2019 Pharmacy Research Summer Interns (PRSI) Faculty Sponsored Projects

Faculty Mentor: Dr. Serge Afeli, PhD

Research Type: Foundational Sciences

Project Description: Bladder cancer accounts for nearly 75,000 new cases and 15,000 deaths yearly with a total cost of $4 billion in the U.S. alone. The combination therapy cisplatin-gemcitabine is currently the hallmark for bladder cancer treatment. In unresectable bladder cancer patients, the cisplatin-gemcitabine response rate is only 49% with about 38% of patients surviving up to 18 months. Failure of this combination therapy is still not fully elucidated. There is evidence that suggests the role of drug efflux transporters in this process. We hypothesize that ABCC5 transporters are key players in bladder cancer cells resistance to chemotherapy. We previously demonstrated RNA and protein expression of ABCC5 in bladder cancer cells and proceeded by suppressing ABCC5 transporter gene using CRISP-KAS9 approach. Our next objective will be to validate ABCC5 gene suppression in bladder cancer cells and further evaluate their sensitivity to an array of anticancer agents including cisplatin and gemcitabine. This experimental series will provide a better understanding of the role of ABCC5 transporters in bladder cancer cells resistance to chemotherapy. Student will help perform cell culture, RNA analysis, western blot, and MTT proliferation assay.

Timeline of the project:

Timeline	Project
Week 1 & 2	Training on cell culture procedure including maintain the colony and cell count
Week 3& 4	Training on Western Blot procedure and continuing cell culture, Student will learn protein extraction from culture cells as well as all the different step involved in WB
Week 5 & 7	Drug treatment of culture cells followed by MTT assay experiments and Western blot. WB will be performed to evaluate the change in protein expression level after drug treatment.
Week 8	Wrap up and poster/podium preparation.

Faculty Mentor: Dr. Christopher Farrell, PhD

Research Type: Foundational Sciences

Project Description: Multi-drug resistance (MDR) is a serious complication in the treatment of cancer patients. MDR can become an obstacle to chemotherapy treatment in tumors of any stage but is more common in late stage and/or aggressive tumors. Patients whose tumor cells develop MDR have a poor prognosis compared to patients whose cells are responsive to chemotherapy. Because the chemotherapy agents are ineffective in killing the all of the tumor cells including cells which have become metastatic, the overall survival rate for patients with MDR-positive tumors is markedly decreased.

A patient's tumor can develop MDR before or after the initiation of chemotherapy treatment. The cause of MDR after the initiation of chemotherapy is well understood, but it is not known how tumors develop MDR before chemotherapy treatment. The most common mechanism of MDR in cells is the activation on transporter proteins. Increased expression of the transporter proteins is associated with MDR in cells that have been subjected to chemotherapeutic drugs. However, researchers have not been able identify how this mechanism is induced in the chemotherapy-naïve cancer cells. We are exploring the connection between chemotherapy resistance tumors in chemotherapy-naïve cancer patients who are taking non-chemotherapy agents. To identify this connection, we have been treating cancer cells with cardiovascular medications for several months. With the help of students, a continual treatment of the non-chemotherapy agents on cancer cells has resulted in the increase of expression and activity of the MDR transporter proteins which lead to resistance of chemotherapy drugs, such as paclitaxel and 5-fluorouracil, and caused the drugs to become ineffective in killing the cancer cells.

Timeline of the project: The student will be testing the cancer cells for the MDR markers. The cells will be treated this spring semester and analyzed with the next-generation sequencing. For the first four weeks, the student will be treating the cells with the non-chemotherapy agent and the second four weeks, the student will review the expression for MDR and other gene markers through the next-generation sequencing data.

