Brief descriptions of each 2017 SURF research project

FACULTY MENTOR:
Salah-uddin Ahmed, Ph.D., Associate Professor, *ASPET member*
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RESEARCH PROJECT:
Identifying novel therapeutic targets in the pathogenesis of rheumatic diseases

DESCRIPTION OF PROJECT:
The Ahmed lab is involved in translational studies aimed at identifying the unknown mechanisms that govern pathogenesis of rheumatic diseases such as rheumatoid arthritis, osteoarthritis, and gout. In particular, our group has been investigating the posttranslational and epigenetic mechanisms that facilitate rheumatic disease propagation. Using synovial cells, tissues, and serum samples from rheumatoid arthritis patient population, we conduct genomics and metabolomics studies to identify some key mediators that promote chronic inflammation and tissue destruction in rheumatoid arthritis. Based on this information, our group in collaboration at international level with computational biologists and medicinal chemists has been designing novel compounds to be tested for their efficacy in vitro and in pre-clinical models of rheumatoid arthritis and other autoimmune diseases.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
The SURF student is assigned a role and/or participation in some ongoing or new projects where they not only get the chance to learn about the inflammatory signal transduction pathways that promote rheumatic diseases, but also get a chance to sharpen their technical skills on running independently procedures such as ELISA, Western blotting, and In-gel zymography. After the training, the SURF fellow will be capable of summarizing his/her progress in the form of poster presentation. The work will be further expanded and presented at one of the national scientific meetings in which SURF students typically serve as co-authors. These studies have also resulted in the publication of manuscripts in the past.

FACULTY MENTOR:
Zhaokang Cheng, Ph.D., Assistant Professor
Email: zhaokang.cheng@wsu.edu

RESEARCH PROJECT:
Novel role of cell cycle regulators in the heart

DESCRIPTION OF PROJECT:
The widely-used anthracycline family anti-cancer drug doxorubicin can cause serious cardiotoxic side effects by inducing apoptotic death of cardiac myocytes. Dr. Cheng has previously identified the cyclin-dependent kinase inhibitor p21 as a critical protective molecule against cardiomyocyte apoptosis. Most recent findings from Dr. Cheng's laboratory revealed that p21

inhibited apoptosis by repressing cyclin-dependent kinase 2 (CDK2). These results support a novel function of the cell cycle regulators p21/CDK2 in promoting cell survival and conferring chemoresistance in the heart. The proposed project will determine the role of CDK2 downstream signaling pathway in doxorubicin-induced apoptosis, and further explore the therapeutic potential of CDK inhibition against doxorubicin-induced cardiotoxicity.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
Upon joining the lab in early summer, the SURF fellow will work with his/her direct mentor in Dr. Cheng's group on the proposed project. The SURF fellow will receive expert training in a plethora of research skills including cell culture, Western blotting and immunofluorescence staining. Both the direct mentor and Dr. Cheng will be available to help the SURF fellow with research-related questions, difficulties, and future directions.

FACULTY MENTOR:
John D. Clarke, Ph.D., Assistant Professor
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RESEARCH PROJECT:
Multifactorial approach to precision medicine

DESCRIPTION OF PROJECT:
Toxicities from xenobiotic exposures are a significant burden on human health. These exposures occur both intentionally (drugs and dietary supplements) and unintentionally (environmental contamination and naturally occurring toxins), and there are several factors in individual variability that determine who is at greater risk for these toxicities. This project is focused on precision medicine and investigates how perturbations in two or more factors in drug absorption, distribution, metabolism, and excretion affect drug exposures and toxicities. These factors include genetics, diseases, and co-exposures, which are investigated using cell culture and rodent models. Particular attention is given to drugs that are dependent on drug transporters and/or metabolism enzymes for elimination.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
After initial training, the fellow will be expected to work in an independent manner on all standard laboratory techniques (cell culture, Western blotting, etc.). The fellow will have the opportunity to work with lab staff on non-routine procedures (animal experiments, small molecule analysis, etc.) with the expectation that the fellow will be able to work in a semi-independent manner towards the goals of the project. The fellow will participate in the weekly lab meetings and meet with Dr. Clarke individually as needed, but no less than once every two weeks.

