

AN INTERPROFESSIONAL PHARMACOTHERAPY ROTATION FOR ADVANCED PHARMACY PRACTICE EXPERIENCE (APPE) STUDENTS AND PGY-1 FAMILY MEDICINE RESIDENT PHYSICIANS

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Poster Number: 1

BACKGROUND

Inter-professional education is now a required element of the 2016 ACPE guidelines. "Medication use" is also an identified in all six core competencies from the ACGME.^{2,3} Medical curricula generally include a single semester of pharmacology, and pharmacotherapy is often a topic subset of this or of pathophysiology. Since 70% of medication errors in primary care can be related to prescribing issues, it seems prudent for pharmacists and physicians to learn collaboratively.^{4,5} A few pharmacist-led experiential rotations for medical residents have been described in the literature, but to date, none are co-educational or specifically address cognitive processes in clinical decision-making.^{3,6,7}

OBJECTIVES

- Implement a required rotation for APPE students and PGY-1 family medicine residents
- Develop and refine evidence-based pharmacotherapeutic knowledge and decision-making of participants

METHODS

- Development occurred during a 1-year longitudinal APPE rotation
- A detailed curriculum includes 7 major disease topics, each embracing
 - Pathophysiology
 - Pharmacotherapy
 - Medications commonly used, by drug class
 - Pharmacology of each drug class
 - Magnitude of clinical effect on disease state
 - Surrogate vs morbidity/mortality effects
 - Number needed to treat to accomplish endpoints
 - Magnitude and mechanism of potential adverse effects
 - Number needed to harm for each adverse effect
 - Risk vs benefit of using the drug class in the specified disease
- Direct application of all topics and decision-making processes to clinic patients

CURRICULUM DESIGN

- Four-week, full-time, required rotation for PGY-1 family medicine residents
- Facilitated, pathophysiology-based topic discussions, medication therapy reviews, and case presentations from 8:00 – 12:00 each morning.
- Residents and students then see pre-reviewed patients together in clinic from 13:00 – 17:00.

EVALUATION

- Written, standardized patient cases administered at beginning and end of rotation evaluated by two raters across 6 quality measures
- Inter-rater reliability will be evaluated using Krippendorff's alpha reliability estimate
- Pre- and post-rotation performance differences will be evaluated using Mann-Whitney U test
- APPE student and resident satisfaction surveys indicate strong satisfaction
- Family medicine faculty indicate strong satisfaction with residents' professional development during the rotation.

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AN EVALUATION OF ADHERENCE IN PATIENTS WITH BOTH EPILEPSY AND OBSTRUCTIVE SLEEP APNEA

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RATIONALE: Antiepileptic drugs (AEDs) are the mainstay of treatment for patients with epilepsy. Adherence to the prescribed drug regimen is a major step in achieving the goal of reduced seizure burden in patients with epilepsy. Decreased AED adherence is associated with more than a 3-fold increase in mortality. Periods of nonadherence in patients with epilepsy were also associated with significantly more emergency department visits, hospital admissions, injuries and fractures. Adherence can be calculated from refill records and measured by the Medication Possession Ratio or MPR. Many patients with epilepsy also have obstructive sleep apnea (OSA). One treatment option for patients with OSA is continuous positive airway pressure (C-PAP). Adherence to this non-pharmacologic device is a key factor in treatment success; especially for patients with epilepsy. For patients who are prescribed C-PAP, examining a piece of their machine indicates how often patients use their device.

PURPOSE: to compare two measures of adherence in patients with epilepsy and OSA.

METHODS: Adult patients seen in the outpatient clinic with a dual diagnosis of epilepsy and OSA were recruited for this cross-sectional study. They were able to provide consent and complete the study questionnaires on their own. They had to be taking an AED and using C-PAP for at least the past 3 months.

RESULTS: Eight patients were recruited (4 women: 4 men). Their average age was 46.75 years, they took an average of 7.63 medications daily and 62.5% had experienced a seizure in the last month. Only 4 of 8 (50%) were adherent to their AEDs and only 3 of 8 (37.5%) were adherent to their C-PAP. Adherence between measures were not consistent within individuals and for some individuals, subjective adherence was incongruent with objective data.

CONCLUSIONS: For this small sample, it is surprising that AED and C-PAP adherence is less than optimal. Data suggest that patients do not place same value on adherence to AEDs and C-PAP. Further investigation into reasons why is an area ripe for discovery. Most patients overestimated their adherence. This “pilot data” will aid in our clinical and educational approach and guide future adherence intervention projects.

HISTORY OF THE STUDY OF THALICTRUM ALKALOIDS AT THE OHIO STATE UNIVERSITY COLLEGE OF PHARMACY

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The genus *Thalictrum* of the plant family Ranunculaceae is widely distributed in different parts of the world. In 1885, J.C. Lecoyer published a monograph on the genus *Thalictrum*. By 1942, approximately 165 species were recognized as U.S. *Thalictrum* species. Multiple uses were reported. At The Ohio State University, in 1958 Jack L. Beal in Pharmacy and Michael Cava in Chemistry launched a life-long project on the isolation and characterization of alkaloids of *Thalictrum*. In 1960, D. Spiggle received his M.S. degree in Chemistry for an investigation of the quaternary alkaloids of *T. revolutum*, and Popat Patil received his M.S. degree for investigating the preliminary pharmacological activities of this same plant, with Arthur Tye, Jack Beal and Michael Cava as mentors. Raymond W. Duskotch joined the college faculty in 1963. The former graduate students Harry Fong, Paul Schiff, Jinn Wu, and Shoei-Sheng Lee, and several postdoctoral fellows worked on the discovery of new isoquinoline alkaloids of *Thalictrum* species. Later, Lester A. Mitscher as well as A. Douglas Kinghorn contributed to this research. Important findings may be summarized, as follows: Richard Hogg, Jack Beal and Michael Cava identified berberine and magnoflorine from the roots of *T. dasycarpum* (*Lloydia*, **24**, 45, 1961). Extracts of 11 different species of *Thalictrum* were screened for hypotensive activity in dogs, with *T. minus*, *T. rochebrunianum*, and *T. rugosum* being the most active in the group (*J. Pharm. Sci.* **54**, 1387, 1965). Many *Thalictrum* alkaloids, including thalicarpine (1965), obamegine (1966), adiantifoline (1968), and thalrugosine and thalrugosidine (1971) were characterized. Importantly, (+)-S-reticuline was isolated from the plant *Thalictrum minus* race B (Liao et al., *Lloydia* **41**, 257, 1978). The brain dopamine receptor-blocking property of (+)-S-reticuline has been recognized, and the associated functional behavioral effects of this alkaloid were correlated (Banning et al., *Life Sci.* **26**, 2083, 1980). In 2015, the conversion of (+)-S-reticuline to (-)-R-reticuline in the production of morphine was reported by Ian A. Graham of the University of York in the U.K. Graduate student Mark Bahar synthesized 5,6-didehydro-8,8-diethyl-13-oxodihydroberberine chloride, which exhibited nanomolar potencies against in vitro models of leishmaniasis, malaria, and trypanosomiasis. The parent compound, berberine, was less active (*Bioorg. Med. Chem. Lett.* **21**, 2606, 2011). In 2015, graduate student C. Benjamin Naman reported on the antileishmanial activity of northalrugosidine in mice, where 5–6 mg/kg of the alkaloid injected intravenously reduced the parasitic burden in spleen and liver by about 70% (*J. Nat. Prod.* **78**, 552, 2015).

Thus, at the Ohio State College of Pharmacy, researchers for over a half century have contributed to the discovery and biological evaluation of the fascinating *Thalictrum* alkaloids.

SINGLE-MOLECULE ANALYSIS OF STRUCTURE AND ASSEMBLY OF RNA NANOPARTICLES

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A customized dual-channel single molecule imaging system has been constructed to study the phi29 DNA-packaging motor that is geared by a hexameric pRNA ring. The motor pRNA molecules have been reported to serve as building blocks in RNA nanotechnology, and as vehicles for specific delivery of therapeutics to treat cancers and viral infections. The understanding of the stoichiometry and the 3D structure of the pRNA is both fundamentally and practically important. The imaging system with single fluorophore sensitivity and multicolor detection ability is the combination of a low-temperature (-80 °C) sensitive electron multiplied CCD camera with both objective- and prism-type TIRF (Total Internal Reflection Fluorescence) mechanism. A laser combiner was introduced to facilitate simultaneous multi-color imaging. Two lasers with different wavelenghtes were delivery synchronically via an optic fiber to the sample chamber with TIRF capability. Single molecule photobleaching combined with binomial distribution analysis clarified the stoichiometry of the pRNA on active motors. Further crystallography and biophysics studies confirmed that the pRNA forms a hexamer ring on the motor. The ability of using single molecule FRET in distance determination within the nanomotor was tested. Single molecule FRET study was carried out to investigate the structure of the pRNA dimer. Ten pRNA monomers labeled with single donor/acceptor fluorophore pairs at various locations were constructed, and eight partner pairs were assembled into dimers. FRET signals were detected for six dimers and utilized to assess the distance between each donor/acceptor pair. The results provided the distance constraints to refine the previously reported 3D model of the pRNA dimer. The analysis of the pRNA structure will help to improve the designs of therapeutic RNA nanoparticles using pRNA as a platform.

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INSUFFICIENT ZINC INTAKE ENHANCES LUNG TISSUE LOSS FOLLOWING CIGARETTE SMOKE EXPOSURE

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Poster Number: 5

Rationale: Cigarette smoke exposure is the major risk factor for developing chronic obstructive pulmonary disease. Cadmium is a major component of cigarette smoke with a biological half-life of greater than 20 years in humans. Cadmium and zinc are highly related metals. Whereas, zinc is an essential metal required for normal health, cadmium is highly toxic. Objective: To determine whether zinc deficiency increases cadmium burden and lung damage following prolonged cigarette smoke exposure. Methods: Data were analyzed from the NHANES 2011-2012 cohort for subjects 50 years or older. Patient demographics including dietary intakes, smoking history, and zinc and cadmium levels were evaluated relative to lung function based upon spirometry recordings. Chronic smoke exposure was also evaluated in the lungs of mice subject to insufficient and sufficient zinc intakes. Measurements and Main Results: Insufficient zinc intake is a predisposing factor for lung damage following prolonged smoke exposure. Analysis of the 2010-2011 NHANES cohort revealed that decreased zinc intake significantly correlates with higher cadmium body content and decreased pulmonary function in smokers when compared to nonsmokers. Marginal depletion of zinc intakes in adult mice also resulted in a significant increase in permanent lung tissue loss following prolonged smoke exposure and corresponded with increased reactive oxygen species formation. Overall, findings were strikingly consistent between human and animal data. Conclusions: Insufficient dietary zinc intake increases susceptibility to permanent lung injury following prolonged first hand cigarette smoke exposure.

RNA NANOTECHNOLOGY FOR DELIVERY OF ANTI-MIRNA FOR SUPPRESSION OF BREAST CANCER

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MicroRNAs play important roles in regulating the gene expression and life cycle of cancer cells. In particular, miR-21, an oncogenic miRNA is a major player involved in tumor initiation, progression, invasion and metastasis in several cancers, including triple negative breast cancer (TNBC). However, delivery of therapeutic miRNA or anti-miRNA specifically into cancer cells in vivo without collateral damage to healthy cells remains challenging. We report here the application of RNA nanotechnology for specific and efficient delivery of anti-miR-21 to block the growth of TNBC in orthotopic mouse models. The 15-nm therapeutic RNA nanoparticles contains the phi29 pRNA-3WJ as a core, an anti-miRNA, and the anti-epidermal growth factor receptor (EGFR) aptamer for internalizing RNA nanoparticles into cancer cells via receptor mediated endocytosis. The RNase resistant and thermodynamically stable RNA nanoparticles remained intact after systemic injection into mice and strongly bound to tumors with little or no accumulation in healthy organs eight hours post-injection, and subsequently repressed tumor growth at low doses. The observed specific cancer targeting and tumor regression is a result of several key attributes of RNA nanoparticles: anionic charge which disallows nonspecific passage across negatively charged cell membrane; 'active' targeting using RNA aptamers which increases the homing of RNA nanoparticles to cancer cells; nanoscale size and shape which avoids rapid renal clearance and engulfment by lung macrophages and liver Kupffer cells; favorable biodistribution profiles with little accumulation in healthy organs, which minimizes non-specific side effects; and favorable pharmacokinetic profiles with extended in vivo half-life. The results demonstrate the clinical potentials of RNA nanotechnology based platform to deliver miRNA based therapeutics for cancer treatment.

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CADMIUM ATTENUATES THE MACROPHAGE RESPONSE TO LPS THROUGH INHIBITION OF THE NF- κ B PATHWAY

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Background: Chronic obstructive pulmonary disease (COPD) in the U.S. is primarily caused by cigarette smoking. COPD patients are highly susceptible to respiratory infections in part due to alveolar macrophage dysfunction despite a substantial increase in macrophages in the lung. Cadmium (Cd) is a toxic metal that is concentrated within tobacco and accumulates in the lung of smokers. We hypothesized that Cd uptake into macrophages alters immune function thereby impairing the macrophage response to invading pathogens. **Methods:** Our hypothesis was tested by comparing THP-1 monocytes with PMA-differentiated THP-1 macrophages (TDMs) and primary human monocytes with monocyte derived macrophages (MDMs). **Results:** Strikingly, Cd exposure followed by LPS stimulation resulted in a significant decrease in nuclear p65 activity in macrophages which was not observed in monocytes (Fig. 1). This corresponded with Cd-mediated inhibition of IKK β in TDMs and an impaired ability to transcribe and release cytokines in response to LPS challenge (Fig. 2). **Conclusions:** These findings provide novel evidence that Cd has the capacity to disrupt macrophage immune function in comparison to monocytes. Importantly, Cd results in immune dysfunction in macrophages through inhibition of the NF- κ B signaling pathway. Based on these findings, we propose that Cd contributes to immune dysfunction in the lung of COPD subjects and may increase susceptibility to infection.

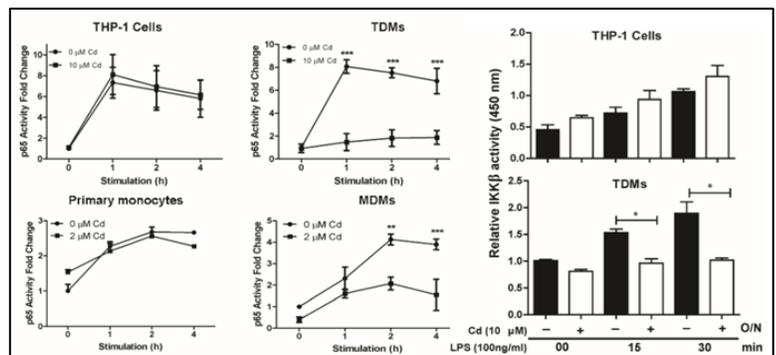


Fig.1. Cadmium inhibits the NF- κ B pathway in macrophages but not in monocytes in response to LPS.

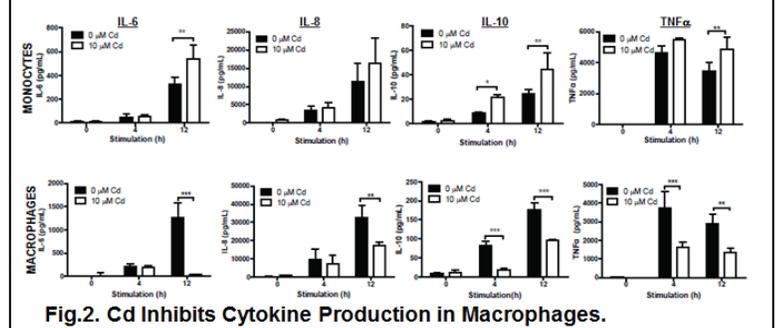


Fig.2. Cd Inhibits Cytokine Production in Macrophages.

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CYTOTOXICITY OF DIGOXIN AND STREBLOSIDE AND THEIR ANALOGUES

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Poster Number: 9

Digoxin, a cardiac glycoside characterized from *Digitalis lanata* Ehrh. (Plantaginaceae), has long been used to treat congestive heart failure. When tested in a prior drug repurposing study, this agent was found to show anticancer efficacy. In a current search for anticancer agents from higher plants, digoxin showed activity and was selected as a lead compound. It exhibited potent cytotoxicity toward the HT-29 human colon cancer cells in a 72-hour incubation, with an IC₅₀ value of 380 nM. Digoxin was found to be highly cytotoxic against the human MV4-11, THP-1, and Kasumi-1 myeloid leukemia cell lines in a 48-hour incubation, with IC₅₀ values of 100, 59, 89 nM, respectively. Interestingly, when tested toward the normal human cell lines, digoxin showed much lower activity. It exhibited cytotoxicity toward CCD-112CoN normal human colon cells that was ten-fold lower than toward HT-29 cells. It showed relatively little cytotoxicity toward normal human peripheral blood mononuclear cells in a 48-hour incubation. Several digoxin analogues have been prepared and evaluated for their cytotoxicity toward HT-29 cells. It was shown that both the C-12 and C-14 hydroxy group and the C-17 lactone ring are critical for this agent to mediate its cytotoxicity, but the C-3 glycosyl residue is not necessary for this effect. A naturally occurring analogue, strebloside, identified from the stem bark of *Streblus asper* Lour. (Moraceae) collected in Vietnam (Ren et al., *Planta Med* **2014**, 80: 796), showed potent cytotoxicity toward the HT-29 and the MDA-MB-231 human breast and OVCAR3 human ovarian cancer cell lines, and toward the MV4-11, THP-1, Kasumi-1 human leukemia cell lines, but a lack of such an effect toward CCD-112CoN normal human colon and toward normal human peripheral blood mononuclear cells. When evaluated in an in vivo hollow fiber assay in mice against the MDA-MB-231 and OVCAR3 cell lines, using paclitaxel as a positive control, treatment with strebloside (ip, 5 mg/kg/day, four days) resulted in significant cell growth inhibition, and no side effects were observed in the test animals at any doses used.

