system [Fitzpatrick et al., Inflammopharmacology, 2014]. We utilized ≈ 4 mm colonic strips (n = 4 to 10 per RORγt inhibitor group) from mice with DSS-induced colitis. Some colonic strips were stimulated with IL-1β (10 ng/ml) plus IL-23 (10 ng/ml) to induce enhanced cytokine secretion. The secretion of IL-17, IL-21 and CCL20 were determined in the cell culture media by ELISA. Results: Mice that were administered DSS showed clear evidence of colitis (enhanced disease activity indices and reduced colon lengths). Ex vivo treatment with VPR 254, 425 and GSK 805 were most effective for inhibiting basal IL-17 secretion from colonic strips of mice with colitis. VPR 425 and GSK 805 most effectively attenuated basal (non-stimulated) secretion of IL-21 and CCL20. For dual cytokine stimulated IL-17 secretion, some IL-17 values (pg/ml) were: 112±35 (Vehicle), 87±21 (VPR 254, 5μM), 64±9 (VPR 425, 5 μM) and 45 ± 9 (GSK 805, 5 μM). The calculated IC50 value of VPR 425 for inhibiting stimulated IL-17 secretion was 0.13 μM, while for GSK 805 it is < 0.05 μM. Three compounds (VPR 254, VPR 425 and GSK 805) significantly attenuated (at certain concentrations) dual cytokine stimulated IL-21 secretion from colonic strips of mice with DSS-induced colitis. Overall, the most effective compounds were VPR 425 and GSK 805. Four compounds (VPR 426, VPR 254, VPR 425 and GSK 805) attenuated (to some degree) stimulated CCL20 chemokine secretion from colonic strips of mice with DSS-induced colitis. Chemokine secretion was reduced to the basal level by ex vivo treatment with VPR 425 (0.5 and 5 μM concentrations). Summary: Ex vivo treatment with structurally diverse RORγt inhibitors attenuated basal and stimulated pro-inflammatory cytokine secretion from colonic strips of mice with DSS-induced colitis. Conclusion: These data further contribute to the identification of optimal RORγt inhibitors, which can be used for follow-up in vivo testing in murine models of colitis.