FACULTY MENTOR:
Travis Denton, Ph.D., Assistant Professor
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DESCRIPTION OF PROJECT:
Projects in the lab focus on small molecule, organic synthesis-based, medicinal chemistry. We also focus on the analytical determination of small molecules in biological matrices (analytical biochemistry). Projects currently ongoing in the lab are multiple, and all focus on trying to make life easier for people who are tormented by devastating neurological diseases.

Project 1: Treatments for ALS, Alzheimer's disease, and other neurological disorders. In this project, we are developing small molecules to enhance cellular autophagy in an effort to fight neurodegenerative diseases. Project 2: Treatments for myc-induced T-cell leukemia (cancer). In this project, we are developing phosphonic acid bioisosteres of fundamental α-ketoacids to inhibit newly identified pathways important for the progression of a number of cancers. Project 3: Treatment of Alzheimer's disease by targeting the α7 nicotinic acetylcholine receptor (nAChR). In this project, we are synthesizing small molecules to target the α7-nAChR, the only nicotinic receptor in the brain of Alzheimer's patients that is not down regulated. Through this approach, we hope to enhance the cognitive function of people with this disease. Project 4: Development of a synthetic strategy and the preparation of biomarkers for human inborn errors of metabolism.

Degree of independence expected of summer fellow:
For Projects 1-3, the SURF student will synthesize, purify, and characterize new molecules that will be tested for biological activity by our collaborators. For Project 4, the undergraduate researcher will prepare the compounds using organic chemistry techniques as well as aiding in the development of extraction and ultra-performance liquid chromatography tandem mass spectrometry techniques for the quantification of these biomarkers. The SURF fellow will receive training from members of the laboratory so that they can perform procedures independently by the end of the summer. Results will be discussed with the mentor and presented in a poster at the end of the training period.

FACULTY MENTOR:
Shobhan Gaddameedhi, Ph.D., Assistant Professor, *ASPET member*
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RESEARCH PROJECT:
Role of the Circadian Clock in Cancer Prevention and Anti-Cancer Therapeutics

DESCRIPTION OF PROJECT:
Every cell in the body has a circadian clock that regulates the cellular processes including the physiology and behavior of an organism. Recent findings suggest that the expression of as many as 43% of protein-coding genes are regulated by the circadian clock at the transcriptional level. Using genetic murine models, our recent findings suggest that the radiation mediated DNA damage signaling including the DNA repair, checkpoint response, apoptosis, sunburn and the carcinogenesis are directly regulated by the circadian clock *(Gaddameedhi et al., PNAS 2011, Cell Cycle 2012, Biochemistry 2014, and J Invest Dermatol. 2015*). Using chronopharmacological strategies, this laboratory is interested in identifying candidate genes or

pathways and defining the functional status of circadian clock proteins-both in normal and tumor tissue-that determine the timing of cellular sensitivity to radiation treatment and anti-cancer therapeutic drugs.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
A summer student will work with Gaddameedhi lab staff to address how the circadian clock plays a role in one of the novel cellular repair processes that is responsible for minimizing drug toxicity in normal tissues and increased therapeutic efficacy by an anti-cancer therapeutic drug. At the end of this training, the student will be able to learn basic cellular and molecular pharmacology techniques including cell culture, PCR, molecular cloning, western blotting, and drug treatment strategies for cellular survival. In addition, the student will be able to interact with our research team on a daily basis and able to participate in weekly lab meetings.

FACULTY MENTOR:
K. Michael Gibson, Ph.D., Professor
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RESEARCH PROJECT:
Pathophysiology of Mendelian disorders of metabolism

DESCRIPTION OF PROJECT:
The focus of this laboratory is understanding the pathophysiology of Mendelian disorders of metabolism, and developing novel pre-clinical treatment approaches with translational relevance. Dr. Gibson's laboratory employs pharmacological, cellular and dietary treatment approaches in disorders such as succinic semialdehyde dehydrogenase deficiency, phenylketonuria, maple syrup urine disease, galactosemia and transaldolase deficiency, a defect of the pentose phosphate pathway. His training is in protein chemistry, molecular and neurobiology, neuropharmacology and genetics, and various analytical methodologies. His laboratory is actively interested in hepatic biology and novel approaches to liver regeneration.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
The student is expected to be self-motivated, and to have some background coursework in molecular/cell biology and biochemistry. To begin, the student will work closely with laboratory members to learn basic laboratory procedures, including molecular and cellular techniques. After the training, the student will work semi-independently with frequent consultation with the mentor and other laboratory members.