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CYTOTOXIC TRITERPENOIDS FROM THE LEAVES AND TWIGS OF SYZYGIUM CORTICOSUM

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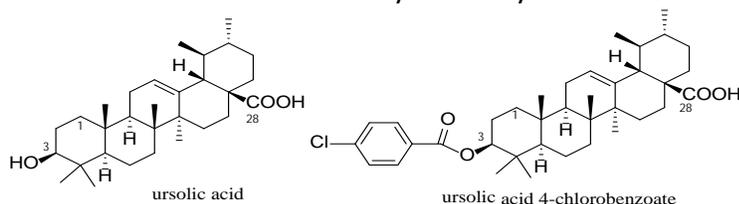
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Poster Number: 10

Syzygium (Myrtaceae) is a large genus containing about 500 species distributed mainly in tropical and subtropical regions. Of these, the clove tree (*Syzygium aromaticum*) is an important economic plant used widely in the food and pharmaceutical industries. Several *Syzygium* species, including the clove tree, have been reported to show cytotoxicity toward human tumor cells, and phenolic and steroid compounds were found to be the main active components, but the chemical constituents of *Syzygium corticosum* (Lour.) Merr. & L.M. Perry have not been reported in any previous investigation. In a continuing search for anticancer agents from higher plants, a chloroform-soluble extract of the leaves and twigs of *S. corticosum* collected from Vietnam was found to be cytotoxic toward the HT-29 human colon cancer cells, showing an IC₅₀ value of 11.6 µg/mL. Using column chromatography guided by this cell line, a large amount of a known triterpenoid, ursolic acid (6 g from 6 kg of the dried plant sample, with a yield of 0.6% w/w), a known natural phenol, trimethylellagic acid, and several other classes of natural products, were isolated and identified from *S. corticosum*. The structures of these isolates were determined by analysis of their ECD, IR, UV, NMR, and mass spectra, and by comparison of these spectroscopic data with literature values, with their cytotoxicity evaluated against HT-29 cells. The known compound, ursolic acid, was found to be weakly active, exhibiting an IC₅₀ value of 10.7 µg/mL (23.5 µM). This agent can be regarded as the major cytotoxic component of *S. corticosum*, and several new analogues have been synthesized from it and evaluated. Both the C-3 hydroxy and the C-28 carboxyl groups were found to play a key role in mediation of cytotoxicity of ursolic acid agent against HT-29 cells.



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CYTOTOXIC LIGNAN ESTERS FROM THE BARK AND ROOTS OF SYZYGIVM CF. LINEATUM

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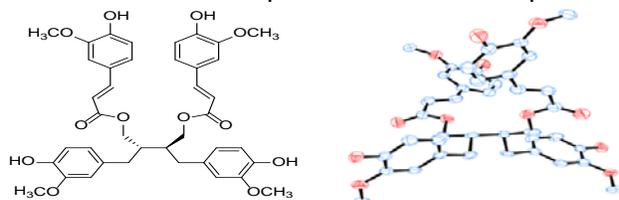
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The plant genus *Syzygium* belongs to the woody family Myrtaceae, which has been divided into two subfamilies, Myrtoideae and Leptospermoideae. Previous studies have shown that phloroglucinol derivatives, C-methylated chalcones, and steroids are the main cytotoxic components of species of this genus, but a detailed phytochemical investigation of the chemical constituents of *Syzygium cf. lineatum* (Bl.) Merr. & Perry has not been reported. In a continuing search for anticancer agents from higher plants, a chloroform-soluble extract of the dried bark and roots of *S. cf. lineatum* collected in Vietnam showed cytotoxicity against the HT-29 human colon cancer cell line and was selected as a lead. Using column chromatography guided by activity against this cell line, three new and several known lignan esters, together with a new triterpene acetate, were isolated and characterized. The structures of the new compounds were elucidated by interpretation of their ECD, IR, UV, NMR, and mass spectra, with those of the known compounds being identified by comparison of their spectroscopic data with literature values. The conformation and relative configuration of a known lignan, (2*S*,3*S*)-2,3-bis[(4-hydroxy-3-methoxyphenyl)methyl]-1,4-butanediol 1,4-diferulate, were determined by analysis of single-crystal X-ray diffraction data, with the absolute configuration of all analogues isolated being established by investigation of their specific rotation values and ECD spectra. All compounds isolated in the present study were evaluated for their cytotoxicity against HT-29 cells, and several lignan esters were found to be active, showing IC₅₀ values of 2.1–2.8 μM. A preliminary structure-activity relationship study showed that both the ester groups and the dimeric units are required for these compounds to mediate cytotoxicity against HT-29 cells.



Structure and X-ray crystallographic ORTEP diagram for (2*S*,3*S*)-2,3-bis[(4-hydroxy-3-methoxyphenyl)methyl]-1,4-butanediol 1,4-diferulate

CHANNEL OF SPP1 DNA PACKAGING MOTOR FOR REAL TIME KINETIC ANALYSIS OF PEPTIDES STATES

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Poster Number: 12

Information about oligomeric states of proteins and peptides in functional forms can convey their biological functions. A simple method to replace conventional sophisticated and labor-intensive methodologies to detect kinetics of protein and peptide conformations in real time is desirable. Nanopore technology has become a powerful tool in single molecule sensing, and protein nanopores appear to be more advantageous than synthetic counterparts with regards to channel amenability, structure homogeneity, and production reproducibility. However, most of the well-studied protein nanopores have too small of a pore diameter to allow passage of protein or peptides that are typically in multiple nanometers scale. To acquire protein channels with larger pore sizes, we engineered a portal channel from bacteriophage SPP1 that allowed the translocation of peptides with higher ordered structures. Utilizing single channel conduction assay and optical single molecule imaging, we observed translocation of peptides quantitatively and analyzed the dynamics of peptide oligomeric states in real-time at single molecule level. The oxidative and the reduced states of peptides were clearly differentiated based on their characteristic electronic signatures. A similar Gibbs free energy (ΔG_0) was obtained when different concentrations of substrates were applied, suggesting that the use of SPP1 nanopore for real-time quantification of peptide oligomeric states is feasible. With the intrinsic nature of size and conjugation amenability, the SPP1 nanopore has the potential for development into a tool for the quantification of peptide and protein structures in real time.

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SEQUENTIAL ACTION OF ASYMMETRICAL HEXAMERIC ATPASE IN DSDNA TRANSLOCATION BIOMOTOR

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Poster Number: 13

Traditionally, biomotors are classified into two categories: linear and rotation motors. Recently, we've discovered a third type of motors with revolution motion without rotation¹⁻³. Subsequent studies lead to the finding that revolution motors are widespread among many organisms including bacteria, virus, and possibly eukaryote cells⁴⁻⁶. Nature has evolved an elegant revolution motor that renders dsDNA void of coiling and tangling during the translocation of the lengthy chromosome. Here, we will focus on the utilization of biophysical, biochemical, nanotechnological, and single molecule optical approaches to elucidate the sequential action of the motor ATPase during the one-way revolution motion. We will present the mechanisms of the sequential action and subunit coordination of the hexameric ATPase, including the mechanisms of complex formation, inter-subunit communication, and changes of entropy and conformation. ATP binding induced conformation and an entropy alterations in ATPase to generate high affinity toward dsDNA; ATP hydrolysis triggered another conformational and entropic change in ATPase to a low affinity for DNA, pushing the dsDNA toward an adjacent ATP-bound subunit. The sequential pulling and pushing of the dsDNA by ATPase enabled the continuation of motor motion. The finding of asymmetrical hexameric organization is supported by structural evidences of many other biological motor systems.

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ACKNOWLEDGEMENTS:

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RNA NANOTECHNOLOGY FOR THE SPECIFIC TARGETING AND DELIVERY OF MIRNA FOR INHIBITION OF PROSTATE CANCER

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Poster Number: 14

Both siRNA and miRNA can serve as powerful gene silencing reagents but their specific delivery to cancer cells in vivo without collateral damage to healthy cells remains challenging. We report here the application of RNA nanotechnology using the three-way junction motif (3WJ) from the phi29 DNA packaging motor packaging RNA for specific and efficient delivery of anti-miRNA seed-targeting sequence to block the growth of prostate cancer in mouse models. Utilizing the thermodynamically ultra-stable three-way junction of the pRNA, RNA nanoparticles were constructed by bottom-up self-assembly containing the anti-Prostate Specific Membrane Antigen aptamer as targeting ligand and anti-miR17 or anti-miR21 as therapeutic modules. The RNase resistant and thermodynamically stable RNA nanoparticles remained intact after systemic injection in mice and strongly bound to tumors with little or no accumulation in healthy organs 8 hr post-injection, and subsequently repressed tumor growth at low doses with high efficiency.

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DISSECTING THE INTERACTIVE MOLECULAR MECHANISMS OF PALBOCICLIB, A CDK4-SPECIFIC INHIBITOR AND ITS POTENTIAL USE IN HEAD AND NECK CANCER

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Poster Number: 15

Uncontrolled cell proliferation is one of the hallmarks of cancers. While cyclin-dependent kinase 4 (CDK4)-mediated phosphorylation of pRb (retinoblastoma susceptible gene product) plays a pivotal role in controlling the G1 to S transition, aberrant CDK4-mediated phosphorylation has been prevalently found in human cancers, such as head and neck cancer, indicating that CDK4 may represent a promising target for novel cancer therapy. Recently, palbociclib (PD-0332991), a CDK4/6-specific inhibitor, has been approved by Food and Drug Administration (FDA) for the treatment of breast cancer. However, the efficacy of palbociclib against head and neck cancers remains to be determined. Here, to investigate the potential of palbociclib as an anti-cancer drug against head and neck cancer, we evaluated the impacts of palbociclib in four human head and neck cancer cell lines, namely, CAL27, SCC4, SCC15, and SCC22A. Our results showed that palbociclib was able to arrest oral cancer cells at the G1 phase at a moderate concentration (2-5 μM), and elevated palbociclib (10 μM) led to a significantly increase in the sub-G0 population of these cells and triggered apoptosis. Moreover, palbociclib exhibited high potency in suppressing the colony formation of these cell lines in a concentration-dependent manner. The IC50 values in suppressing the colony formation were about 80 nM (CAL27, SCC4, and SCC22A) and 0.65 μM (SCC15), respectively. Albeit proven clinical benefits in the advanced breast cancer patient population, further investigation is still much needed to better understand its underlying interactive molecular mechanisms in order to identify individuals who will respond to CDK4/6 inhibitor and design effective combination therapy regimen to enhance clinical outcomes. Taken together, these preliminary results strongly support further in vitro and pre-clinical in vivo studies of palbociclib using head and neck cancer as our disease model.

ARYLIMIDAMIDE-AZOLE COMBINATIONS IN MODELS OF VISCERAL LEISHMANIASIS

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Currently, miltefosine is the only approved oral treatment for visceral leishmaniasis. However, miltefosine has significant weaknesses, and no oral antileishmanial drug combinations are available. Given the utility of oral combination therapy for HIV, tuberculosis, and malaria, the development of such a regimen against visceral leishmaniasis should be a high priority.

We previously showed the antileishmanial activity of arylimidamide (AIA) DB766 and demonstrated synergy between DB766 and posaconazole against intracellular *Leishmania donovani* in vitro. Follow-up studies have shown that DB766-ketoconazole combinations are also synergistic against *L. donovani* in vitro, giving a mean sum fractional inhibitory value (mean Σ FIC) of 0.36 ± 0.13 . Pharmacokinetic analysis of the DB766-posaconazole combination in CD-1 mice revealed that DB766 exposure was increased in the presence of posaconazole. In *L. donovani*-infected BALB/C mice, DB766-posaconazole combinations given by the oral route for five consecutive days were more effective than the agents given alone. For example, a combination of 37.5 mg/kg DB766 + 15 mg/kg posaconazole gave $81 \pm 3\%$ (mean \pm standard deviation) inhibition of liver parasitemia, while doses of 37.5 mg/kg DB766 alone and 15 mg/kg posaconazole alone gave $41 \pm 9\%$ and $22 \pm 5\%$ inhibition, respectively. Analysis of these combinations by the method of Chou to calculate combination indexes (CIs) indicates that moderate synergy was observed at most of the combined doses. Studies are in progress to determine the in vitro and in vivo effects of additional AIA-azole combinations.

We would like to thank the Department of Defense (W81XWH-14-2-0017) for supporting this work.

PARTHENOLIDE-INDUCED DNA DAMAGE AND CYTOTOXICITY IN HUMAN LEUKEMIA HL60 CELLS: ROLE OF MYELOPEROXIDASE (MPO) AND GLUTATHIONE (GSH)

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Poster Number: 17

Parthenolide (PTL), a sesquiterpene lactone derived from feverfew (*Tanacetum parthenium*), and its analogs, are pro-apoptotic in a variety of malignant cells (including leukemia stem cells), in part by decreasing glutathione (GSH) and by targeting NF- κ B^{1,2}. PTL activity is also influenced by the presence of myeloperoxidase (MPO)³. Utilizing MPO+ and shRNA MPO knockdown HL60 cells, we determined the role of PTL and analogs on the generation of reactive oxygen species (ROS), oxidative DNA damage, DNA strand breaks, NF- κ B expression, and cytotoxicity. Apoptosis/cytotoxicity with PTL and its analogs was greater in MPO+ cells compared to MPO knockdowns by trypan blue exclusion, Hoechst staining, and Caspase-3 activation. Using 3'-(*p*-hydroxyphenyl) fluorescein (HPF), PTL and analogs were pro-oxidant in MPO+ cells and anti-oxidant in MPO knockdown and MPO depleted (succinylacetone-treated) cells. MPO dependency was also demonstrated for PTL-induced DNA strand breakage, abasic site formation, and inhibition of NF- κ B.

Paradoxically, in MPO+ cells, depletion of GSH by buthionine sulfoximine (BSO) decreased PTL-induced DNA damage and ROS generation. Conversely, in MPO knockdown HL60 cells, depletion of GSH increased PTL-induced DNA damage without an increase in ROS generation. Together our results suggest that, in MPO+ cells, GSH contributes to PTL activity likely through a redox cycling mechanism downstream of MPO. In cells lacking MPO, GSH serves to protect cells from PTL-induced cytotoxicity through direct binding/conjugation by Michael addition. Further studies are underway to characterize MPO-dependent effects on PTL oxidation and redox cycling of GSH and to generate strategies to better target/kill leukemia stem cells.

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INCREASED ALTERNATIVE RNA PROCESSING OF TOPOISOMERASE II α IN ETOPOSIDE RESISTANT HUMAN LEUKEMIA K562 CELLS: A RETAINED INTRON RESULTS IN A NOVEL C-TERMINAL TRUNCATED 90 kDa ISOFORM

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Poster Number: 18

DNA topoisomerase II α (TOP2 α) is a prominent target for clinically utilized anticancer drugs. However, the efficacy of these agents is limited by chemoresistance. We previously characterized acquired resistance to etoposide (VP-16) in a cloned human K562 leukemia cell line, K/VP.5, containing reduced TOP2 α (1). In the present study, using an antibody specific for the amino-terminus of TOP2 α /170 protein, immunoassays indicated the existence of two TOP2 α proteins, 170 and 90 kDa, in both parental K562 and K/VP.5 cell lysates. TOP2 α /90 was dramatically increased in VP-16-resistant K/VP.5 compared to parental K562 cells. An antibody specific for the carboxy-terminus revealed only the TOP2 α /170 protein which was reduced in K/VP.5 compared to K562 cells. We hypothesized that TOP2 α /90 was the translation product of a novel alternatively processed pre-mRNA, subsequently confirmed by 3'-RACE (Rapid Amplification of cDNA Ends), PCR, and sequencing studies. This novel mRNA harbors an in-frame stop codon, a consensus poly(A) site and a predicted 90,076 Da translation product. TOP2 α /90 is missing the carboxyl-terminal 770 amino acids present in TOP2 α /170 which are replaced by 25 unique amino acids encoded by translation of the exon 19/intron 19 'read-through' ("exon 19b"). Immunoassays, utilizing antisera raised against these unique amino acids, confirmed that TOP2 α /90 is expressed in both cell types, with overexpression in VP-16 resistant K/VP.5 cells. Finally, we demonstrate that the TOP2 α /90 mRNA splice variant is expressed in most human tissues suggesting that this novel protein isoform is functional. Since TOP2 α /90 does not harbor the active site tyrosine (Tyr805) needed to generate double-strand DNA breaks, this protein may exhibit dominant-negative properties and/or impact on nuclear levels/accumulation of active TOP2 α . Further studies are underway to characterize the role of this truncated form of TOP2 α /170.

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THE EFFECTS OF KPT-330, A SELECTIVE INHIBITOR OF NUCLEAR EXPORT, ON NUCLEAR TOPOISOMERASE II α LEVELS AND ETOPOSIDE ACTIVITY IN HUMAN MYELOID LEUKEMIA HL-60 CELLS

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Poster Number: 19

DNA topoisomerase II α (topo II) is a known cargo protein for exportin 1 (XPO1, CRM1) for nuclear export¹. Here we utilized KPT-330, a selective inhibitor of nuclear export (SINE), to evaluate its cytotoxicity, its effects on the nuclear content of topo II in human myeloid leukemia HL60 cells and on the subsequent activity of the topo II targeting agent etoposide. Since KPT-330 is a potential Michael acceptor and is known to interact with the CRM1 active site Cys528 to inhibit its activity, we first analyzed interaction of KPT-330 with glutathione (GSH). In an in vitro binding study KPT-330 was weakly bound to GSH with a $K_d = 130 \pm 24 \mu\text{M}$. In contrast, the natural product parthenolide, also a Michael acceptor, bound to GSH with 30-fold greater affinity. Depletion of cellular GSH with buthionine sulfoximine (BSO) did not significantly alter the 72 hr growth inhibitory effects of KPT-330 yielding I_{50} -values of 109 ± 19 and $80 \pm 44 \text{ nM}$ ($p=0.133$) in the absence or presence of BSO. In contrast, GSH depletion significantly enhanced the activity of parthenolide yielding I_{50} -values of 2.59 ± 0.16 and $1.35 \pm 0.15 \mu\text{M}$ ($p<0.001$) in the absence or presence of BSO, respectively. KPT-330 ($50 \mu\text{M}$) did not alter cellular GSH levels in HL60 cells. Using 3'-(p-hydroxyphenyl) fluorescein, KPT-330 was antioxidant in GSH replete and depleted HL60 cells. Together results indicate that conjugation with GSH does not play a significant role in KPT-330 activity.

Nuclear content of topoisomerase II α in exponential phase cells was $85.9 \pm 2.3\%$ and $86.5 \pm 1.8\%$ of total cell content in the absence or presence of KPT-330 (100 nM), respectively, after a 16 hr incubation. In plateau phase cells there was a statistically significant decrease in nuclear topoisomerase II α to $74.1 \pm 1.8\%$ compared to exponentially growing cells ($p<0.05$). In these plateau phase cells, a similar 16 hr incubation with 100 nM KPT-330 resulted in a significant increase in nuclear topoisomerase II α to $82.6 \pm 2.5\%$ of total compared to controls ($p<0.05$). Results are in accord with the known CRM1-mediated shuttling of topo II from the nucleus only in cells approaching or in plateau phase².

In exponentially growing cells, less than additive cytotoxicity (trypan blue) and apoptosis (Hoechst) were observed using a single fixed ratio of KPT-330 and etoposide incubated either simultaneously or after overnight pre-incubation with KPT-330. Similarly, using the Chou and Talalay technique, KPT-330/etoposide growth inhibitory combinations were less than additive in exponentially growing HL60 cells. Evaluation of apoptosis in plateau phase HL60 cells indicated antagonistic effects using a 16 hr preincubation with KPT-330 followed by etoposide

incubation. The mechanism(s) for this apparent antagonism using this combination are under investigation. Together results suggest that XBO1 inhibitors should not be utilized in combination with the topoisomerase II inhibitor etoposide.