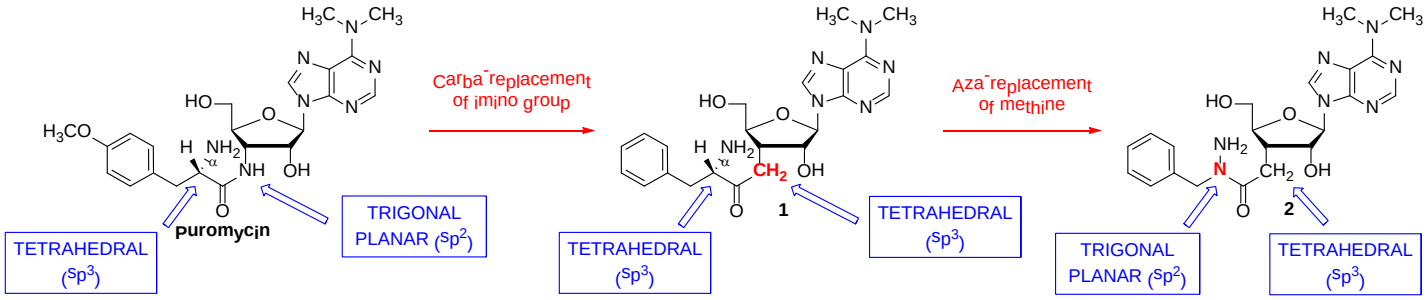
Faculty Mentor: Dr. Giuseppe Gumina, PhD

Research Type: Foundational Sciences

Project Description: Puromycin Analogs as Potential Novel Antimicrobial Agents. A number of natural peptidyl nucleosides related to puromycin (Figure 1) are endowed with potent antimicrobial and antitumor properties. Despite its promise for therapeutic potential, puromycin is not useful because of the nephrotoxicity of one of its metabolites. In search of a puromycin-like molecule that could not be metabolized to a simple nucleoside, we designed compounds **1**, which is incapable to undergo metabolism to the nephrotoxic metabolite of puromycin. In antimicrobial assays, **1** showed similar antibiotic profile as puromycin on MRSA and *S. epidermidis* cell lines, proving that replacement of the imino-portion of the amide group with a methylene bridge did not affect activity. However, the replacement of the amide functionality of puromycin with the ketone functionality in **1** generated a molecule with limited chemical stability (Gumina *et al.*, 2016). In order to address the stability issue, we synthesized compound **2**, which was stable, but failed to inhibit the growth of *S. epidermidis* and MRSA (Carter *et al.*, 2017).

Structure-activity relationship considerations of our molecules have defined some important chemical features that are required for antimicrobial activity. Based on these features, we designed a new analog. Our current project is the synthesis and microbiological evaluation of our new target.

Figure 1. Non-nephrotoxic puromycin analogs.



Faculty Mentor: **Dr. Wei Lei, PhD**

Research Type: Foundational Sciences

Project Description: Opioids are the most efficacious and widely used drugs for the treatment of moderate to severe pain, such as cancer-induced pain. However, the side effects of opioids, such as respiratory depression, tolerance, dependence and addiction, and constipation, limit their use in the clinic. Heat shock protein 90 (Hsp90) is a ubiquitous and highly expressed regulator for various signaling pathways. Hsp90 has been well studied as a potential cancer therapeutic target, and Hsp90 inhibitors such as 17-AAG have been designed as anti-cancer therapeutics in preclinical studies, and are currently in the process of clinical trials. We also have shown that Hsp90 can strongly impact opioid signaling and anti-nociception.

This project is designed to investigate the modulatory activities of Hsp90 on opioid-induced inflammatory responses. By using in vitro models, I will investigate the impact of Hsp90 inhibitors (i.e. 17-AAG and KU-32) on opioid-induced generation of nitric oxide (NO), prostaglandin E2 (PGE2), and inflammatory cytokines. The activation of cyclooxygenase-2 (enzyme for producing PGE2) and inducible nitric oxide synthase (enzyme for producing NO) will be also investigated after the treatment using Western blot. For determination of mechanism, we will design experiments to investigate which receptors opioids target for inducing the inflammation, and the activation of inflammation-related signaling pathways, including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs).

Student will culture the cells, measure the concentrations of NO, PGE2, and inflammatory cytokines in cell cultural media, collect the cell lysates, and run Western blot.