FACULTY MENTOR:
Philip Lazarus, Ph.D., Professor and Chair of Pharmaceutical Sciences, *ASPET member*
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RESEARCH PROJECT:
Effects of menthol on the metabolism of tobacco carcinogens

DESCRIPTION OF PROJECT:
Tobacco is the leading cause of preventable premature death worldwide. In particular, African Americans (AAs) exhibit lower smoking prevalence rates and initiate smoking at older ages than European Americans (EAs), and exhibit smoking intensities that are comparable to EAs, yet AAs exhibit higher rates of lung and other tobacco-related cancers. In addition, tobacco-associated morbidity and mortality rates are disproportionately higher in AAs. While disease prediction models have not explained disease causal pathways in AAs, it has been hypothesized that menthol cigarette smoking, which is disproportionately high among African Americans, may be a factor in this pathway. The Tobacco Products Scientific Advisory Committee (TPSAC), in a report submitted to the FDA in 2011, recommended a ban on menthol in cigarettes. This ban was based on the public health risk of menthol being marketed towards young smokers and people of color, primarily African Americans (AAs). The conclusion was that menthol poses a major public health risk because it increases the number of people who start smoking in the US and decreases the number of people who quit smoking. However, a direct role for menthol in tobacco-related cancer risk has not been established. While the 2011 TPSAC report indicated that epidemiological and biochemical studies focusing on the role of menthol in cancer risk was lacking, the role of menthol in cancer risk in subsequent epidemiologic studies were inconclusive.

A long-term goal of our laboratory is to understand the mechanism of interaction between tobacco flavoring agents and tobacco carcinogens as well as to assess the health risks that may be associated with these interactions. A potential project for a SURF student in our laboratory would be to determine menthol's inhibition mechanism within the NNAL glucuronidation pathway. This project would involve examining the inhibition by menthol of individual glucuronidating enzymes, previously cloned and over-expressed in cell lines in our laboratory, that are known to detoxify NNAL. IC50's will be compared for the L- and D-menthol isomers to identify any stereospecific differences in inhibition of NNAL by different menthol enantiomers. A liquid chromatography-mass spectrometry method has been previously developed to identify the NNAL-glucuronide product. This study will provide much needed insight into the mechanism of NNAL inhibition by menthol and would provide insight regarding the role of menthol in tobacco carcinogenesis.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
Students will be trained in the enzyme activity assays and analytical techniques needed to accomplish the experiments described above. The student will work directly with a postdoctoral trainee and have weekly meetings with the mentor, as well as attending weekly laboratory meetings. Once trained, the student will be able to work fairly independently, and will report on progress at the weekly laboratory meetings.

FACULTY MENTOR:
David X. Liu, Ph.D., Associate Professor, Pharmaceutical Sciences
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RESEARCH PROJECT:

Delineation of the signal transduction pathways that implicate ATF5 as a cancer cell-specific survival factor

DESCRIPTION OF PROJECT:
The focus of this laboratory is to understand the signaling mechanisms that control proliferation and survival of cancer cells. One goal is to understand how ATF5, a bZIP protein of the ATF/CREB family of transcription factors, promotes survival of cancer cells but is dispensable in normal cells. Studies have revealed that survival of cancer cells (including breast, colon, brain, pancreatic, and lung cancers among others), but not non-cancer cells, requires ATF5 function. It was recently shown that the abundance of ATF5 in cancer cells is critically regulated by both caspase-dependent and proteosome-dependent protein degradation processes. It may be possible to exploit this "vulnerability" of cancer cells for their selective elimination.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
The student will be trained in basic molecular and cellular techniques, and then work semi-independently on a research project chosen mutually between the mentor and student. The student will have the opportunity to interact with other laboratory members for support, and will have frequent interactions with the mentor to discuss research progress.