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CONSTRUCTION, PURIFICATION, AND CHARACTERIZATION OF RNA DENDRIMERS WITH PHI29 PRNA REPEATS

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Poster Number: 20

We report the design and self-assembly of five generations (G0-G4) of monodisperse, globular, and nanoscale-sized RNA dendrimers using the ultrastable three-way junction (3WJ) motif of bacteriophage phi29 as building block. This series of dendrimer generations is assembled around a central, square-shaped RNA core with a 3WJ motif at each corner (G0). Incorporation of overhanging sticky-ends allows radial growth in a controlled and step-wise manner by addition of 3WJ layers up to G4. All five generations can be efficiently self-assembled using one-pot synthesis into monodisperse samples, which is a significant advantage over conventional dendrimers that typically require step-wise synthesis or produce heterogeneous particle sizes. Products can further be purified using Sucrose Gradient Ultracentrifugation to yield highly purified and homogeneous samples, as demonstrated by gel electrophoresis and AFM imaging. Information from structure prediction, AFM and DLS suggests a compact globular shape in solution with diameters ranging from 2.8 nm (G0) to 26 nm (G4). Thermal gradient fluorescence and gel electrophoresis (TGGE) reveal a bi-phasic assembly/disassembly mechanism in which the outer most layers form around a preformed thermodynamically stable core. This feature allows thermodynamic control over release and degradation of the external 3WJ strands that can be modified to contain targeting and therapeutic moieties. Upon incorporation of folate on the peripheral branches, RNA dendrimers showed high binding and internalization into cancer cells. RNA dendrimers are envisioned to have a major impact in targeting, disease therapy, molecular diagnostics and bioelectronics in the near future.

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HIGHLY ORIENTED SINGLE DIRECTIONAL INSERTION OF THE NANOCHANNEL OF BACTERIOPHAGE SPP1 DNA PACKAGING MOTOR INTO LIPID BILAYER

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Poster Number: 21

Insertion of biological channel into membrane is of fundamental importance in nanotechnology. Many applications require control and knowledge of channel orientation. In this work, we investigated the orientation of the SPP1 and phi29 DNA packaging motor channels inserted into lipid membranes. Single molecule electrophysiological assays and Ni²⁺-NTA-nanogold binding assays revealed that both SPP1 and phi29 motor channels exhibited a one-way traffic property for TAT peptide translocation from N- to C-terminal end of the motor channels. By making use of this property, TAT translocation revealed that the channel of the DNA packaging motor of bacteriophage SPP1 preferentially inserts into liposomes with their C-terminal wider region facing inward. In contrast, the DNA packaging motor channel of bacteriophage phi29 is randomly oriented after membrane insertion. We propose that the specificity in motor channel orientation is a result of the hydrophilic/hydrophobic interaction at the air/water interface when the channels are incorporating into liposome membranes.

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EVALUATION OF A DENIALS PREVENTION PROGRAM AT TWO OUTPATIENT HOSPITAL-BASED INFUSION CENTERS

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Poster Number: 22

Purpose: High cost medications are increasing at a rate of 20 percent annually and predicted to represent 50 percent of total health plan pharmacy costs by 2018.¹⁻² The Centers for Medicare and Medicaid Services make quarterly updates of medication coverage, which affect claims reimbursement for high cost medications.³ Additionally, claims reimbursement is affected by payer types and non-standardized clinical criteria imposed by payers. OhioHealth infusion centers receive referrals from various medical practices for infusion services. No formal denials management process is in place. Insurance verification and prior authorization approval status are assumed to be completed by the referring practice prior to infusion. Recurring denials prompted a thorough review of insurance verification and prior authorization processes. The objective of the study is to evaluate a denials prevention program for infliximab therapy at two outpatient hospital-based infusion centers.

Methods: An observational, pre-post implementation analysis was conducted for all insurance claims for infliximab therapy at OhioHealth Grant Arthritis Infusion Center and OhioHealth Bing Cancer and Infusion Center. A denials prevention team, led by pharmacy services, consisted of reimbursement analysts, patient assistance coordinator, infusion center registration and scheduling, and clinical staff which established integrated workflow processes with a new electronic health record system. Outcomes included insurance claims denial rates and financial performance.

Results: The pre-implementation (July-September 2015) and post-implementation (October-December 2015) analysis demonstrated a decrease in infliximab claims denials at OhioHealth Grant Arthritis Infusion Center from 14.4% to 0.7% ($p \leq 0.05$) and OhioHealth Bing Cancer and Infusion Center from 18.4% to 11.1% ($p \leq 0.05$), equating to a \$471,299 and \$211,293 reduction in denied charges respectively.

Discussion: The denials prevention program at OhioHealth Grant Arthritis Infusion Center and OhioHealth Bing Cancer and Infusion Center showed a statistically significant decrease in claims denials and denied charges associated with infliximab therapy. Future plans consist of expansion of the denial prevention program by leveraging other high cost infusion therapies and infusion centers and further optimization of electronic resources for revenue integrity.

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EVALUATION OF MEDICATION THERAPY MANAGEMENT AT A CHARITABLE PHARMACY

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Poster Number: 23

Background: The Charitable Pharmacy of Central Ohio (CPCO) provides medication at no cost to residents of Franklin County who fall at or below 200% of the federal poverty level. One of the pharmacy services provided at CPCO is Medication Therapy Management (MTM). These MTM encounters are similar to those conducted by pharmacists through OutcomesMTM™, as patients at CPCO are identified for MTMs based on the existence of drug-related problems. Once a patient is identified for an MTM, the pharmacist or 4th year Advanced Pharmacy Practice Experience (APPE) student performs a review of the patient's medication record. The student prepares adapted MTM forms and drafts a faxed intervention to be reviewed by the pharmacist preceptors. Despite the fact that a faxed intervention is sent to the prescriber of record for specific drug-related problem, it is often unclear if this prescriber is actively coordinating care and is considered the patient's primary care provider (PCP). Acknowledgement and resolution of drug-related problems is also difficult to assess. Lastly, paper charts result in inconsistent data collection and recorded information as part of the patient's progress note. The main objective of this study is to help determine if the Charitable Pharmacy of Central Ohio is sending its MTM interventions to the appropriate prescribers, and how describing the MTM intervention can help with process improvement and encourage greater collaboration with area prescribers to enhance a patient's overall care.

Methods: The design of this project is a retrospective chart review conducted at an outpatient charitable pharmacy. This study will utilize MTM interventions that were conducted between July 1, 2014 and July 31, 2015 by pharmacists and APPE students. The Ohio State University IRB has approved this study. The patient charts with MTM encounters will be used to collect data including but not limited to: identification of a primary care provider by the patient when care was established at CPCO and at the time of the MTM intervention, documentation of the MTM interventions being sent, number of prescribers contacted per MTM, classification of drug related problems, number of drug related problems resolved, and documented pharmacy follow-up related to the MTM interventions. All data will be recorded in Qualtrics,® which is serving as a data collection tool.

Results: Research in progress. All collected demographic and clinical data will be summarized using appropriate descriptive statistics. As the primary goal of this study is descriptive, no formal statistical tests are planned.

Future Directions: This research project has helped identify areas of improvement in CPCO's MTM process, as well as the current paper documentation system. The data gathered will help inform changes in the MTM process as well as potential implementation of an Electronic Medical Record (EMR) at CPCO. Externally it could provide more supporting data about how a charitable pharmacy's services, specifically MTM, positively impact patient care.

The authors would like to gratefully acknowledge Victoria Gray and Erin Gordon for their help with the data collection.

ASSESSMENT OF PHARMACISTS' ATTITUDES TOWARD EXPANDED SCOPE OF CLINICAL COMMUNITY AND AMBULATORY CARE PRACTICE IN OHIO

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Poster Number: 24

The objective of this study was to determine pharmacists' attitudes toward expanded scope of practice opportunities available collaborative practice legislative changes and proposed provider status legislation in Ohio. As new legislation is passed in states around the country, the role of the pharmacist is changing. This study explored community and ambulatory care pharmacists' attitudes to transitions in clinical practice made possible by expanded collaborative practice and provider status legislation. In addition, we assessed how prepared pharmacists feel for the impending changes to practice. A random sample of 500 pharmacists who identified themselves as ambulatory or community practitioners in Ohio State Board of Pharmacy renewal database were mailed a self-administered questionnaire. An incentive of \$1 was included with the mailed materials and no reminders were sent. A Likert-type scale was utilized to collect the data whereas one equals "Strongly Disagree" and seven equals "Strongly Agree". The questions in the instrument focused on the following constructs: potential clinical services to be offered, additional training needed to prepare pharmacists, knowledge of current legislation, liability concerns, workflow/space concerns, support from current practice site, potential credentialing/privileging requirements, payment options, and demographics. Data collection began in January 2016 and was completed in March 2016. Data was analyzed using descriptive statistics, one-way analysis of variance, and Chi-square analysis. Of the 500 surveys mailed, 196 were included in the study resulting in a response rate of 39.2%. In general, pharmacists were very positive about potential changes to clinical practice in the community and ambulatory care settings. Pharmacists felt strongly that patients would not pay out-of-pocket for services provided and that they should be reimbursed by the patient's insurance. Pharmacists also felt that that targeted continuing education should be required to provide clinical services. Most respondents felt that his/her workflow and dispensing software would have to be changed or updated in order to accommodate additional services. Interestingly, 47.7% of respondents reported not being a member of any professional organization while 38.8% were members of the Ohio Pharmacists Association. Overall, it seems that pharmacists agree with expansion of clinical services. However, when respondents were polled about specific clinical services that he/she would like to offer no one service appeared to be favored by the group. In addition, subgroup analyses revealed that there were no relevant differences in response based on gender, age, years in practice or practice setting. Nearly 50% of the respondents reported not being a member of any professional organization. This appears to be an opportunity to increase participation in advocacy efforts to be an active part of the shaping of upcoming clinical changes.

VALUE AND DESIGN OF PHARMACY RESIDENCY RESEARCH PROGRAMS

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Poster Number: 25

American Society of Health-System Pharmacists (ASHP) objectives around pharmacy resident major projects and research training focus on resident exposure to process and skills development.^{1,2} Individual residency programs, however, may also prioritize projects with high impact to the organization (e.g., through building pharmacy services) and/or the profession (e.g., through scholarship). Thus, values outside of residency standards may influence programs' design of their research training to emphasize additional outcomes. The purpose of this study was to characterize the extent to which different residency programs value project/research output of residents, and to explore how research programs are designed to achieve various organizational objectives. A survey directed to residency program directors at ASHP-accredited PGY1 pharmacy practice programs was created to gather demographic data, residency research program objectives and design characteristics, and perceptions related to project/research values. Values were categorized within three domains: skills development, impact to the organization, and scholarship. Skills development measures were drawn from ASHP objectives. Organizational impact measures included service/process development, enhancement, and/or validation. Scholarship measures included resident publications, podium presentations, and national and/or regional poster presentations. The online survey was distributed via emails obtained from the ASHP online residency directory, during February and March 2016. Program characteristics will be described by summary statistics, and research program quality in the different value domains will be measured on a Likert scale. Comparisons among programs ranking high in the different value domains will be made using chi-square tests. This study was deemed IRB-exempt. Preliminary results and conclusions will be presented at the 2016 College of Pharmacy Research Day.

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WHEN PERSONAL MEDICINE MEETS PILL MEDICINE: USE AND ACCEPTANCE OF SELF-CARE IN MENTAL HEALTH MANAGEMENT IN AN UNDERSERVED POPULATION

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Poster Number: 26

Objective: This study seeks to explore whether patients with mental health conditions engage in self-care as part of their treatment regimen, and how this may impact medication use and adherence. Self-care management in chronic disease states is a patient initiated behavior change to improve health outcomes. In the setting of mental health conditions, patients may have identified their own self-care activities that improve mood and promote a sense of wellbeing. These empowerment activities, which encompass self-care, differ for each patient and are often referred to as Personal Medicine. Primary objectives include: 1) identify the percent of patients with mental health conditions who are engaging in Personal Medicine (self-care activities); 2) assess how self-care may impact medication use and adherence. **Methods:** This study will gather data from an IRB approved interview with patients who fill their medications for mental health conditions at an outpatient charitable pharmacy. Patients will be recruited into the study when they present for medication refills and the 20-30 minute interview will occur during the time they wait for their prescriptions. Dimensions of self-care assessed include social, physical, psychological, emotional and spiritual. Five pharmacy students were trained as research assistants to help the research team conduct the interviews. Inclusion criteria include patients who fill medications typically prescribed for mental health conditions. Exclusion criteria include the use of mental health medications for non-mental health related conditions, < 18 years old and non-English speaking. Patient interviews will yield quantitative data including engagement in self-care, perceived benefit of self-care and rate of medication adherence. **Results:** Research currently in progress. **Future Direction:** The results of this study are intended to be descriptive in nature, and will help pharmacists better understand the use of self-care by patients with mental health conditions. This data will help to assess the need for pharmacist-led targeted patient counseling that may expand patients' awareness and exposure to self-care as a mechanism to improve mental health. Additionally, this research will help describe patients' knowledge of community resources for mental health and therefore serve as a mechanism to expand community outreach and patient care coordination.

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VALUE ADDED BY PHARMACISTS IN A PATIENT-CENTERED MEDICAL HOME

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Poster Number: 27

The purpose of this study was to demonstrate the value added by pharmacists in a patient-centered medical home (PCMH). The primary objective was to identify and quantify the types of interventions made by pharmacists in this setting. Secondary objectives were to determine the number of pharmacist recommendations accepted, the number of interventions resulting in reimbursement, and average time spent per encounter. For this prospective, descriptive study, participants included pharmacists (n=8) employed at five PCMH locations. Over 20 business days, pharmacists completed a Qualtrics™ survey after each intervention made, characterizing and detailing the outcome(s) of that specific encounter. A total of 581 surveys were submitted. Patients were 45% male, mean age 58 years, 67% Caucasian, 97% insured, and were prescribed ~14 home medications. Twenty-nine percent of encounters were scheduled, 71% occurred unpredictably. Encounters included individual pharmacy visits (13%), multidisciplinary team visits (32%), drug information requests (23%) and communication by phone or secure portal (30%). The most common health-related interventions (N=878) included diabetes management (130), diabetes education (88), anticoagulation (105), comprehensive medication reviews (71), mental health (52), hypertension (50), and transitions of care (45). The majority of interventions involved shared-decision making between the patient, provider, and/or the patient. Of 918 pharmacist recommendations made to providers, 830 (90%) were implemented. Of 412 pharmacist recommendations made to patients, 393 (95%) were accepted. Forty percent of encounters resulted in direct reimbursement. The average time spent per encounter was 20 minutes. Pharmacists are highly accessible and involved in managing many health-related problems as integral members of the PCMH healthcare team. Recommendations made by pharmacists were implemented at high rates, demonstrating the value added by pharmacy services in this setting. Pharmacists should continue to advocate for provider status so that the value added by pharmacists is recognized.

The investigators of this study would like to acknowledge the pharmacists at General Internal Medicine who participated in this study.

COMMUNITY PHARMACY MEDICATION THERAPY MANAGEMENT: IMPACT OF PHARMACY TECHNICIAN INVOLVEMENT

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Poster Number: 28

Community pharmacists can improve patient outcomes through medication therapy management (MTM). However, there are reported MTM workflow obstacles including a lack of time to engage with patients, difficulty documenting MTM services, and inadequate staffing support. Technician involvement with MTM in the community pharmacy setting could help address many of these reported obstacles. The primary objective of the study was to assess the impact of technician involvement on the completion of MTM services in a community pharmacy setting. Secondary objectives were to describe pharmacists' and technicians' perceptions of technician impact on MTM-related tasks, as well as their satisfaction with the technician MTM role. In October and November of 2015, 98 pharmacists and 84 technicians from 32 pharmacies in a grocery store-based, community pharmacy chain were trained on how to utilize technicians within MTM services. Competencies taught in training included an overview of MTM, identifying MTM opportunities, preparing MTM materials, and documenting MTM services. For the primary objective, completed MTM claims were evaluated at all pharmacies for 3 months pre-training (an equivalent time period of the previous year) and post-training. A survey, used to measure secondary objectives, was developed using competencies taught in the training and relevant published literature. The electronic survey was distributed via email to all trained employees approximately 3 months post-training. Descriptive statistics were used to summarize all outcomes of interest, including MTM completion counts and survey responses. The total number of completed MTM claims at the 32 pharmacy sites was higher during the post-training time period (2,687 claims) versus the pre training period (1,735 claims). Of the 182 training participants, 112 (61.5%) completed the survey; 47.6% of the technicians (n=40) and 73.4% of the pharmacists (n=72). Generally, technician involvement in many of the trained MTM tasks was reported as rare to never by technicians and pharmacists. Identifying MTM opportunities through the dispensing platform was the most commonly reported technician MTM task, with 62.5% of technicians and 47.2% of pharmacists reporting technician involvement as sometimes or often. Nearly half of technicians (42.5%) and pharmacists (44.0%) agreed or strongly agreed they were satisfied with the technician's role in MTM services, and 40.0% of technicians agreed that they were more satisfied with their work in the pharmacy after involvement in MTM. The majority of technicians agreed that the MTM role added an additional challenge to their job (62.5%) and gave them the chance to make use of their abilities (70.0%). Although the total number of completed MTM claims at the 32 pharmacies was higher during the post-training period, future research is needed evaluate whether the higher number was reflective of a higher completion rate and to determine whether this can be

attributed to technician involvement. Overall, technician involvement in MTM services reported in the survey was lower than expected. Technicians were most often involved in identifying MTM opportunities, which may provide a focus for future technician MTM training and development. Additionally, expanding the technicians' roles to include MTM could lead to increased job satisfaction for some technicians. Future research is needed to assess what barriers limit technician involvement in MTM and how to best utilize technicians to assist with MTM services.

THE FEASIBILITY OF PHARMACY AND HOME HEALTHCARE TRANSITIONS OF CARE SERVICES IN AN EMERGENCY DEPARTMENT POPULATION

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Poster Number: 29

Background/Rational: While 30-day hospital readmission rates have been a large focus on healthcare costs recently, emergency department (ED) revisit rates are beginning to burden the healthcare system, as well. The non-admitted ED patients who quickly return after being discharged are a group of high utilizers of emergency care, ultimately leading to ED crowding, unnecessary resource utilization, and increased costs to both the patient and the healthcare system. While many transitions of care studies have focused on 30-day hospital readmission rates, there has been no research focused on services impacting ED revisit rates for non-admitted patients. The aim of this project is to determine the feasibility of pharmacy-only or pharmacy plus home healthcare transitions of care services in an emergency department population. The secondary aims are to assess ED revisit rates and/or hospital admissions, medication adherence to newly prescribed medications, identification and resolution of medication-related problems, and describe patient satisfaction with the services.