Timeline of the project: We will begin with cell culture at the beginning of June and start the treatment in the week of June, 10th. We anticipate completing the measurement of NO, PGE2, and inflammatory cytokines by the end of June. The mechanism experiments will start at the beginning of July. Throughout the project period, we will be analyzing data and preparing for the Research Symposium.

Faculty Mentor: Dr. Amy Messersmith, PhD

Research Type: Foundational Sciences

Project (1) Description: Multidrug resistance (MDR) in cancer cells can decrease the effectiveness of chemotherapy in the treatment of a patient's cancer resulting in a poorer prognosis for the patient. The factors responsible for MDR in chemotherapy-naïve cancer cells are incompletely understood. This project involves the development of an in vitro model of MDR in human cancer cells in an attempt to elucidate some of the factors that contribute to MDR in chemotherapy-naïve cells. The project will involve tissue culture and genetic analysis techniques.

Timeline of the project: Over the course of the program, the student will be responsible for culturing and treating the cells. The student will collect RNA at points throughout the course of the drug treatment to identify drug resistance in the cells. At the end of the term of the program, the student will have longitudinal quantitative PCR data that can be used to substantiate the *in vitro* model.

Faculty Mentor: Dr. Amy Messersmith, PhD

Research Type: Foundational Sciences

Project (2) Description: Vaccination rates for Human Papillomavirus (HPV) in South Carolina lag behind most states in the United States. This is particularly true in many of the rural counties in South Carolina which also bare a larger percentage of the cancer mortality for HPV-associated cancers. Many barriers to HPV vaccination have been identified in South Carolina. Among these barriers, access to the vaccine has emerged as one of the top reasons that adolescents are not receiving the HPV vaccine. This project will involve investigating the factors that affect access to the HPV vaccine in South Carolina. The goal of this project is to provide data that can be used to influence change in the state to improve the vaccination rate for HPV.

Timeline of the project: Over the course of the program, the student will be responsible for collecting information from insurance companies and pharmacies throughout the state. The student will spend the first part of the project identifying the sources from which data will need to be collected. After these sources have been determined, the next phase of the project will include contacting those entities to collect data. Once all of the data has been collected, it will be compiled into a reference resource that can be used in the state to inform pharmacists and agencies in the state about the landscape of vaccine availability in the state.

Faculty Mentor: Dr. Kayce Shealy, PharmD, BCPS, BCACP, CDE & Dr. Eileen Ward, PharmD, BCACP, TTS

Research Type: Clinical Sciences

Project Description: Students will work with faculty to complete a retrospective cross-sectional study on health outcomes within an employee wellness program. Students will conduct a literature review on related health outcomes in various populations to compare to the results of this study.

Timeline of the project: The results of this study will be submitted for presentation at a local, state, and/or national meeting as well as submitted for publication in a relevant peer-reviewed journal.

Faculty Mentor: Dr. Erika Tillery, PharmD, BCPP, BCGP

Research Type: Teaching & Learning

Project Description: "Suicide prevention in pharmacy: raising awareness and reducing stigma" Suicide is a significant public health problem and is the tenth leading cause of death in the United States. Pharmacists are uniquely accessible health care professionals who routinely interact with at-risk individuals and have the potential to assist with suicide prevention. Previous studies have shown that suicide prevention education is needed for pharmacy students and pharmacists. This study aims to identify the type and presence of stigmas associated with suicide in pharmacy students and may provide areas of improvement by identifying opportunities to overcome these stigmas and enhance education. The educational materials that are developed as a result of the project may be used in pharmacist continuing education programs and/or other healthcare professional programs to ensure adequate suicide prevention training.

Timeline of the project: This is a longitudinal project that began in spring 2019 and may not conclude until fall 2020. During the 8-week PRSI program, student(s) may be analyzing survey data and creating educational interventions about suicide prevention and stigma that is tailored toward pharmacy students. A poster presentation at the Summer Research Symposium on PC main campus is expected with the potential for future presentations at state and/or national professional meetings.