FACULTY MENTOR:
Susan Marsh, Ph.D., Associate Professor, Experimental and Systems Pharmacology
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RESEARCH PROJECT:
Mechanisms of exercise-induced cardioprotection

DESCRIPTION OF PROJECT:
This laboratory is focused on understanding how the heart responds to exercise, diabetes and diet. Dr. Marsh's group has examined the role of post-translational modification of proteins in exercise-induced cardioprotection, as well as investigating the cardiac response of the O-GlcNAc pathway to high fat diets and diabetes. The aim is to understand how post-translational modifications of proteins and their regulatory pathways alter gene regulation of proteins that modulate or contribute to the ability of the heart to remodel or grow in response to various interventions.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
The student and mentor will develop the research project and expectations at the start of the summer. Students will then be trained in basic experimental techniques such as Western blotting, fluorescent microscopy and PCR, and will be exposed to procedures in animals such as exercise and isolated heart perfusion. Once trained, the student will work with other lab members semi-independently with frequent interaction with the mentor.

FACULTY MENTOR:
Senthil Natesan, Ph.D., Assistant Professor
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RESEARCH PROJECT:
Structure-based prediction of lipid bilayer partitioning and CYP metabolism for drug candidates

DESCRIPTION OF PROJECT:
The interaction of drugs with cell membranes dictates their pharmacological properties because it affects the drug distribution, transport, accumulation, partitioning, and metabolism. A drug must be passively or actively transported across the cell membrane before it can reach its target and perform its biological role. Passive transport depends on membrane structure, dynamics, and its permeability for a particular drug molecule. Recently, it has been suggested that the positioning of drugs on lipid bilayer might also affect their interaction with drug metabolizing cytochrome P450 (CYP) enzymes, which are anchored to the membrane of the endoplasmic reticulum, and as a consequence affect the metabolism of drugs. This project aims to investigate the relationship between partitioning, accumulation, and orientation in dioleoylphosphatidylcholine (DOPC) bilayer and CYP3A4 metabolism for a set of approved drugs with well-known pharmacokinetics using molecular dynamics (MD) simulation and other structure-based *in-silico* techniques. The expected results will enable us to develop predictive models for bilayer transport and CYP3A4 metabolism and to screen potential new drug candidates.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
The SURF fellow will learn basic to intermediate level computational techniques including building 3D structures of small molecules, geometry optimization, QM charge calculations, preparation of protein structures, performing MD simulations using GROMACS, calculating potential mean force (PMF), determining partition coefficients and preferred accumulation and orientations within the bilayer etc. As these techniques require extensive initial training, the fellow will work very closely with Dr. Natesan in the beginning and will become semi-independent towards the completion of the project. The student will have plenty of opportunity to interact with the mentor and his group members to discuss the progress and future directions.

FACULTY MENTOR:
Mary Paine, Ph.D., Associate Professor, *ASPET member*
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RESEARCH PROJECT:
Interactions between conventional medications and herbal products

DESCRIPTION OF PROJECT:
This laboratory is applying a translational research approach, guided by pharmacokinetic and pharmacodynamic modeling and simulation, to address real-world challenges. Specifically, they are developing novel methodologies to evaluate drug-dietary substance and herbal-supplement

interactions prospectively. The lab is also advancing the development of promising orally-active antiparasitic agents for treatment of African sleeping sickness.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
The SURF fellow will initially learn relevant laboratory skills under the direction of a graduate student or postdoctoral fellow. The fellow will meet regularly with the mentor and will also participate in laboratory meetings. By the end of the summer, the fellow will be able to perform experiments semi-indepepndently.