Methods: This prospective, feasibility study will provide interprofessional transitions of care services to older adult patients treated and discharged from an urban, academic medical center ED. Patients discharged from the ED will receive pharmacy-only or pharmacy plus home healthcare transitions of care services over a 30-day period. The pharmacy-only service will provide free delivery of new medication(s) to the patient's home and conduct two follow-up calls at days 3 and 10 post-discharge to perform medication and disease state education, and a pharmacist will consult the patient's primary care physician with potential medication-related problems. Discharged patients receiving the pharmacy plus home healthcare service will receive pharmacy-only services in addition to a home visit by a home healthcare nurse within 24-48 hours post-discharge to conduct medication reconciliation and provide additional education. The patient will also receive additional home visits as necessary over the 30-day period. Outcomes will be documented throughout the 30-day period. Post-intervention, at 30-days post-ED visit, the patient will complete a telephone survey focusing on ED revisits or hospital admissions, adherence to new medications prescribed in the ED, and patient satisfaction with the service he or she received.

Preliminary Results/Outcomes (financial viability): Results will address stated objectives. This study is the first step in developing a sustainable way for community pharmacists to assist patients with urgent needs.

Future Implications: This project will determine the feasibility of these services as applied to patients treated and discharged from the ED. Results from this study could be used as a guide

for other organizations to follow to implement a successful and sustainable transitions of care service.

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CLINICAL ROUNDING IN A COMMUNITY PHARMACY

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Poster Number: 30

Despite advances in Medication Therapy Management (MTM) services, community pharmacists still face barriers and challenges that prevent them from performing MTM to all eligible patients. This study aims to describe development and implementation of clinical rounding within traditional dispensing activities of a community pharmacy. The secondary outcome is to determine if the use of clinical rounding within a community pharmacy increases the number of MTM services delivered. The descriptive study will occur at 119 grocery store-based community pharmacies in Ohio, West Virginia, and Michigan. Daily clinical rounding will consist of pharmacists and technicians reviewing a clinical opportunity report to identify patients and then conducting clinical interventions. The clinical opportunity report is similar to patient census reports in inpatient clinical rounding models. It is created from the pharmacy's prescription dispensing software and includes medications filled the previous day awaiting pickup by MTM eligible patients. Each patient on the clinical opportunity report will be queried through an online MTM platform to identify if clinical interventions are needed. For targeted and comprehensive medication reviews, drug-related problems (DRPs) will be identified and resolved upon patient intervention. All materials used to prepare the intervention will be placed with the patient's filled prescription(s). When the patient is present, the pharmacist will perform the MTM and any additional clinical services deemed appropriate. Collaboration with the patient's prescriber will be performed as needed for clinically necessary reasons. The study describes the workflow process of clinical rounding and analyzes the number of MTM cases completed pre- and post- implementation of clinical rounding. Data is analyzed using descriptive statistics and assessed by a pre-post Wilcoxon signed-rank test. Pharmacists completed a total of 4,677 MTM cases pre-implementation and 6,970 MTM cases post-implementation ($p < 0.001$). In conclusion, clinical rounding in the community pharmacy consists of pharmacists reviewing a clinical opportunity report everyday, using that report to identify MTM opportunities, and then performing clinical interventions. Additionally, implementation of a clinical rounding model into a community pharmacy appears to be an effective method to increase the amount of MTM services pharmacists are able to perform.

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PATIENT BENEFIT AND SATISFACTION WITH A PHARMACIST-LED MEDICARE PART D PRESCRIPTION DRUG PLAN SELECTION PROGRAM

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Poster Number: 31

Statement of Purpose: The purpose of this study is to evaluate patient benefit and satisfaction with a pharmacist-led Medicare Part D prescription drug plan (PDP) selection program within a patient-centered medical home (PCMH). The primary objective of this study is to assess patient's perceptions of their current Medicare PDP in 2015 compared to 2014. A secondary objective is to evaluate patient's interest in returning for a visit with a pharmacist in 2015.

Methodology: A report was generated from the electronic medical record to identify all patients at an academic general internal medicine PCMH who participated in a pharmacist-led Medicare Part D plan selection service in 2014. Pharmacists made 3 attempts to contact patients in August or September of 2015 to offer participation in this study. Patients were given the opportunity to provide verbal consent for their participation in the telephonic survey prior to answering a series of standardized multiple-choice questions. Answers to each question were collected in a Microsoft Excel spreadsheet and later analyzed using descriptive statistics. At the end of each survey, patients were offered the opportunity to meet face to face with a pharmacist to discuss PDP selection during open enrollment between October-December of 2015.

Results and Discussion: A total of 111 patients at a general internal medicine PCMH participated in a pharmacist-led Medicare Part D Plan selection program in 2014 and were contacted for participation in this study. Of these patients, 88 answered their phones, provided verbal consent, and completed the survey. Response data has been collected and analyzed using descriptive statistics. Only 6 of these patients reported not being satisfied with their current plan, and 7 stated their current plan was more expensive. All others reported they were either more satisfied or just as satisfied and felt their overall medication costs were less expensive or the same as the previous year. Most patients felt neutral when asked if they were more or less likely to take their medications as prescribed with their current PDP. Over 50% of patients were interested in returning for a visit with the pharmacist in 2015 and more than 10% felt they could now make changes to their PDP on their own without any assistance from a pharmacist.

Conclusion: In conclusion, the value of a pharmacist-led Medicare Part D plan selection service in a PCMH has been demonstrated through reported patient satisfaction with their PDPs, medication cost savings, and further interest in returning for a visit with the pharmacist the following year. Further studies should be performed to better assess changes in adherence based on participation in this service.

AN EVALUATION OF PATIENTS' AWARENESS AND VIEWS OF PHARMACISTS IN THE AMBULATORY CARE SETTING

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Poster Number: 32

The public is generally unaware of the true scope and responsibilities of pharmacists. With pharmacy practice actively evolving, it is imperative that both patients and healthcare providers are aware of the wide range and benefits of clinical pharmacy services. Studies have identified a need for increased marketing and education for pharmacy services. As the profession of pharmacy is seeking national provider status, it is essential that patient and provider education of pharmacy value is not overlooked. The primary objective of this study is to assess patients' baseline knowledge and opinions of the scope of practice and available services offered by pharmacists in the ambulatory care setting. The secondary objectives of this study are to identify pre-conceived notions and barriers to the utilization of ambulatory care pharmacy services as well as compare the levels of awareness between patients who work as healthcare providers and those who do not.

This study is a cross-sectional, descriptive survey administered to patients prior to a scheduled appointment at multiple ambulatory care clinics throughout Columbus, Ohio. All clinics surveyed have at least one pharmacist integrated into their practice workflow and/or engage in a team-based approach to patient care. Adult patients (18 years of age or greater) who are English-readers and visit one of the eleven included clinic sites will be eligible for participation. A 29-item original survey was developed which gathers information on the participants': (1) awareness of ambulatory care pharmacist's roles, activities, and training; (2) opinions on ambulatory care pharmacists; (3) past experiences interacting with pharmacists, and (4) demographic data. The paper survey designed for participant self-administration is de-identified except for clinic location. The survey utilizes both five-point Likert scale and categorical-type questions. Survey responses will be summarized using appropriate descriptive statistics. This research study has been approved by The Ohio State University Institutional Review Board.

Selected preliminary data of 132 surveys from a total of four clinic sites has indicated that 50.4% (n=131) of patients are aware of pharmacist presence within the ambulatory care site. In addition, preliminary results include 73.2% (n=127) of patients who "agree" or "strongly agree" that pharmacists are healthcare providers.

Upon further data collection, the results will potentially assist in defining the gap that exists between pharmacists, patients, and healthcare providers. This study will look to identify the level of understanding that patients have grasped about pharmacists in the ambulatory care setting, reveal areas of unawareness that could be targeted for future public education, and further promote patient utilization of ambulatory care pharmacists.

EVALUATION OF OHIO PHARMACISTS' KNOWLEDGE OF CENTERS FOR MEDICARE AND MEDICAID SERVICES STAR RATINGS

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Poster Number: 33

The objectives of this study are to evaluate Ohio pharmacists' awareness regarding Centers for Medicare and Medicaid Services (CMS) Star Ratings System (Star Ratings), identify gaps in knowledge of Star Ratings, and determine Ohio pharmacists' interest in continuing education opportunities focused on Star Ratings. This cross-sectional study was conducted via an online survey sent to Ohio pharmacists in February 2015 to gather perceptions of Star Ratings. Email addresses were acquired from the State Board of Pharmacy. The non-validated, 17 question survey was pilot-tested and gathered demographics as well as addressed stated objectives. Participant responses were included if the participant was currently practicing in the ambulatory care or community setting. Data were summarized and aggregate knowledge scores were calculated; analysis of variance (ANOVA) and chi-square tests were used to compare knowledge scores between self-reported knowledge groups. In total, 13,235 surveys were sent to current Ohio pharmacists. 913 (6.9% response rate) respondents participated; 467 (3.5%) responses were included for analysis based on practice setting. 390 (84%) of the 467 responses were aware of Star Ratings and 342 (73%) respondents answered at least 1 knowledge question. 132 (39%) indicated being "not at all knowledgeable" on the topic, 194 (57%) "knowledgeable", and 16 (5%) "very knowledgeable", with mean performance scores (i.e., the proportion of correct responses out of 17 knowledge questions) of 37.7%, 56.5%, and 71%, respectively. Higher self-reported knowledge was associated with higher mean performance scores ($p < .01$). The largest gaps of knowledge included believing pharmacies receive an overall Star Rating and incorrectly identifying specific medication therapies as rated quality measures. 379 (81%) respondents expressed interest in continuing education on the topic, ranking employers and pharmacy organizations as the most preferred sources. In conclusion, Ohio ambulatory care and community pharmacist respondents are aware of the Star Ratings System, yet few indicated adequate knowledge on the topic. Additionally, respondents are interested in continuing education opportunities on the subject. This study highlights a potential need for continuing education opportunities for pharmacists and future studies in other states.

MEASURING THE IMPACT OF IN-HOUSE SPECIALTY PHARMACY SERVICES ON MEDICATION ADHERENCE IN A CYSTIC FIBROSIS PATIENT POPULATION

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Poster Number: 34

This project will measure cystic fibrosis (CF) medication adherence rates pre and post implementation of specialty pharmacy services at a free-standing children's hospital serving approximately 500 pediatric and adult CF patients. Patients managed by external specialty pharmacies currently experience significant barriers to accessing specialty medications that lead to poor adherence. This project aims to increase patient access and improve adherence rates by providing specialty pharmacy services to patients and delivering education and counseling by a pharmacist in the CF clinic. This study was conducted pre and post implementation of specialty pharmacy services. Adherence data was obtained through a retrospective analysis of claims and health outcomes data for patients prescribed at least one of five CF specialty medications intended for chronic use pre and post implementation. Six potential therapy combinations were also identified and assessed for patient adherence to their intended combination regimen. Chart reviews were conducted to assess the intended medication regimen for each patient. Baseline demographics will be assessed using descriptive statistics. Adherence scores will be calculated using the Medication Possession Ratio and Proportion of Days Covered equations and compared before and after implementation using the chi-squared test. Time to treatment for each of the five CF specialty medications will be compared before and after implementation as a secondary measure. Time to treatment will be calculated as the average number of days between the date that the prescription was written and the date that the prescription was filled based on claims data. Patient and staff satisfaction will also be evaluated pre and post implementation using an internally validated survey. This project was deemed quality improvement and, therefore, is considered IRB-exempt.

THE IMPACT OF AN INTERDISCIPLINARY APPROACH ON PATIENTS' GLYCEMIC CONTROL: DIABETES CLINIC VERSUS USUAL CARE

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Background: Over twenty-nine million people in the United States have diabetes, with costs for diabetes management totaling \$245 billion in 2012. Pharmacist intervention improves glycemic control, but the impact of sustained interdisciplinary care has not been studied.

Objectives/Methods: The primary objective was to compare glycemic control for patients while receiving care in an interdisciplinary diabetes clinic to glycemic control while receiving usual care. The secondary objective was to track healthcare utilization for these patients. A retrospective chart review was conducted for all patients age 18 years and older who presented to at least one interdisciplinary diabetes clinic visit in a tier-3 patient-centered medical home between 1/1/2008-7/1/2015. Patients were included if they had at least one Hemoglobin A1c (HgA1c) during and during the 12 months prior to treatment in the diabetes clinic. To compare differences in glycemic control as patients cycle in and out of the interdisciplinary diabetes clinic and usual care, a linear mixed effects model will be fit to the outcome HgA1c. A random subject effect with spatial power correlation structure will be used to account for correlation of measures from the same patient. Parameter contrasts will be constructed to test for differences in mean HgA1c between phases. Additional variables, such as demographics, will be included as covariates if they change the contrast estimate for the phase effect by 15% or more. Differences in healthcare will be expressed using descriptive statistics.

Results: 647 patients were identified that fit inclusion criteria. Data analysis is currently underway. Descriptive statistics will be used to report demographics. Differences in HgA1c will be assessed using a linear mixed effects model and health care utilization will be reported using descriptive statistics.

Implications: Results are expected to demonstrate the need for sustained interdisciplinary team-based care and pharmacist involvement in diabetes management to improve patient outcomes.

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SYNTHESIS OF HETEROCYCLIC COMPOUNDS AS ANTILEISHMANIAL AGENTS

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Poster Number: 36

Leishmaniasis is considered to be a neglected disease, yet an estimated 350 million people are believed to be at risk of contracting this infection. Leishmania parasites have developed resistance to first-line pentavalent antimonial drugs in the Indian subcontinent region, and nephrotoxicity is a side effect of the second line antileishmanial drug amphotericin B. Thus, introduction of newer chemotherapeutic agents is crucial to manage infection worldwide. Currently our lab is working on the development of a new class of compounds for treatment of both *L. donovani* (which causes visceral leishmaniasis) and *L. amazonensis* (which causes cutaneous leishmaniasis), namely cyanines. Previous high-throughput screening of a 196,146 compound library from the PubChem database led to the discovery of 70 compounds with submicromolar activity against *L. major* promastigotes. Further testing of a subset of these compounds against intracellular *L. amazonensis* and *L. donovani* led to the discovery of benzothiazole cyanine (1-methyl-4-((3-methylbenzo[d]thiazol-2(3H)-ylidene)methyl)quinolin-1-ium tosylate as an antileishmanial agent with in vitro and in vivo activity. Currently a series of 12 compounds were synthesized following the Topliss series approach by the introduction of chloride, methyl or methoxy group on the quinolone ring system of the cyanine scaffold at positions 5 through 8. Four cyanines with a phenyl substituent on the quinoline ring system were prepared to examine the role of a planar ring system on activity. Substitution of the methyl group of the quinolinium moiety by ethyl, propyl and benzyl groups was achieved. An aromatic ring was removed from both the benzothiazole and the quinolinium moiety in order to further investigate the cyanine pharmacophore. Biological testing against *L. amazonensis* amastigotes as well as cytotoxicity testing against J774 macrophages is in progress; the 8-methoxy analog displayed 10 fold improvement in activity compared to the parent lead compound. However, cytotoxicity against J774 macrophages has been observed and is a concern for this series of compounds.

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A FUNGAL ENDOPHYTE OF LIVERWORT TRICHOCOLEA TOMENTELLA AS A NEW SOURCE OF ANTICANCER AGENTS

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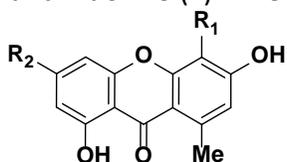
Presenting Author: Tehane Ali

Program of Presenting Author: Medicinal Chemistry & Pharmacognosy

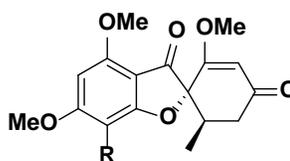
Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 37

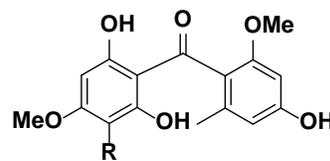
Liverwort Endophytes are plant tissue-associated microorganisms that represent a rich resource of underexplored bio- and chemo-diverse secondary metabolites¹ that can have a potential application in the field of cancer chemotherapy. Since liverworts grow on the soil surface, they are capable of hosting bioactive soil microbes as endophytes. This association results in the production of secondary metabolites by the endophytic microorganisms. As part of our systematic search to discover new antiproliferative (against human breast adenocarcinoma, MCF-7 and the human colorectal adenocarcinoma, HT-29) compounds from liverworts endophytes, we screened twenty microbial extracts and obtained activity ranging from 0.07 to >20 µg/mL against the two cell lines. In the present study, we selected a *Trichoclea tomentella* (Trichocoleaceae) endophytic fungus *Penicillium chrysogenum* for further investigation due to its promising activity (ED₅₀ values of 2.2 and 12.0 µg/mL against MCF-7 and HT-29, respectively). Bioassay guided fractionation and isolation of an ethyl acetate extract of *P. chrysogenum* cultured on rice medium yielded two new bioactive methylxanthenes (**1** and **2**), griseofulvin (**3**), dechlorogriseofulvin (**4**), griseophenone B (**5**), griseophenone C (**6**), together with nine known compounds (**7–15**).² The structures of the new compounds **1** and **2** were elucidated through extensive analyses of their spectroscopic data. The isolated compounds showed cytotoxic activities against MCF-7 and HT-29 ranging from 6.4 to 62.5 µM. Our results also demonstrated that chlorinated grisan (**4**) and griseophenone (**5**) scaffolds from *P. chrysogenum* were more effective against MCF-7 and HT-29 than their dechlorinated counterpart. This selectivity incited us to investigate the possibility of biosynthesizing non-natural-halogenated natural product. Studies on the bio-incorporation of halogens such as bromine (Br) and Fluorine (F) in *Penicillium* secondary metabolites are in progress.



1: R₁ = OH, R₂ = OMe
2: R₁ = H, R₂ = Cl



3: R = Cl
4: R = H



5: R = Cl
6: R = H

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CIRCADIAN TIMING IN THE FOREBRAIN AND THE MODULATION OF MEMORY FORMATION

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Poster Number: 38

Behavioral studies have shown that circadian rhythms impact the ability to form new memories, but the exact cellular and molecular mechanisms are not fully understood. The most widely accepted theory suggests that memories are encoded in neuronal ensembles or engrams. Unfortunately, previous efforts to find the memory engrams were unsuccessful. However, the recent development of new transgenic tools has allowed the observation and manipulation of memory engrams, thus offering new opportunities to clarify how circadian rhythms affect memory formation. Given that studies in the hippocampus have shown that activation of neuronal ensembles is essential for the encoding and retrieval of contextual memories, and that key components of the molecular circadian clock are present in hippocampal neurons, the present study seeks to understand the relationship between the phase of the circadian clock and the activation of hippocampal memory engrams during the retrieval of contextual fear memories. Our first approach was to determine if circadian rhythms are present in hippocampal neurons. Using the mPeriod1-Venus transgenic mouse line, which allows for the cellular resolution of circadian clock timing, we found robust oscillator capacity in hippocampal neurons. Additionally, we noticed that cellular oscillations are not homogeneous; rather cells exhibited diverse phases of the circadian clock. Next, we use a hippocampal-dependent model of associative memory (contextual fear conditioning) to study differences in memory retrieval at two different times of the day: early morning and early night. In this model, the animals are exposed to a new environment and receive a mild electric shock; subsequent exposures to the novel environment will elicit a freezing (fear) behavior that can be quantified, reflecting the formation and retrieval of a new fear memory. Interestingly, we observed that the ability of mice to retrieve contextual fear conditioning memories differs according to the time-of-day. Along these lines, mice exhibited an increased amount of freezing at the early day when compared with the early night. The aforementioned results led us to posit that the circadian oscillation in hippocampal cells could underlie the time-of-day difference in memory retrieval. In order to test this hypothesis, we plan to analyze fear memory-evoked activation of hippocampal neuronal ensembles in mPeriod1-Venus transgenic mouse, and to test memory retrieval in circadian clock mutant mice. Taken together our results raise the possibility that the circadian clock modulates the efficiency of neuronal ensemble activation, which in turn, underlies the time-of-day efficiency of contextual memory retrieval.

FUNCTIONALIZATION OF INDOLE SCAFFOLD AS ALLOSTERIC HIV-1 INTEGRASE INHIBITORS

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 39

HIV-1 integrase (IN) is an attractive target for HIV therapy due to its role in the incorporation of viral double stranded DNA into host chromosomal DNA. Current FDA approved IN inhibitors raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) target the active site and resistance has already been observed for both RAL and EVG. A new approach to targeting IN is the development of allosteric inhibitors that specifically target the protein-protein interaction between IN and its cellular cofactor LEDGF/p75. A number of quinoline-, and pyridine-containing compounds have been previously synthesized and they inhibit IN activity by binding to the IN LEDGF/p75 binding site. Based on mechanistic studies, quinoline containing compounds have been shown to display multimodal activity leading to the inhibition of IN. One key component of this mechanism is the promotion of aberrant IN multimerization. Subsequently, pyridine-containing compounds were found to more potently promote IN multimerization. In order to explore the steric and electronic features required for the promotion of integrase multimerization which is a key mechanism for IN inhibition, the central scaffold of these systems has been further modified to facilitate the synthesis of previously unexplored functionality. To this end, several 5 and 6-membered heteroaromatic ring systems, including thiophenes, pyrroles, pyrazoles, and indoles, have been synthesized in our labs and tested. Of the synthesized compounds, the indole analogues have shown the most promising IN inhibitory activity. Indole compounds bind in the LEDGF/p75 site and can promote IN multimerization but at a weaker potency as compared to the quinolone/pyridine systems. However the short synthetic route and the ability to perform late stage functionalization allows for rapid generation of a library of structurally diverse compounds which have facilitated more thorough mechanistic studies. The synthesis of the indole compounds, biological data and X-ray crystallography data and reported herein.

THE USE OF ATP-COMPETITIVE m-TOR INHIBITORS FOR TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 40

Sorafenib, an oral multikinase inhibitor, is the only approved treatment option for patients diagnosed with advanced hepatocellular carcinoma (HCC). Unfortunately, sorafenib resistance remains a major clinical challenge. The mTOR pathway has been reported to be activated in sorafenib resistance. Our data and that of others report CD44 overexpression in sorafenib insensitive cell lines. We hypothesize that CD44 is acting downstream of mTOR in HCC, and is involved in sorafenib resistance. We propose INK128, an ATP-competitive mTOR inhibitor, as an alternative treatment option for sorafenib insensitive patients because of its ability to completely inhibit both mTOR complexes (mTORC1 and mTORC2). To explore the role of CD44 in sorafenib resistance, a sorafenib resistant Huh-7 cell line and CD44-overexpressing cells were generated. The expression level of CD44 in various HCC cell lines was evaluated using western blotting. WST-1 proliferation and in vitro migration assays were used to evaluate cellular response under different treatments. Luciferase expressing CD44+ cells have been developed in order to generate an orthotopic HCC mouse model for in vivo testing. In vitro proliferation data in HCC cells showed that CD44+ cells (SNU-423, SNU-449 and SK-Hep1) were more sensitive to the anti-proliferative effects of sorafenib than CD44- cells (Huh7 and HepG2). Moreover, sorafenib resistant Huh7 was found to express CD44 while wild type cells do not. Overexpression of CD44 enhanced cellular proliferation and migration in cells but did not affect sorafenib sensitivity. INK128 was significantly more effective against CD44+ cell lines, and CD44 overexpressing Huh-7 and PLC/PRF/5 cells. However, INK128 was inactive against CD44- Huh-7 cells. Finally in vitro combination index studies showed that the sorafenib and INK128 combination was indifferent. Collectively our data shows that the overexpression of CD44 alone does not drive sorafenib resistance. However CD44 expression indicates activation of the mTOR pathway, and might serve as a biomarker predicting sorafenib response. Our work also suggests that INK128 monotherapy might serve as an alternative treatment for CD44+ HCC patients.

Acknowledgement: Frank Graduate Fellowship

PODOLACTONE DERIVATIVES WITH ANTIPROLIFERATIVE ACTIVITY ISOLATED FROM THE ROOTS OF *PODOCARPUS NERIIFOLIUS*

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 41

As part of an ongoing effort to discover potential anticancer agents of natural origin, plant samples collected in Southeast Asian rainforests were subjected to initial screening in a HT-29 human colon cancer cell line cytotoxicity assay. *Podocarpus neriifolius* D. Don (Podocarpaceae), collected in Vietnam, showed antiproliferative activity against the HT-29 cells, and this plant is being investigated in the current study to isolate its bioactive constituents. Through the bioactivity-guided purification of the ethyl acetate fraction of the root sample of *P. neriifolius*, three bisnorditerpene dilactones, namely, makilactones E (**1**) and G (**2**) and inumakilactone A (**3**) have been isolated so far.^{1,2} These diterpenes are characterized by the presence of a 7 α ,8 α -epoxy-9(11)-enolide functionality, and thus they are classified as type-B podolactones.³ Their structure determination was carried out through extensive spectroscopic data interpretation, including 1D and 2D-NMR spectroscopy and single X-ray crystallography, and comparison with the literature values.^{1,2} While **3** was potent against HT-29 cells with an IC₅₀ value of 1.1 μ M, **1** and **2** did not exhibit cytotoxicity in this assay (IC₅₀ > 10 μ M). Continuing purification of the remaining active fractions from this plant suggests the presence of additional active podolactone derivatives, and their structural characterization and bioactivity will be described along with those of the above-mentioned isolates.

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A PHENYLPROPANOID AND NEOLIGNANS FROM MYRISTICA FRAGRANS WITH PARP-1 AND NF-kB INHIBITORY ACTIVITY

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Poster Number: 42

Bioassay-guided fractionation of the arils of *Myristica fragrans* (Myristicaceae) yielded five phenolic compounds, one new acyclic bis-phenylpropanoid (**1**) and four previously known neolignans. Isolates were identified as (S)-1-(3,4,5-trimethoxyphenyl)-2-(3-methoxy-5-(prop-1-yl) phenyl)-propan-1-ol (**1**), benzenemethanol; α -[1-[2,6-dimethoxy-4-(2-propen-1-yl)phenoxy]ethyl]-3,4-dimethoxy-1-acetate (**2**), odoratisol A; 4-[(2S,3S)-2,3-dihydro-7-methoxy-3-methyl-5-(1E)-1-propenyl-2-benzofuranyl]-2,6-dimethoxy phenol (**3**), 1,3-benzodioxate-5-methanol, α -[1-[2,6-dimethoxy-4-(2-propenyl)phenoxy]ethyl]-acetate (**4**), and licarin C; 2,3-dihydro-7-methoxy-3-methyl-5-(1E)-1-yl-2-(3,4,5-trimethoxyphenyl) benzofuran (**5**). A NMR tube Mosher ester reaction was used to determine the absolute configuration of the new isolated chiral alcohol (**1**). PARP-1 inhibitory activity was evaluated for compound (**1**) (IC₅₀ = 3.0 μ M), compound **2** (IC₅₀ = 0.001 μ M), compound **4** (IC₅₀ = 22.07 μ M) and compound **5** (IC₅₀ = 3.1 μ M). All isolated secondary metabolites were also tested for NF-kB (p65) and K-Ras inhibitory activity. Compounds **2** and **4** displayed potent NF-kB inhibition, IC₅₀ = 1.5 nM and 3.4 nM, respectively.

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CB1 RECEPTORS MODULATE ROD-CONE GAP JUNCTIONAL COUPLING IN THE DAY AND NIGHT

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Poster Number: 43

In the vertebrate retina, rod and cone photoreceptor cells express cannabinoid 1 (CB1) receptors (Yazulla,2008) . Rods and cones, which are connected by gap junctions, detect light stimuli and transmit visual information to post-synaptic neurons. Studies of goldfish, rabbit and mouse retinas have shown that the circadian clock in the retina opens rod-cone gap junctions at night by increasing intracellular cAMP via lowering dopamine release so that Dopamine 2 (D2) receptors are not activated, but closes the gap junctions in the day by lowering intracellular cAMP via increasing dopamine release and D2 receptor activation (Ribelayga et al., 2008; Ribelayga and Mangel, 2010). Interestingly, although dopamine release is about 3-times higher in the day than at night, the day/night difference in rod-cone coupling is remarkably large; injecting a membrane impermeable tracer molecule that can diffuse through open gap junctions into a single goldfish cone results in its diffusion into two nearby rods in the day, but into 1,200 rods at night. Other studies on goldfish cones have shown that the CB1 agonist WIN 55212-2 exhibits biphasic activity, such that a low concentration increases cAMP levels and activates PKA by signaling through Gs, whereas a higher concentration signals through Gi/o (Fan and Yazulla,2003). Based on all these previous findings, we are using anatomical (cut loading, tracer injection) and electrical (patch clamp) techniques to test the hypothesis that interaction between the D2 and CB1 receptors expressed by cones increases the day/night difference in rod-cone coupling compared to the effect of D2 receptors acting alone. Preliminary data showed that under dark-adapted conditions, the CB1 antagonist SR141716A increased rod-cone coupling when it was applied in the day but decreased rod-cone coupling when it was applied at night.

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POPULATION PHARMACOKINETIC AND PHARMACODYNAMIC MODELING FOR PERSONALIZED MELPHALAN REGIMEN IN MULTIPLE MYELOMA PATIENTS

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Poster Number: 44

BACKGROUND: Multiple myeloma (MM) is the second most frequent blood malignancy in the United States. High dose melphalan is effective in MM patients receiving autologous stem cell transplantation (ASCT). However, high inter-patient variability to melphalan could cause prolonged severe neutropenia (absolute neutrophil count < 0.5 K/ μ L).

METHODS: Plasma samples, peripheral blood mononuclear cells, and clinical data from 118 patients were collected prior to and during melphalan treatment. Patients received melphalan followed by ASCT and G-CSF adjuvant therapy. Plasma melphalan concentration was quantified using a validated LC-MS/MS assay. PBMCs were treated ex vivo with melphalan to measure TP53 gene expression and IC50 cytotoxicity level as potential biomarkers. Population PK-PD modeling was performed using a nonlinear mixed effects approach to evaluate the impact of melphalan exposure on neutropenia.

RESULTS/CONCLUSION: Melphalan plasma concentrations in 118 patients were used for population PK modeling. Four covariates (creatinine clearance, hematocrit, SLC7A5, fat free mass) were chosen for the final PK model. G-CSF regimen influenced neutropenia significantly, and it was therefore incorporated into the PD model. Seven covariates (ANC, WBC, HCT, G-CSF, SEX, BUN, and TP53 gene expression level) were chosen in the final PD model predicting neutropenia. The final PK-PD model was used to simulate melphalan doses for individuals to minimize severe neutropenia. This new developed model may guide a personalized melphalan therapy to maximize chemotherapeutic efficacy and minimize prolonged neutropenia.

This work was supported by Multiple Myeloma Opportunities for Research and Education (MMORE), a Pelotonia IDEA award, the Ohio State University Comprehensive Cancer Center Core Grant (P30 CA016058), and Eli-Lilly fellowship.

GENETIC INHIBITION OF PI3K P110 δ ANTAGONIZES SURVIVAL SIGNALS AND INDUCES IMMUNE ACTIVATION IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Poster Number: 45

Chronic lymphocytic leukemia (CLL), the most common adult leukemia in the western world, is characterized by the accumulation of malignant mature B cells in the blood, lymph nodes, spleen and bone marrow. CLL cells display up-regulated B cell receptor (BCR) activation, which maintains B cell survival and proliferation through transmitting microenvironmental stimuli. Due to aberrant regulation of the BCR, CLL cells display constitutively activated survival and proliferation pathways, such as phosphoinositide-3 kinase (PI3K) p110 δ pathways. Small molecule inhibitor of p110 δ , idelalisib, has shown promising activity at antagonizing prosurvival signals in the leukemic cells. In addition, immune tolerance, a critical mechanism for cancer immune invasion, remains a major barrier for effective anti-cancer therapy. PI3K p110 δ also plays critical roles in T cell development and function. Studies using genetic p110 δ kinase-inactivating mice have showed that p110 δ inhibition can reverse the tumor induced immune tolerance, impairs the expansion of regulatory T cells (Treg) thereby enhancing the cytotoxic CD8+ T cells to induce tumor regression in various solid tumor models.

Here we use a genetic engineered PI3K p110 δ -inactivating and the TCL1 leukemia murine models to delineate the role of PI3K p110 δ signaling in CLL leukemia pathogenesis and immune tolerance. Our study indicates that systemic disruption of PI3K p110 δ function prevents spontaneous leukemia development. Systemic double allele inactivation of PI3K p110 δ in TCL1 mouse significantly prevents spontaneous leukemia development, indicating that PI3K p110 δ is a critical kinase for CLL disease initiation and expansion. Moreover, microenvironmental disruption of PI3K p110 δ prevents leukemia engraftment. Inactivation of PI3K p110 δ in the microenvironment showed a dose dependent effect in delaying leukemia development. Whole blood from mice with inactivated p110 δ exhibited higher cytotoxicity to engrafted leukemic cells despite their impaired development of the antigen specific anti-tumor CD8+ T cells.

This study demonstrated that blocking p110 δ in CLL not only abrogate survival signals in leukemic cells but also has the potential to reverse immune suppression in the microenvironment. The finding from this study will suggest that idelalisib, the small molecule p110 δ inhibitor recently approved by FDA for the treatment of CLL, can potentially be used to treat a wide range of cancers by unleashing host anti-tumor immunity.

ANTI-ANDROGEN ENZALUTAMIDE AS CHEMOPREVENTION IN THE DIETHYLNITROSAMINE (DEN) MODEL OF RODENT HEPATOCELLULAR CARCINOGENESIS: A PILOT STUDY

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 46

Hepatocellular carcinoma (HCC), which represents about 90 % of primary liver cancer, is the second leading cause of cancer-related mortality worldwide. HCC is a deadly malignancy with a short survival time. The majority of HCC patients will die within twelve months of diagnosis. Sadly, HCC is most frequently diagnosed at the advanced stage where curative treatment options, surgical resection, and liver transplantation, cannot be implemented. Currently, there are no effective treatment options available for advanced stage HCC. Various risk factors such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, aflatoxin B1 (AFB1) exposure, alcohol abuse, smoking, non-alcoholic steatohepatitis (NASH), type 2 diabetes mellitus and obesity are known to contribute to the initiation and promotion of HCC. Regardless to the global distribution of risk factors, there is sexual dimorphism in HCC incidence and the incidence rate is 2 to 4 fold higher in men than women. This sexual dimorphism in part is due to HCC promotion effect of the androgen receptor (AR). In the current study Enzalutamide (ENZ), three dose groups: 10 mg/kg (mpk), 30 mpk and 100 mpk, were used to antagonize AR in 6 weeks old Sprague Dawley male rats challenged with 2 doses (50 mpk) of chemical carcinogen diethylnitrosamine (DEN) known to induce HCC. Vehicle treated and orchiectomy (ORX) groups were respectively used as a negative and positive controls. The rats, n = 6 in each group were treated with either ENZ or vehicle for 6 weeks, 3 weeks before and DEN challenge. The aim of the pilot study was to determine ENZ tolerability and the impact of ORX and ENZ treatment on hepatocyte initiation in DEN-mediated HCC as measure by immunohistochemically staining for placental glutathione-S-transferase (p-GST). Our preliminary results indicated 100 mpk ENZ was toxic as 4 rats (out of 6) expired before the end of the study. Body weight normalized liver weight significantly increased in 30 mpk and 100 mpk dose groups ($p = 0.0039$) relative to vehicle controls by the end of the study. The weight of androgen regulated organs, urogenital tract ($P = 0.0003$) and seminal vesicle ($p = 0.007$), significantly reduced in 10 mpk, 30 mpk and ORX groups which indicate effective AR antagonism by ENZ and androgen ablation by ORX. Liver toxicity damage marker, serum alanine aminotransferase (ALT), was assessed at several times during the study. ALT levels were reduced in the 10 mpk, 30 mpk and ORX groups,

relative to vehicle controls, suggesting that ENZ targeting of the AR-axis may be effective in reducing DEN-induced hepatotoxicity in male rats and subsequently DEN mediated HCC.

RNA TRIANGLE, SQUARE AND PENTAGON NANOPARTICLES FOR POTENT IMMUNOMODULATION

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Poster Number: 47

Modulation of immune response through cytokine induction is a vital process in vaccine development and immunology therapy. Herein, we report the development of a new generation of potent immunomodulators using RNA nanotechnology. RNA triangle, square and pentagon nanoparticles are successfully self-assembled by stretching the interior angle of thermodynamically stable 3WJ motif of phi29 bacteriophage DNA packaging motor pRNA. When immunological adjuvants were incorporated, their immunomodulation effect for cytokine TNF-alpha and IL-6 induction was greatly enhanced in vitro and in vivo, while RNA polygon controls alone induced negligible effects. The RNA nanoparticles were delivered to macrophages specifically. The degree of immunostimulation is size and shape dependent as well as the number of the payload per nanoparticles. Stronger immune response was observed as the number of adjuvants per polygon was increased. This finding demonstrates that RNA nanotechnology such as developing pRNA-based nanoparticles has the great potential to develop potent immunomodulators.

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C-H FUNCTIONALIZATION OF PHYLLANTHUSMIN NATURAL PRODUCTS

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Poster Number: 48

The phyllanthusmins are a class of arynaphthalene lignans isolated from the *Phyllanthus poilanei* species by the Kinghorn lab in 2014. This series of compounds is composed of a glycoside - typically arabinose attached to the diphyllin aglycone - and possesses potent cytotoxic activity against several cancer cell lines including HT-29. Despite a strong structural resemblance to etoposide, a known topoisomerase II inhibitor, the phyllanthusmins have been shown to exert their cytotoxic effects through alternative mechanisms. Several structural analogues have been synthesized in our lab and evaluated for biological activity resulting in more potent derivatives. In an attempt to improve the physicochemical properties of the analogues, while maintaining activity, late-stage functionalization to the diphyllin core through direct C-H activation is currently under exploration. These changes are anticipated to modulate the potency, solubility and metabolism of the analogues. The development of these methods in this highly collaborative project will be highlighted.