FACULTY MENTOR: Grant D. Trobridge, Ph.D., Associate Professor
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RESEARCH PROJECT:
Retroviral vectors for gene therapy and cancer research

DESCRIPTION OF PROJECT:
Research in the lab is focused on developing retroviral vectors for gene therapy and using vectors as tools for cancer research. The student will have the opportunity to choose a project developing safer retroviral vectors, performing bioinformatics to assess the unwanted side-effect of vector genotoxicity, or using vectors to identify cancer genes by mutagenesis and high-throughput sequencing.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
The student is expected to be self-motivated, and to have some background coursework in molecular/cell biology, microbiology, or bioinformatics. The student will be trained in specific molecular biology or bioinformatic techniques, and will have the opportunity to work fairly independently. Frequent discussions between the student and Dr. Trobridge will provide a framework for the research direction, and will be used to assess progress.

FACULTY MENTOR:
Boyang (Jason) Wu, Ph.D., Assistant Professor
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RESEARCH PROJECT:
Role of Monoamine Oxidase A in Neuroendocrine Prostate Cancer

DESCRIPTION OF PROJECT:
This laboratory currently centers on prostate cancer research, with particular interests in exploring the mechanism underlying the development of lethal forms of prostate cancer and developing new therapeutic strategies. Dr. Wu's group has recently identified aberrantly high expression of monoamine oxidase A (MAOA), a mitochondrial enzyme responsible for degrading monoamines, such as serotonin, in neuroendocrine prostate cancer, a high-risk, lethal subset of disease, which remains a major challenge in clinical management. Using a panel of neuroendocrine, neuroendocrine-mimicking human prostate cancer cell lines, and derived

xenograft mouse models, the role of MAOA in the initiation and progression of neuroendocrine prostate cancer will be studied, with special mechanistic emphasis on converged kinase signaling and serotonin-centric pathway mediated by both MAOA and neuroendocrine effectors. The effects of MAOA inhibitors as mono- or combination therapy with existing drugs on growth inhibition of neuroendocrine prostate cancer cells and xenograft tumors will also be assessed.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
At the beginning of the summer, the fellow will work closely with Dr. Wu's postdoc to learn basic cell and molecular biology techniques necessary to execute the project in the in vitro setting, including cell culture, DNA and RNA purification, Western blot, RT-qPCR, ELISA, MTS assays, etc. Meanwhile, the fellow will be exposed to reading scientific papers assigned by mentor, which are not only related to the project but also in a broad way to allow the fellow to learn the frontier research in prostate cancer filed specifically and cancer field in general. After obtaining required training for animal studies, the fellow is also expected to participate in observing animal experiments and assisting other lab staffs with animal experimental procedures, such as measurement of tumor growth and scoring body condition of mice. After the training, the fellow will work semi-independently on his/her project. The fellow will report research progress at every weekly lab meeting and give a research summary presentation to the lab at the end of summer.

FACULTY MENTOR:
Hui Zhang, PhD, Assistant Professor
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RESEARCH PROJECT:
Suppression of anti-tumor immunity by chronic alcohol intake

DESCRIPTION OF PROJECT:
This laboratory is focused on how chronic alcohol consumption compromises anti-tumor immunity and on selecting appropriate targets counter the negative effects. They have shown that chronic alcohol consumption compromises CD8+ T cell function. CD8+ T cells are the key players in anti-tumor immunity and in controlling the survival of the tumor-bearing host. The function of CD8+ T cells are regulated by several immune regulatory cells including myeloid-derived suppressor cells (MDSC), tumor associated macrophage (TAM), regulatory T cells (Treg), NKT cells, and B cells. They also showed that chronic alcohol consumption increases MDSC and NKT cells, decreases B cells, and shifts the NKT cell cytokine profile from Th1 (anti-tumor) to Th2 (tumor-evasive). Chronic alcohol consumption does not alter TAM or Treg in the tumor-bearing mice. Two potential projects are examining the signaling pathways that are modulated by chronic alcohol consumption and tumor cells to 1) regulate B cell circulation and 2) alter the cytokine profile of NKT cells.

DEGREE OF INDEPENDENCE EXPECTED OF SUMMER FELLOW:
At the beginning the summer, the fellow will work closely with Dr. Zhang to learn some basic and specific procedures such as animal handling and molecular and cellular techniques. After the

training, the fellow will work semi-independently on his/her project. There will be a lab meeting weekly to discuss progress and future directions.