LEAD OPTIMIZATION OF ANTIPROLIFERATIVE CONSTITUENTS FROM PHYLLANTHUS POILANEI

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 49

Natural products such as the taxanes, vinca alkaloids, podophyllotoxins, camptothecin, and their derivatives have proven to be important weapons in the war on cancer. In search of additional novel antiproliferative agents, the bioassay guided fractionation of *Phyllanthus poilanei* afforded a promising lead compound which possesses an ED₅₀ value of 170 nM against an HT-29 cell line.¹ Phyllanthusmin D is an aryl-naphthalene lignan natural product possessing a synthetically accessible core that can be prepared on a gram scale, thereby encouraging analogue development for SAR studies. For this reason, our most extensive SAR work has focused on the glycone moiety, although several of our analogues also explore peripheral changes to the diphyllin core. Differential functionalization of the glycosides following coupling to diphyllin has led to a series of highly potent analogues with ED₅₀ values in the low nanomolar range. While efforts to map out SAR and improve activity continue, a solubility study on several preliminary analogues revealed that in vivo dosing would be difficult without proper formulation. This common problem in drug development which accounts for a large fraction of drug attrition in the pharmaceutical industry cannot be ignored. Therefore, our current focus is on developing a series of potent analogues which contain a free hydroxyl substituent. This will allow for future studies towards solubility improvement via the attachment of water soluble functional groups in a prodrug approach. Another difficulty that has yet to be addressed is the drug target for these phyllanthusmin and phyllanthusmin derived compounds. In this regard, the free hydroxyl group(s) will also be utilized for the attachment of biolinkers, facilitating pull-down assays to identify any key proteins that our compounds are affecting.

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Acknowledgements:

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SYNTHESIS AND BIOLOGICAL EVALUATION OF THIAZOLE DERIVATIVES AGAINST HISTOPLASMA CAPSULATUM AND CRYPTOCOCCUS NEOFORMANS

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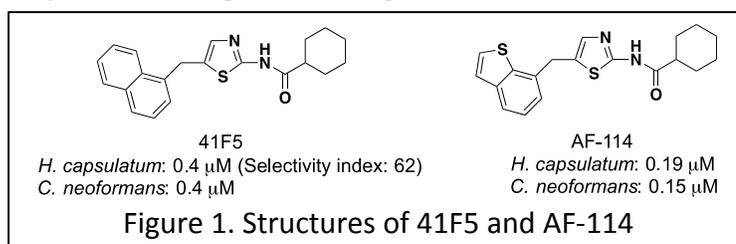
Poster Number: 50

Invasive fungal infections have emerged as a serious threat against human health. Cryptococcus causes more than 500,000 deaths annually among immunocompromised individuals in the world¹. Furthermore, endemic fungi such as *Histoplasma capsulatum* cause respiratory and systemic disease even in immunocompetent individuals, causing more than 6,000 hospitalizations annually in the United States². Owing to the shared eukaryotic nature of fungi and the host, most current antifungal agents are also toxic to the host. To discover novel antifungals, a phenotypic screening of 3,600 compounds that structurally mimic purines/purine analogues was carried out against *H. capsulatum* and seven hit compounds were identified³. Among these hits, the aminothiazole derivative, 41F5 (Fig. 1.), which has naphthalene at the 5-position and cyclohexane at the 2-position of the thiazole core, was found to be most active with an IC₅₀ value of 0.4 μM against *H. capsulatum*⁴. It also had the best selectivity index (at least 62-fold) relative to P388D1 macrophages³. Later, 41F5 was also found to be active with an IC₅₀ value of 0.4 μM against *Cryptococcus neoformans*⁴. Consequently, 68 1st-generation aminothiazole analogues of 41F5 were prepared or obtained for biological evaluation against *H. capsulatum* and *C. neoformans* to establish a basic structure-activity relationship (SAR). Unfortunately, none of these analogues was found to be significantly superior to 41F5⁴. However, the obtained SAR spurred the synthesis of eighteen 2nd-generation aminothiazoles.

Of these agents, AF-114 (Fig. 1.), carrying a benzothiophene- and a cyclohexane- group at the 5- and 2-position, respectively, was found to be active with IC₅₀ values of 0.19 μM against *H. capsulatum* and 0.15 μM against *C. neoformans*, which are

approximately 2 ~ 3 times better than 41F5. This result suggests that other bicyclic ring systems should be explored at the 5-position to further improve activity and physicochemical properties.

Results of studies related to the new 2nd-generation aminothiazole library will be presented.



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PHI29 NANOCHANNEL FOR SINGLE MOLECULE DETECTION OF PEPTIDES BIOMARKERS OF CANCER

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Poster Number: 51

Living systems contain a wide variety of nanomachines and highly-ordered structures of macromolecules that could serve as modules, tool boxes, or building blocks in nanotechnology. The ingenious design of the bacteriophage phi29 DNA packaging motor with an elegant and elaborate channel has inspired its application for single molecule detection and sensing. The central component of the phi29 motor is the connector composed of twelve copies of the protein gp10, which form a dodecamer channel. The connector after incorporation into a lipid bilayer can serve as a detector for extremely sensitive, reliable, and precise sensing and fingerprinting of ions and macromolecules at the single molecule level. Double stranded and single stranded DNA can be electrophoretically driven through the channel in a concentration and voltage dependent manner. Herein, we demonstrate the capability of reengineered phi29 connector to detect varieties of peptides based on single channel conduction assays. Information about the structure, length and conformational dynamics can then be deduced by their characteristic dwell times during translocation and by their relative percentage in current blockades. This protein nanopore system with explicit engineering capability has potential technological applications such as detection and validation of peptide biomarkers from clinical samples at extremely low in concentration in the presence of many contaminants.

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THERMODYNAMICALLY STABLE RNA NANOPARTICLES FOR CANCER TARGETING

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Poster Number: 52

RNA nanotechnology encompasses the use of RNA as a construction material to build homogeneous nanostructures by bottom-up self-assembly with defined size, structure, and stoichiometry; this pioneering concept first demonstrated in 1998 has now created an unexpected paradigm of materials engineering and synthetic structural biology. Our platform is based on the packaging RNA (pRNA) of bacteriophage phi29 DNA packaging motor. The pRNA is a versatile molecule and possesses three structural features which has been used for constructing multivalent 3D architectures with diverse sizes and shapes: loop-loop (hand-in-hand) interactions; palindrome sequences (foot-foot-interactions); and three-way junction motif. These RNA nanoparticles are thermodynamically stable, resistant to RNase degradation, and can harbor resourceful functionalities for therapeutic applications. All incorporated functional modules, such as siRNA, ribozymes, aptamers, miRNAs, anti-miRNAs and other functionalities, folded correctly and functioned independently within the nanoparticles. The incorporation of all functionalities was achieved prior, but not subsequent, to the assembly of the RNA nanoparticles, thus ensuring the production of homogeneous therapeutic nanoparticles. More importantly, upon systemic injection, these RNA nanoparticles targeted varieties of cancer xenografts and metastatic cells exclusively in vivo with little or no accumulation in healthy vital organs and tissues. The observed specific cancer targeting is a result of several key attributes of RNA nanoparticles: anionic charge which disallows nonspecific passage across negatively charged cell membrane; 'active' targeting using RNA aptamers or chemical ligands which increases the homing of RNA nanoparticles to cancer cells; nanoscale size and shape which avoids rapid renal clearance and engulfment by lung macrophages and liver Kupffer cells; favorable biodistribution profiles with little accumulation in healthy organs, which minimizes non-specific side effects; and favorable pharmacokinetic profiles with extended in vivo half-life, non-induction of interferon and cytokine responses. The results demonstrate the clinical potentials of RNA nanotechnology based platform for cancer targeting.

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DELIVERY OF CHEMICALLY MODIFIED mRNA USING LIPID-LIKE NANOPARTICLES FOR HEMOPHILIA TREATMENT

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Poster Number: 53

Chemically modified nucleotides play significant roles in mRNA translation.¹ First, we describe the synthesis of two sets of chemically modified mRNAs [encoding firefly Luciferase (FLuc) and enhanced green fluorescent protein (eGFP), respectively], evaluation of protein expression, and correlation analysis of expression level under various conditions.² The results indicated that chemical modifications of mRNAs are able to significantly improve protein expression, which is dependent on cell types and coding sequences. We identified N1-methylpseudouridine (me1ψ), 5-methoxyuridine (5moU), and pseudouridine (ψ) as promising nucleotides for mRNA modifications. With these results obtained, we designed and formulated new lipid-like nanoparticles (TT-LLNs) for mRNA delivery, a key challenge for the mRNA-based therapeutics in preclinical and clinical studies.³⁻⁶ The results demonstrated improved delivery efficiency of mRNA encoding luciferase in vitro by over 350-fold using an orthogonal experimental design. One optimized TT3 LLN, termed O-TT3 LLNs, was able to restore the human factor IX (hFIX) level to normal physiological values in FIX-knockout mice. Consequently, these mRNA nanomedicines merit further development for broad biomedical applications.

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DESIGN AND SYNTHESIS OF NEW ALLOSTERIC HIV-1 INTEGRASE INHIBITORS.

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Poster Number: 54

HIV-1 integrase (IN) is the enzyme responsible for the incorporation of viral double stranded DNA into host chromosomal DNA. Recently, three drugs targeting the active site of IN have been approved for HIV therapy. Raltegravir was the first FDA approved IN inhibitor, although resistance to this drug in the clinic has been observed. Based on this resistance, second generation integrase inhibitors, including elvitegravir and dolutegravir have also been developed. A new approach to targeting HIV-1 IN is the development of allosteric integrase inhibitors (ALLINIs). Specifically, these small molecules inhibit the protein-protein interaction between IN and its cellular cofactor LEDGF/p75 or target the LEDGF/p75 site and promote aberrant IN multimerization. Various ligands that bind at the IN CCD dimer interface effectively bridge the interacting IN subunits and promote aberrant IN multimerization, resulting in the formation of catalytically inactive higher order IN oligomers. We have designed a series of analogues in an effort to probe interactions with the subunits of IN, allowing us to explore the mechanism of HIV-1 IN multimerization. These compounds include variation of substituents capable of interacting with the IN subunits and exploration of additional pockets within the LEDGF binding site.

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BIOASSAY-GUIDED ISOLATION OF ANTIPROLIFERATIVE COMPOUNDS FROM AN ENDOPHYTIC STREPTOMYCES SP. OF BAZZANIA TRILOBATA

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 55

Despite recent advances in the early detection, surgical intervention, and chemotherapeutic treatment of colorectal cancer, it is estimated that over 584,000 Americans die from it each year¹. The development of drug resistance², genetic variability of patients, and side effects associated with current therapies substantiate the need for novel cancer treatments. The importance of natural products in obtaining novel therapies is confirmed by recent literature indicating it as the source of 44% of current anticancer drugs³. As part of an ongoing search for antiproliferative compounds from microbial associates of liverworts, our lab has identified an endophytic *Streptomyces* sp. from *Bazzania trilobata* that produces a crude extract active against the human adenocarcinoma cell line (HT-29, IC₅₀ = 16.5 µg/mL) in the sulforhodamine B assay. Bio-assay guided fractionation using column chromatography afforded a fraction with significant activity (HT-29, IC₅₀ = 0.80 µg/mL). Following scale-up fermentation, compound (1) was isolated and its structure assigned by interpretation of NMR data. The isolation and structure elucidation of the compound will be discussed herein.

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INHIBITION OF S-ADENOSYLMETHIONINE-DEPENDENT METHYLTRANSFERASE ATTENUATES TGF- β 1-INDUCED EMT AND METASTASIS IN PANCREATIC CANCER: PUTATIVE ROLES OF MIR-663A & MIR-4787-5P

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Poster Number: 56

Identification of epigenetic reversal agents for use in combination chemotherapies to treat human pancreatic ductal adenocarcinomas (PDAC) remains an unmet clinical need. Pharmacological inhibitors of Enhancer of Zeste homolog 2 (EZH2) are emerging as potential histone methylation reversal agents for the treatment of various solid tumors and leukemia; however, the surprisingly small set of mRNA targets identified with EZH2 knockdown suggests novel mechanisms contribute to their anti-tumorigenic effects. Here we report 3-deazaneplanocin-A (DZNep), an inhibitor of S-adenosyl-L-homocysteine hydrolase and EZH2 histone lysine-N-methyltransferase, to significantly reprogram noncoding miRNA expression and dampen TGF- β 1-induced epithelial-to-mesenchymal (EMT) signals in pancreatic cancer. In particular, we identify miR-663a and miR-4787-5p as PDAC-downregulated miRNAs that are reactivated by DZNep to directly target TGF- β 1 for RNA interference. Lentiviral overexpression of miR-663a and miR-4787-5p reduced TGF- β 1 synthesis and secretion in PDAC cells and partially phenocopied DZNep's EMT-resisting effects, whereas locked nucleic acid (LNA) antagomiRs counteracted them. *In vivo*, DZNep, miR-663a, and miR-4787-5p reduced tumor burden and metastases in an orthotopic mouse pancreatic tumor model. Taken together, these findings suggest the epigenetic reprogramming of miRNAs by synthetic histone methylation reversal agents as a viable approach to attenuate TGF- β 1-induced EMT features in human PDAC and uncover putative miRNA targets involved in the process.

NEW APPROACH TO DEVELOPE ULTRA-HIGH INHIBITORY DRUG USING THE POWER-FUNCTION OF THE STOICHIOMETRY OF THE TARGETED NANOMACHINE OR BIOCOMPLEX

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 57

To find a method for developing potent anticancer drugs and to prove a hypothesis that drug inhibition potency depends on the stoichiometry of the targeted biocomplex, we tested this model with phi29 DNA-packaging motor components with different stoichiometries. Virion assembly efficiency was assayed and analyzed with Yang Hui's Triangle: $(p + q)^Z = \sum_{M=0}^Z \binom{Z}{M} p^{Z-M} q^M$, where Z=stoichiometry of biocomplex, M=drugged subunits in each biocomplex, p and q represent the fraction of drugged and non-drugged subunits in the population. Results showed that inhibition efficiency follows a power function of the stoichiometry of the targeted biocomplexes. When number of drugged subunits to block the function of the biocomplex K=1, the fraction of uninhibited biocomplex equals q^Z . Thus, stoichiometry has a multiplicative effect on inhibition. Targets with a thousand subunits showed the highest inhibition effect, followed by those with six and a single subunit. Complete inhibition of virus replication was found when Z = 6. In conclusion, drug inhibition potency depends on the stoichiometry of the targeted components of the biocomplex or nano-machine. The inhibition effect follows a power function of the stoichiometry of the target biocomplex. Since biomotors share certain common structures and operation mechanisms, the approach in drug development reported here should have general applications especially in developing new generations of drugs for combating the rising acquired drug resistance in viruses, bacteria, and cancers.

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ZINC IMPACTS ENDOTOXIN-INDUCED MACROPHAGE INFLAMMATION THROUGH ZIP8 INDUCTION AND C/EBP-BETA INHIBITION

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Presenting Author: Charlie Pyle

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 58

Two vital functions of the innate immune system are to initiate inflammation and to redistribute micronutrients in favor of the host. Zinc is an essential micronutrient utilized in host defense. The zinc importer ZIP8 is uniquely induced through stimulation of the NF- κ B pathway by LPS in monocytes and functions to regulate inflammation in a zinc-dependent manner. Macrophages also respond to LPS through activation of the NF- κ B and MAPK signaling pathways, and subsequently release pro-inflammatory and immune modulatory cytokines and chemokines. Herein we determined the impact of zinc metabolism following LPS-induced inflammation in human macrophages. We observed that ZIP8 is constitutively expressed in resting macrophages and strikingly elevated following LPS exposure, a response that is unique compared to the 13 other known zinc import proteins. During LPS exposure, extracellular zinc concentrations within the physiological range markedly reduced IL-10 mRNA expression and protein release but increased mRNA expression of IL-6 and IL-8. ZIP8 knockdown partially reversed zinc-dependent reduction of IL-10 release. Further, zinc supplementation attenuated C/EBP β nuclear accumulation and activation, a transcription factor known to drive IL-10 expression. These studies demonstrate for the first time that zinc regulates LPS-mediated immune activation of human macrophages in a ZIP8-dependent manner. Based on these findings we predict that macrophage zinc metabolism is critical in host defense against bacterial pathogens.

THE NATURAL PRODUCT CAPSICODENDRIN INDUCES APOPTOSIS AND CYTOTOXICITY IN HUMAN MYELOID LEUKEMIA CELLS: MODULATION BY GLUTATHIONE

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Poster Number: 59

Capsicodendrin (CPCD), a dimeric drimane-type sesquiterpene isolated from *Cinnamosma fragrans*, is used as a chemopreventive in Madagascan traditional medicine. It is known to demonstrate cytostatic properties (1). However, its mechanism of action remains largely unknown. In the present study, we demonstrate time- and concentration-dependent cytotoxicity (trypan blue exclusion) and apoptosis (Hoechst nuclear staining) in human acute myeloid leukemia HL60 cells. CPCD was found to bind avidly to glutathione (GSH) via Michael addition. To examine the effects of GSH on CPCD activity, HL60 and human chronic myelogenous K562 leukemia cells were treated with buthionine sulfoximine (BSO) to decrease the synthesis and cellular content of GSH. Depletion of GSH significantly ($p < 0.05$) enhanced the growth inhibitory effects of CPCD in HL60 cells yielding IC_{50} -values of 0.20 ± 0.03 and 0.09 ± 0.02 μM in the absence or presence of BSO, respectively. For K562 cells, CPCD IC_{50} -values were 0.40 ± 0.06 and 0.22 ± 0.04 μM ($p < 0.05$) in the absence or presence of BSO, respectively. Similarly, compared to GSH replete HL60 cells, BSO treatment resulted in significantly ($p < 0.05$) greater CPCD-induced cytotoxicity and apoptosis. Finally, CPCD-induced DNA strand breaks, measured by COMET assays, were increased in GSH-depleted compared to GSH replete HL60 cells.

Together results indicate that CPCD cytotoxic activity is modulated by its adduction with GSH. This CPCD-GSH complex may impact its chemopreventive and/or direct anticancer activity. Studies are underway to isolate and evaluate the activity of CPCD-glutathione adducts.

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EFFECT OF DEPLETION OF ATYPICAL CYCLIN DEPENDENT KINASES ON ENDOTHELIAL CELL MIGRATION.

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Poster Number: 60

Angiogenesis is important to maintain homeostasis of normal organs and it contributes to tumor growth. Angiogenesis requires migration and proliferation of endothelial cells, processes that are regulated by biochemical signals. The atypical cyclin dependent kinases (**CDK**) 5, 7, 8 and 9, whose activity does not correlate with cell cycling, may affect endothelial cell migration. Thus in the present study we evaluated the role of these atypical CDK's in endothelial cell migration. To assess migration, a scratch was made in a confluent monolayer of mouse aortic endothelial cells, in 6 well petri dishes, with a pipette tip. Surrounding cells respond to this by migrating into the newly formed open space. Migration was quantified by photographing the scratch immediately and after 15 h at the same location. Images were analyzed using a wound healing macro for ImageJ to measure the cell- free area. The ratio of cell-free area at 0 h to the area at the end indicated the degree of migration. To investigate the effect of CDK 5, 7, 8 and 9 they were depleted by electroporation with the specific small inhibitory RNAs. Endothelial cells were also treated with a non-targeted RNA. Contrary to previous reports, CDK5 knockdown increased cell migration. Depletion of CDK7 or 8 had no effect. However, CDK9 knockdown impaired cell migration. The results suggest that CDK5 and 9 regulate endothelial cell migration. These atypical CDK's might serve as useful targets for antiangiogenic therapy.

IMPLICATIONS OF CRISPR CAS GENERATED MICRORNA KNOCKOUT MOUSE MODELS IN EARLY AND LATE DEVELOPMENT OF PANCREATIC CANCER

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Poster Number: 61

Pancreatic adenocarcinoma (PDAC) is one of the most lethal forms of cancer. While much has been learned over the past decade regarding the influence of mutations in protein coding genes in PDAC, recent evidence suggests that noncoding microRNAs (miRNAs) play an active role in the initiation of this disease. We and others have shown that three pancreatic enriched miRNAs (e.g. miR-216a/-216b and miR-217) are reduced in human PDAC. In other solid tumors (e.g. liver, brain and muscle), tissue specific or enriched miRNAs have a tumor suppressor role and their loss contributes to the cancer phenotype. Based on this accumulated knowledge, we hypothesize that miR-216 and miR-217 function as tumor suppressors in PDAC. We tested this hypothesis by knocking out a 17 kbp genomic segment containing the three miRNAs in mice. No homozygous mutants were detected after genotyping over 250 pups, suggesting that the germ line deletion is embryonic lethal. To overcome this obstacle and better dissect the role of each member of the cluster, we have developed 3 individual knockout mouse models. To accomplish our goal of generating this new mouse models, we have used the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology. We are currently focused on determining the phenotypic effect that these three knockout mice will have on the early PDAC development stage, namely during acinar-ductal transdifferentiation and by inducing acute pancreatitis using caerulein. Knockout mice are also being crossed with KrasG12D mice which have been well studied to develop pancreatic cancer. Resultant bigenic offspring will be evaluated to determine if loss of the miR-216/-217 further enhances precursor lesion progression (i.e. PanINs) and development of PDAC. Mice will be examined to see if the miR-216/217 ablation enhances cancer progression and reduces survival. Results from this project will provide fundamental new information related to the role of the 3 miRNA's on pancreatic carcinogenesis and progression. In the long term, the knowledge gained may provide novel targets for miRNA replacement in pancreatic cancer treatment.

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BIOASSAY GUIDED FRACTIONATION AND ISOLATION OF NOVEL CYTOTOXIC COMPOUNDS FROM PORELLA CORDAEANA

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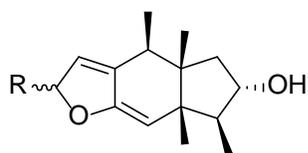
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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 62

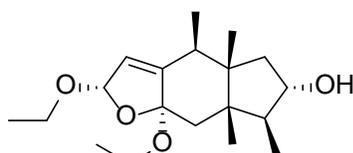
The bryophyte *Porella* is a largely common and widespread genus of liverwort which has at least 100 species documented. To date, 29 species have been explored for its chemical constituents¹ and they are notable to produce bioactive terpenoids, such as pinguisanes, drimanes and sacculatanes.² Previous studies on *Porella cordaeana* extracts have reported anti-inflammatory, analgesic and antimicrobial and antiproliferative activities,³⁻⁵ though specific chemical constituents of this species that contributed to these effects have yet to be pinpointed. In the course of our ongoing search of bioactive compounds from liverworts and their microbial associates, an extract of *Porella cordaeana* collected from Turkey displayed significant cytotoxicity against MCF-7, a human breast adenocarcinoma cell line. Therefore, this study aims to employ MCF-7, alongside with HT-29, a human colorectal adenocarcinoma cell line, to systematically guide our discovery towards novel cytotoxic compounds from *Porella cordaeana*. Thus far, from our comprehensive spectroscopic studies, four new compounds, namely porellacetal A-D (**1-4**), from one of the bioactive fractions of the diethyl ether extract of *Porella cordaeana* have been isolated and elucidated. The structure elucidation and cytotoxic evaluation of the four isolated compounds against MCF-7 and HT-29 cell lines will be discussed.



1 : R = OH

2 : R = α -OCH₂CH₃

3 : R = β -OCH₂CH₃



4

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BRAFV600E INDUCES ABCB1/P-GLYCOPROTEIN EXPRESSION AND DRUG RESISTANCE IN B-CELLS VIA AP-1 ACTIVATION

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Keywords: BRAF, vemurafenib, B-cell, ABCB1, P-glycoprotein

A subset of patients with chronic lymphocytic leukemia (CLL) and nearly all patients with classic hairy cell leukemia (HCL) harbor somatic BRAF activating mutations. However, the pathological role of activated BRAF in B-cell leukemia development and progression remains unclear. In addition, although HCL patients respond well to the BRAFV600E inhibitor vemurafenib, relapses are being observed, suggesting the development of drug resistance in patients with this mutation.

Cell line models to study the mechanism of BRAFV600E in B cell leukemia do not exist. Therefore, we utilized the CLL-like B-cell line OSUCLL (PLoS One 2013, 8(10):e76607) to generate cells with doxycycline (dox)-inducible BRAFV600E expression to examine transcriptional and biochemical features induced by this mutation in B-cells. We observed that BRAFV600E induction enhanced proliferation and activation of MAPK signaling in these cells. Microarray using Affymetrix U133 Plus 2.0 GeneChips demonstrated that 235 genes were up-regulated at least 2-fold, and 227 genes were down-regulated at least 2-fold. Several were confirmed by real-time RT-PCR analysis, including ABCB1 ($p < 0.001$, vehicle versus dox-treated). Increased expression of the ABCB1 gene product, P-glycoprotein (P-gp), was also confirmed by immunoblot. This increase resulted in enhanced P-gp function as determined by rhodamine exclusion assays ($p < 0.005$), an effect that was significantly reversed by the P-gp inhibitor verapamil ($p < 0.005$). As an additional demonstration of P-gp function, BRAFV600E induction via dox treatment resulted in a significant increase in resistance to the P-gp substrate vincristine, and the addition of verapamil significantly reduced vincristine resistance. Importantly, pharmacological inhibition of BRAFV600E and MEK, by vemurafenib and CI-1040 respectively, diminished BRAFV600E-induced MAPK pathway activation and enhancement of ABCB1/P-gp expression. To further understand the transcriptional mechanism of BRAFV600E-induced P-gp expression, we performed luciferase assays using a vector containing 1 kb of ABCB1 promoter driving a luciferase reporter, co-transfected into HEK293 cells with either an empty vector or a vector containing BRAFV600E. These assays showed that BRAFV600E expression enhanced luciferase activity ($p < 0.001$), and this effect was down-regulated by vemurafenib and CI-1040

($p < 0.001$). The role of AP-1 has been reported in ABCB1 regulation. Thus, we conducted electrophoretic mobility shift assays in the BRAFV600E-transfected OSUCLL B-cells, with or without dox treatment, to identify AP-1 factor(s) involved in ABCB1 regulation by BRAFV600E. In these experiments, a supershift in the AP-1 complex was produced by an antibody to JunD in the presence of dox treatment, demonstrating that at least JunD activity is important in this mechanism.

Based on these observations, we conclude that BRAFV600E activates AP-1 proteins including JunD to induce ABCB1/P-gp expression and drug resistance in B-cells. This study uncovers a new pathological role for BRAFV600E in B-cell leukemia, and provides further evidence that combination strategies with inhibitors of BRAFV600E and MEK may be beneficial in delaying disease progression and occurrence of resistance to drugs that are substrates of P-gp.

PRECLINICAL INVESTIGATION OF THE HDAC INHIBITOR AR-42 FOR THE TREATMENT OF CANCER-INDUCED CACHEXIA

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Rank of Presenting Author: Graduate (MS, PhD) Student

Poster Number: 64

Cachexia is characterized by extreme loss of skeletal muscle mass with or without adipose tissue wasting and cannot be reversed by nutritional support, finally leads to pronounced weight loss and weakness that contributes significantly to morbidity and mortality. Cachexia occurs in more than 50% of cancer patients, and is particularly prevalent in those suffering from pancreatic, gastric, or esophageal cancer. Cachectic cancer patients are often weak and fatigued, respond poorly to therapy, and have a lower tolerance to therapy and surgery. Thus, the development of effective therapies for cancer cachexia, which could provide tangible clinical benefits to patients, is clearly warranted.

AR-42 is a novel class I/II histone deacetylase (HDAC) inhibitor that was developed in our laboratory and is currently in Phase I/IB trials in both hematological malignancies and solid tumors at The Ohio State University James Cancer Hospital. Here, we report the anti-cachectic activity of AR-42 in two murine models of cancer cachexia. In the colon-26 (C-26) adenocarcinoma model, oral AR-42 attenuated cachexia-induced losses of skeletal muscle mass, adipose tissue, and body weight, with minimal effects on C-26 tumor growth, and prolonged survival time relative to mice treated with vehicle or other HDAC inhibitors (vorinostat and romidepsin). Metabolomic and gene expression analyses revealed that these anti-cachectic effects of AR-42 were associated with its ability to maintain metabolic and gene expression profiles in skeletal muscle comparable to those in non-cachectic muscle from tumor-free mice. Consistent with the protective effect on muscle mass, handgrip dynamometry and histological cross-sectional area of muscle fiber measurement showed that AR-42 was able to preserve muscle function and morphology in drug treatment groups comparing to vehicle control. Importantly, this AR-42-induced abrogation of cachexia and rescue of muscle weight was confirmed in the Lewis lung carcinoma (LLC) model of cancer cachexia. Moreover, we proved that in a delay treatment experiment, AR-42 still able to prevent part of muscle atrophy in C26 model. In the AR-42 PK studies, we reported 10mg/Kg of AR-42 daily treatment can show significant benefits on C-26 tumor bearing models, comparing to previous dosage 50mg/Kg every other day. Together, these results support further evaluation of AR-42 as a potential treatment for cancer cachexia.

Pancreatic cancer is among the top four leading causes of cancer deaths in the U.S. A major factor contributing to death from pancreatic cancer is cachexia, a debilitating condition characterized by depletion of skeletal muscle and adipose tissue that leads to pronounced weight loss, weakness, fatigue, lower tolerance to chemotherapy and radiation, and ultimately

decreased survival. After a careful review of the literature, we identified two different orthotopic pancreatic cancer xenograft models, AsPC-1 and COLO-357 that have been reported to induce body weight loss and muscle atrophy during tumor growth. Direct injection of AsPC-1 human pancreatic cancer cells (1×10^6 cells/mouse) into the pancreas of athymic nude mice (female, 6-8 weeks of age, Harlan) generated orthotopic tumors. Reductions in muscle weight were observed at 54 days after surgery. As described in the published report, subcutaneous injection of COLO-357 cells suspension into athymic nude mice was performed to generate tumors to be used as source material for the surgical transplantation of tumor fragments to the surface of the pancreas of recipient nude mice. At this time, the survival surgical techniques have been refined and successful transplantations and subsequent orthotopic tumor growth have been achieved. By 2 weeks post-transplantation, mice begin to exhibit weight loss. In both orthotopic models, AR-42 showed protective effects on muscle weight against cancer induced muscle wasting. This result supported our hypothesis that AR-42 can suppress cancer induced cachexia in multiple animal models; not only suppress body weight loss, muscle wasting, but also maintain functional muscle strength compared to vehicle treated group.

Significant

Cancer cachexia is a debilitating condition that occurs in more than 50% of all cancer patients and in over 80% of those with pancreatic cancer. It is characterized by dramatic weight loss, muscle wasting, and weakness, leading to diminished quality of life and ultimately decreased survival. This study is aimed at the potential of the HDAC inhibitor, AR-42, for the treatment of cancer cachexia on different cancer induced animal models. The potential impact of this study is tremendous in that may establish AR-42 as an effective inhibitor of this devastating condition, for which no effective treatments currently exist.

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FUNCTIONAL REGULATION OF CREB VIA CRTC1 AND SERINE-133 PHOSPHORYLATION INFLUENCES CLOCK TIMING AND ENTRAINMENT OF THE SUPRACHIASMATIC NUCLEUS

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Poster Number: 65

In response to the earth's rotation on its axis, and the resulting 24-hour oscillation of the rising and setting of the sun, circadian rhythms have evolved to provide selective advantages for survival. Essential physiological functions such as heart rate, sleep/wakefulness and learning are tethered to time of day and have defined circadian rhythms. Examining the circuitry involved in setting and maintaining our daily physiological rhythms will ultimately aid in tackling issues such as metabolic disorders, depression, insomnia and consequences of jet-lag and shift work. The road to understanding circadian rhythms begins at the suprachiasmatic nucleus (SCN). Within the SCN, the locus of the master circadian clock, transcriptional regulation mediated by the cyclic-AMP response element binding protein (CREB)/cyclic-AMP response element (CRE) pathway has been implicated in the functioning of the molecular clock timing process, and has been shown to be a key conduit through which photic input entrains the SCN oscillator. A key event driving CRE-mediated transcription is the phosphorylation of CREB at Serine-133. Indeed, numerous reported gene assays have shown that that point mutagenesis of serine 133 to an alanine potentially abrogates CREB-mediated transcription. Here, we sought to examine the contribution of Ser-133 to the functional role of CREB in SCN timing in vivo. To this end, we utilized a CREB Serine 133-to-Alanine 133 (CREB S/A) knock-in mouse strain to test the role of this phosphorylation event in SCN clock physiology. Under a standard 12 hr light/dark cycle CREB S/A mice exhibited a marked alteration in clock gating of wheel running activity. Thus, relative to WT mice, CREB S/A mice exhibited highly fragmented bouts of locomotor activity during the night phase, elevated daytime activity, and a delayed phase angle of entrainment. Further, under free running conditions, CREB S/A mice exhibited a significantly longer tau than WT mice. Clock entrainment using both Aschoff type 1 light entrainment paradigms was also affected in CREB S/A mice. Surprisingly, in CREB S/A mice expression of the CREB-regulated gene arginine vasopressin (AVP) was increased within the SCN, thus raising the prospect that compensatory genetic mechanisms may be actuated to offset the loss of CREB phosphorylation. In line with this possibility, the expression of CREB transcriptional co-regulator CRTC1 was significantly upregulated in CREB S/A mice. Further, we provide immunohistochemical and RNA-seq data indicating that the CRTC1 in the SCN is mediated by microRNA miR132. Together, these results indicate signaling through CREB is a

principal pathway by which photic input is routed, and that the relative contribution of CREB phosphorylation and CRTC signaling can be tuned (via miR132) to ensure the functional fidelity of the CRE transcriptional pathway.

SYNTHESIS AND EXPLORATION OF THE STRUCTURE-ACTIVITY RELATIONSHIP OF THE NOVEL 20S PROTEASOME INHIBITOR SCYTONEMIDE A

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Poster Number: 66

In eukaryotic cells, the 26S proteasome complex, containing the 20S proteolytic core, is capable of catalyzing the degradation of intracellular regulatory proteins, helping to control the cell cycle and maintain homeostasis. Thus, it is not surprising that there has been significant interest in the discovery of proteasome inhibitors as potential anticancer agents. In an effort to identify novel proteasome inhibitors, scytonemide A (scy A) was recently isolated by Orjala et al. from the freshwater cyanobacterium *Scytonema hofmannii*. The cyclic polypeptide natural product consists of seven amino acids connected through a highly unusual imine linkage. Although scy A could be isolated in only very small quantities, it showed promising in vitro activity in the proteasome inhibition assay with an IC₅₀ of 96 nM. Scy A also demonstrated 80% inhibition at 6.7 μM in a luminescence-based cellular 20S proteasome assay.

With low isolation yields limiting the ability to fully explore the biological activity of scy A, our lab has pursued its first total synthesis. Using solid phase peptide synthesis on a Weinreb amide resin, we assembled the linear heptapeptide that upon reduction from the resin spontaneously cyclized to afford a side-chain protected version of scy A. Global trifluoroacetic acid deprotection followed by aqueous sodium carbonate re-cyclization afforded scy A. Purification of the final product is still being optimized, but a crude sample has been sent to the Orjala lab at UIC to be purified and compared to the isolated natural product. With a viable synthetic approach in hand, we are now poised to explore the structure-activity relationships (SAR) of this compound. The ultimate goal is to understand the key binding interactions between scy A and the 20S proteasome that account for its potent inhibitory activity. Understanding this will also make it possible to carry out the rational design of new analogues that maintain the same or better activity, while aiming to improve upon the possible chemical or metabolic instability associated with this natural product.

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DEVELOPMENT OF STABLE BOILING-RESISTANT PHI29 PRNA NANOPARTICLES FOR SPECIFIC TARGETING AND TREATMENT OF CANCERS

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Poster Number: 67

The field of RNA nanotechnology necessitates creation of stable and tunable, functional RNA nanoparticles. We have shown that the three-way junction of bacteriophage phi29 motor pRNA has unusual stability and can self-assemble from three fragments with high efficiency, while displaying thermos and chemical stability. We have fabricated a variety of RNA architectures with precise control of shape, and stoichiometry by exploiting the flexibility of the pRNA-3WJ. The stable 3WJ was used to construct planar triangular, square and pentagon scaffolds – through the stretching of the 60° angle of the pRNA-3WJ to 90° and 108°. The resulting scaffolds were shown to be tunable in size and chemical and thermodynamic stability through simple modification of the scaffold's core strand. Additionally, nucleotides resulted in RNA nanoparticles resistant to RNase degradation. Furthermore, all RNA scaffolds were incorporated with siRNA, ribozyme, and fluorogenic aptamers, keeping the original folding and functionalities of the RNA functional groups. RNA nanoparticles were then used for specific targeting and binding to prostate cancer, breast cancer, and glioblastoma cells through the use of RNA aptamers or chemical ligands. The RNA nanoparticles were shown to specifically target tumors *in vivo* with no detectable accumulation in healthy vital organs and tissues four hours post systemic injection and delivered therapeutics modules *in vitro* and *in vivo*. Furthermore, the RNA nanoparticles are non-toxic and display favorable pharmacological profiles *in vivo*.

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GASTRIC CANCER THERAPY BY SYSTEM INJECTION OF RNA NANOPARTICLES CARRYING BOTH LIGAND AND SIRNA

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Poster Number: 68

Gastric cancer is one of the leading causes of cancer-related death worldwide and is difficult to treat. Recently, RNA nanotechnology has emerged as an important and novel platform due to its tremendous versatility, high thermodynamic stability, less toxicity and favorable in vivo attributes. Using RNA nanotechnology to construct nanoparticles, exosomes and micelles have become a promising method for cancer therapy. Here we report the use of the three-way junction (3WJ) of the bacteriophage phi29 motor pRNA as a scaffold to incorporate targeting ligands, a NIR imaging marker and siRNA for gene silencing and regression of gastric cancer tumors in animal models. In vitro assay revealed that the folate incorporated RNA nanoparticles specifically bound to gastric cancer cells, knocked down oncogenic genes and was able to induce gastric cancer cell apoptosis. Animal trials confirmed that these RNA nanoparticles could be used to target gastric tumors in vivo, while showing little accumulation in other vital organs and tissues. Furthermore, the volume of gastric tumors noticeably decreased during the course of the treatment. The results indicate that this novel RNA nanotechnology can overcome conventional cancer therapeutics to stomach cancer without damaging normal cells and tissues and improve the therapeutic effects.

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INHIBITORS OF CYCLIN DEPENDENT KINASES 7 AND 9 DECREASE MIGRATION OF MOUSE AORTIC ENDOTHELIAL CELLS

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Angiogenesis is critical for homeostasis in normal tissues and for tumor development, during which endothelial cells proliferate and migrate under the influence of various biochemical signals. Manipulation of signals controlling cell migration might be therapeutically beneficial for a number of diseases. Cyclin dependent kinases (CDK) 7 and 9 are necessary for the proper maintenance of cell cycle and gene transcription. CDK 7 is present in CDK-activating kinase (CAK), which activates other CDKs. CDK 7 and 9 also enhance transcription by phosphorylating the C-terminal domain of RNA polymerase II. Here we tested two CDK inhibitors on migration of mouse aortic endothelial cells. THZ1 and CDK9I inhibit CDKs 7 and 9 at different IC50 values and by different mechanisms. Cells were cultured to confluence and scratched with a pipette tip to mimic a wound. After scratching, cells were treated without or with 0.33-30 μ M CDK9I or 0.0625-30 μ M THZ1. Migration of cells into the open space was measured by capturing images immediately after scratching and at the same positions 16 h later. A 'Migration Index' was calculated from the ratio of the area lacking cells at 16 vs 0 h. Cultures were also observed qualitatively for detachment as an indication of cytotoxicity. Each drug inhibited migration in a concentration-dependent manner, with IC50 values of 0.36-0.37 and 5-7 μ M for THZ1 and CDK9I, respectively. THZ1 was induced noticeable detachment of cells at concentrations above 1 μ M. The results indicate that these CDK inhibitors antagonize endothelial cell migration.

LOW VITAMIN D LEVEL ON ADMISSION FOR BURN INJURY IS ASSOCIATED WITH INCREASED LENGTH OF STAY

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Poster Number: 70

Background/Introduction: Currently, there have been few studies that have evaluated the incidence of vitamin D deficiency in adult burn patients or correlated vitamin D levels with burn related outcomes. The primary objective of the study was to identify the incidence of vitamin D deficiency and insufficiency in an adult burn population. The secondary objective was to determine the impact of vitamin D deficiency and insufficiency on clinical outcomes in burn care.

Materials and Methods: A single-center, retrospective, and observational cohort analysis of adult patients admitted for initial management of burn injury, who had a 25-hydroxyvitamin D level measured on admission, was performed. Patients were categorized as vitamin D deficient (25-hydroxyvitamin D <10 ng/mL), insufficient (10-29 ng/mL), or sufficient (30-100 ng/mL) based on admission measurements. Clinical outcomes including complications, ICU and hospital LOS, and survival were compared between patients with vitamin D deficiency/insufficiency and patients with vitamin D sufficiency.

Results: Three-hundred and eighteen patients were eligible for evaluation. Admission 25-hydroxyvitamin D level correlated with deficiency in 47 patients (14.5%), insufficiency in 209 (64.3%), and normal in 69 (21.2%). Patients with vitamin D deficiency or insufficiency experienced higher rates of complications and longer ICU and hospital length of stay compared to those with normal vitamin D levels.

Conclusions/Discussion: A large proportion of patients with burn injury presented with vitamin D insufficiency and deficiency. Vitamin D insufficiency and deficiency was associated with poor outcomes in this population, including prolonged ICU and hospital LOS. Additional studies are needed to further describe the relationship between vitamin D status and clinical outcomes.

IMPACT OF A NURSING-DRIVEN SEDATION PROTOCOL WITH CRITERIA FOR INFUSION INITIATION IN THE SURGICAL INTENSIVE CARE UNIT

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Poster Number: 71

Sedation management in critically ill patients who require mechanical ventilation poses a challenge for healthcare providers. The surgical intensive care unit (SICU) implemented a nursing-driven sedation protocol with criteria for infusion initiation in April 2011. This study aimed to assess the impact of this protocol. This single-center, retrospective cohort study included patients aged 18-89 years who required at least 24 hours of mechanical ventilation. Patients admitted to the SICU from November 1, 2009 to October 31, 2010 were grouped in the pre-implementation period and patients admitted November 1, 2011 to October 31, 2012 were grouped in a post-implementation period. The pre- and post-implementation groups were compared with a primary endpoint of ventilator-free days at day 28. Secondary endpoints included proportion of patients administered continuous infusion opioid and/or sedative agents, proportion of RASS scores within target sedation range, incidence of delirium and requirement of antipsychotic medication for delirium, restraint requirements and ICU and hospital length of stay. Data was collected from the electronic medical records; Essentris was utilized for the pre-implementation group and EPIC for the post-implementation group. One hundred thirty-two patients were included for evaluation with 66 in the pre- and 66 in the post-implementation group. Baseline characteristics were similar with the exception of a lower percentage males and lower SAPS II scores in the post-implementation group. Analysis of the data showed an increase in the ventilator free days at day 28 from a median of 13 [1-23] days in the pre-implementation group to 21 [11-24] days in the post-implementation group ($p=0.022$). The percent of RASS scores within the target range for sedation was also increased from 65.2% to 88% for the post-implementation cohort ($p<0.001$). Continuous infusion utilization for sedation decreased from 86.4% of patients in the pre-implementation group to 42.4% in the post-implementation group ($p<0.001$). Continuous infusion for analgesia also decreased from 80.3% to 24.2% ($p<0.001$). Intravenous morphine equivalents administered per ventilator day decreased from a median of 77.1 [22-136] equivalents in the pre-implementation cohort to 29.5 [17-52.5] equivalents in the post-implementation cohort ($p<0.001$). Lengths of ICU and hospital stay were not different between the groups. A nurse-driven protocol for care of mechanically ventilated patients decreased the length of mechanical ventilation and was associated with improvement in sedation within target range through minimization of opioid and sedatives administered for sedation.

STUDENT LEARNING THROUGH ROLE-BASED PROCESSES IN TELEPHONIC MEDICATION THERAPY MANAGEMENT

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Background: Role-based processes is a business model used in a variety of settings to enhance work efficiency by assigning clearly defined tasks to employees based on education, training, ability, and certification. The Ohio State University Institute for Therapeutic Innovations and Outcomes Medication Management Program (ITIO-MMP) and the University of Arizona Medication Management Center (UAMMC) have trained student pharmacists using this model to perform telephonic medication therapy management (MTM) services. Beyond facilitating work efficiency, role-based processes also provide a unique training opportunity for student pharmacists. By addressing certain drug-related problems in a structured and monitored MTM environment, students establish effective communication skills and learn about key counseling points and guideline recommendations.

Objectives: This study will assess and compare self-reported confidence at completing MTM sessions, and MTM clinical knowledge of student pharmacists working in the ITIO-MMP, UAMMC, community pharmacies, and hospital pharmacies.

Methods: This cross-sectional, multi-center study will utilize an electronic survey to collect data from Doctor of Pharmacy students. The survey consists of three sections: demographics, MTM-confidence, and MTM clinical knowledge. In the demographics section, basic background information such as pharmacy school year and work setting will be obtained. In the second section, students will be asked to use a scale of 1 to 5 to report their confidence level in completing various MTM tasks such as making a recommendation to a prescriber. In the final section, students will answer questions assessing their knowledge of clinical practice guidelines, medications, and MTM regulations. The data will be analyzed statistically to compare self-reported confidence levels and clinical knowledge of students working in a role-based processes environment versus those who are not.

Results: Results are pending at the time of abstract submission.

Conclusions: This study will assess real-world evidence to determine if applying role-based processes in an MTM program facilitates student pharmacists learning, as well as increases their confidence when providing MTM services.

Sponsorship: This independent study is partially funded by The Ohio State University Medication Management Program.

RISK FACTORS FOR RECURRENT PNEUMONIA IN THE SURGICAL INTENSIVE CARE UNIT

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Poster Number: 73

Purpose: Pneumonia is one of the leading causes of infectious mortality in the intensive care unit (ICU) and is associated with high rates of recurrence and the potential for increased institutional liability with possible implications on hospital reimbursement.^{1,2} Recurrent pneumonia may result from several risk factors including inappropriate initial antibiotic therapy, multi-drug resistant organisms, and severity of illness.^{3,4} This study aims to determine the rate of pneumonia recurrence among patients in the surgical ICU and to identify risk factors associated with recurrent pneumonia. Identification of potentially modifiable risk factors of recurrence may help change practice and help prevent recurrent pneumonia.

Methods: A single-center, retrospective risk factor analysis will be used to compare patients who had a single episode of pneumonia to those who had an additional episode of recurrent pneumonia while in the surgical ICU. Adult patients admitted to the OSUWMC surgical ICU between January 1, 2014 and December 31, 2014 will be eligible for inclusion. All patients with pneumonia confirmed by respiratory culture who were treated with newly initiated empiric antibiotics within 24 hours of culture obtainment and received at least 7 days of antibiotic therapy for the pneumonia will be included. Exclusion criteria include pregnancy, incarceration, and age less than 18 or greater than 89 years. The primary endpoint will be the rate of pneumonia recurrence and to identify risk factors for recurrence in the surgical ICU population. Recurrence will be defined as a repeat respiratory culture with isolation of a respiratory pathogen. Secondary endpoints will include rate of relapse pneumonia, ICU and hospital length of stay, and all-cause hospital mortality. Relapse will be defined as a subsequent respiratory culture with isolation of the original pathogen. A multivariable logistic regression model will be performed for assessment of the primary outcome.

Results: Data analysis is on going. Results to be presented on poster.

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ASSESSING MENTAL HEALTH AND WELLNESS IN PHARMACY STUDENTS: RESULTS FROM A SURVEY THAT INITIATED CHANGE

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Poster Number: 74

A student initiated wellness survey was designed to assess pharmacy student mental health need and to ultimately advocate for increased access to counseling services for pharmacy students with the implementation of an in-house counselor or psychologist.

The survey was distributed to first through fourth year Doctor of Pharmacy students at The Ohio State University (OSU) College of Pharmacy in October of 2014. The survey was distributed through class email listserv. Students anonymously and voluntarily completed and submitted the survey. The survey asked students to recall the past four weeks prior to taking the survey and respond by selecting not at all, some of the time, a lot of the time, or most or all of the time with respect to a multitude of mental health and wellness measures. The survey probed for stress, anxiety, depression, sleep quality, disordered eating, suicidality, substance abuse, overall quality of life, and utilization of counseling services. Gender and year in pharmacy school was also collected. The end of the survey included a free response section for students to respond to the prompt: is there anything that has been particularly stressful for you that might be contributing to how you are feeling?

Out of 100 respondents, 17 were first year, 30 were second year, 38 were third year pharmacy students, and 15 responded as other. There were 21 males, 73 females, and 6 who declined to answer. A total of 54 respondents indicated that they have considered taking medications for or are currently taking medication for mental health reasons. Of this group of 54, 34 students indicated they would consider taking medication for anxiety in particular. Out of 99 respondents, 53% selected that their stress made it somewhat difficult to complete tasks in school, home, and get along with others. There were 46 students who selected a lot of the time with respect to feeling nervous or worrying a lot. There were eight students who indicated some of the time, one student indicated a lot of the time, and one student indicated most or all of the time with regard to having thoughts of self-harm. Eleven students indicated they had thoughts of taking their own life some of the time and one indicated having thoughts most or all of the time. Eight students attested to having planned ways to take their own life.

The anonymous results of the survey identified various stressors that affect the lives of pharmacy students and the impact stress has on their mental health and wellbeing. As a quality improvement standard, colleges of pharmacy should consider student mental health and wellness among their highest priority and strive to create a safe and supportive learning environment for pharmacy students.

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QUANTITATIVE DETAILS OF AMPHETAMINE MOBILIZATION OF NEWLY SYNTHESIZED DOPAMINE

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Poster Number: 75

Amphetamine is a drug used to treat ADHD and narcolepsy and has a relatively high abuse/addiction liability. An important initial action of amphetamine is to increase extracellular or signaling dopamine. Behavioral experiments done years ago strongly suggest that amphetamine mobilizes newly synthesized dopamine into extracellular space. The goal of this work is to use a quantitative model of a dopaminergic signaling unit to determine how many newly synthesized dopamine molecules are required for this effect. Components used in the computational model include dopamine secretion into extracellular space from a stored pool, dopamine secretion from a newly synthesized pool, dopamine removal from extracellular space by dopamine transporter (DAT), and amphetamine molecules in extracellular space. Values of kinetic parameters associated with DAT were determined from published data. The rate of dopamine secretion from each pool was varied to determine values for which simulation output matched published data for dose response for amphetamine-elicited increases in extracellular dopamine. This process was done for control, inhibition of dopamine synthesis (amphetamine after alpha-methyl-p-tyrosine), and depletion of dopamine storage conditions (amphetamine after reserpine). A set of conditions was found for which the simulation output matched published data for all three conditions. Parameter values included 2500 DAT with turnover rate of 5 dopamine molecules per second associated with each dopamine signaling unit, k_{on} for dopamine interaction with DAT of $1.5 \times 10^6 \text{ M}^{-1}\text{sec}^{-1}$, k_{on} for amphetamine interaction with DAT of $3.5 \times 10^6 \text{ M}^{-1}\text{sec}^{-1}$. The rate of stored dopamine release was 6 molecules at each signaling event for baseline (no amphetamine) and decreased with increasing dose of amphetamine. The rate of newly synthesized dopamine release was 0 for baseline, increased to a peak value of 14 at 2 mg/kg amphetamine, and decreased to 3 dopamine molecules associated with each signaling event at 10 mg/kg amphetamine. These values for rate of release of newly synthesized dopamine quantitatively match published data for effects of amphetamine on the rate of dopamine synthesis. This work documents that the rate of dopamine synthesis in the presence of amphetamine is sufficient to increase extracellular dopamine to the high values measured experimentally. Furthermore, the results are compatible with recent studies indicating that the probability of dopamine release associated with each firing event is low but incompatible with the hypothesis that amphetamine mobilizes stored dopamine via the DAT working in the reverse direction.

Na⁺/Ca²⁺ SIGNALOSOME: IDENTIFICATION OF STRUCTURAL UNDERPINNINGS OF CATECHOLAMINE-PROMOTED ATRIAL ARRHYTHMIAS

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Poster Number: 76

Cardiac disease is the leading cause of death in the US. Atrial arrhythmias are a prevalent manifestation of cardiac disease, contributing largely to the morbidity and mortality associated with this disease. Atrial arrhythmias are often generated by electrochemical aberrancies that result in diastolic calcium release (DCR) from the sarcoplasmic reticulum (SR). DCR is a hallmark feature of catecholamine-promoted arrhythmias. Despite the Ca²⁺-dependent nature of these pathologies, patients suffering from catecholamine-induced arrhythmias often respond to treatment with Na⁺ channel blockers. This would suggest a close interaction between Na⁺ and Ca²⁺; however, the specific structural underpinning resulting in Na⁺/Ca²⁺ dysregulation and how this contributes to repetitive DCR in atrial arrhythmias remains elusive. In order to investigate the structural underpinnings of catecholamine-mediated arrhythmias, immunofluorescence was performed in a mouse model with a genetic susceptibility to catecholamine-promoted aberrant Ca²⁺ release. These studies revealed a structural platform of sodium and calcium handling proteins in close proximity within atrial cardiomyocytes. Specifically, a subpopulation of neuronal Na⁺ channels (Nav1.1, 1.3 and 1.6) that co-localize with Ca²⁺ release channels on the SR, ryanodine receptors (RyR2), as well as with the sarcolemmal Na⁺/Ca²⁺ exchanger (NCX) was demonstrated for the first time. In order to gain further insight into this functional microdomain, proximity ligation assay was performed which allowed greater spatial assessment of co-localization. These experiments revealed that the aforementioned Na⁺ and Ca²⁺ handling proteins are in very close proximity (<40nm) and are widely distributed throughout the cardiomyocyte. Taken together, these findings suggest a potential relationship between the structural and physiological functioning of Na⁺ and Ca²⁺ handling proteins during normal heart contraction and pathologic arrhythmias. Therefore, the microdomain identified herein provides a platform for further studies that may help identify new treatments of atrial fibrillation, thereby alleviating the morbidity and mortality burden associated with cardiac disease.

COMPARISON OF HYPER-HYDRATION ALONE VS. HYPER-HYDRATION AND URINE ALKALIZATION IN MANAGEMENT OF HYPERURICEMIA OF TUMOR LYSIS SYNDROME IN PEDIATRIC CANCER PATIENTS

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Poster Number: 77

Tumor lysis syndrome (TLS), a complication observed in cancer patients, results in hyperuricemia due to tumor cell lysis. Uric acid (UA) can crystallize in the kidneys causing renal tubular damage and decreased renal function. Hyper-hydration and alkalization (pH 7 or greater) increases UA urine solubility and excretion.^{1,2} Urine is typically alkalized by intravenous (IV) administration of sodium bicarbonate (NaHCO₃). This requires frequent monitoring of urine pH and increases the risk of precipitation with inadvertent concurrent administration of incompatible medications. There is no data to support that urine alkalization and hyper-hydration prevent renal damage compared to hyper-hydration alone. This retrospective IRB approved study compared the effect of hyper-hydration alone to urine alkalization and hyper-hydration in preventing renal damage due hyperuricemia of TLS. A total of 244 patients less than 19 years of age with lymphoma or acute leukemia were identified from Nationwide Children's Hospital Hematology/Oncology/BMT Cancer Registry. Demographics, daily serum creatinine (SCr) values, need for continuous renal replacement therapy (CRRT) due to renal failure, and number of urine pH measurement. Change in SCr ratio [ratio of highest SCr value of the day to baseline value (day 0)] was used to measure change in renal function. Increase in this ratio over time indicates decrease in renal function. Of 244, 100 patients received NaHCO₃ and hyper-hydration (bicarbonate group) and 144 received hyper-hydration alone (no bicarbonate group). The mean SCr ratio was 0.03 units higher in the bicarbonate group compared to the no bicarbonate group (confidence interval: 0.005 – 0.056, p=0.02). The ratio decreased in both groups by 0.022 units per day (p<0.001). On day 1 the odds of SCr ratio being >1 was 20% less in the bicarbonate group when compared to the no bicarbonate group (p=0.319). However, by day 7 the odds were 17% higher in the bicarbonate group compared to the no bicarbonate group (p=0.48). No patient required CRRT. A mean of 25 urine pH measurements were conducted in the bicarbonate group compared to 3 in the no bicarbonate group. Lack of sufficient subjects in each group precluded non-inferiority test. This data suggests that patients receiving hyper-hydration alone are not at an increased risk of renal damage due to lack of urine alkalization.

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