WSU College of Pharmacy
Potential 499 Independent Study and 599 Special Projects
Spokane Fall 2017

Spokane Pharmacy students can enroll in these elective courses, either as Pharmacy 499 Independent Study or Pharmacy 599 Special Projects, as indicated below.

Faculty Mentor	Project
Travis Denton, PhD travis.denton@wsu.edu	**Location: Spokane only** **Please contact Dr. Denton to set-up an appointment for discussing the projects listed** The focus of research in Dr. Denton's lab is on synthetic medicinal chemistry to study neurodegenerative diseases and cancer. Dr. Denton has supplied a handout with four potential projects (see descriptions below).
Brian J. Gates, PharmD, CGP brian.gates@wsu.edu Jeffrey Clark, PharmD, BCGP jeffrey_clark@wsu.edu	**Location: Spokane or Yakima** **499 or 599** A 499 independent study of geriatrics related articles and cases. A 599 project of interest to the student and related to geriatrics. Both the 499 and 599 could be done in either Spokane or Yakima.
David Liu, PhD d.liu@wsu.edu	**Location: Spokane only** **Please contact Dr. Liu to set-up an appointment for discussing the projects listed** Dr. Liu's laboratory studies the molecular and cellular mechanisms that control cell proliferation, survival, genomic stability, and the organization of intracellular/subcellular structures (see descriptions below).

***Please contact the faculty mentor listed for more specific information about the project.**

Denton Lab Research Opportunities

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 the 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. Autophagy is a cellular process in which cells recycle cellular components in an effort to replenish energy levels. In many neurological diseases the autophagy pathway is interrupted and we have identified a pathway that can be manipulated with small molecules to afford neurotrophic, neuroprotective and antineuroinflammatory activities. The input from undergraduate researchers to this project would be the synthesis and characterization of new small molecules that will be sent to our collaborative team at the University of Toronto, School of Medicine for assessment of autophagy enhancement.

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. Our team (collaboration with Hui Feng, Boston University

School of Medicine) has identified a novel target for the treatment of myc-induced T-cell leukemia and we have been developing new phosphonic acids that are proving to be well equipped to inhibit the leukemia while not influencing fish development, in a zebrafish model system. Undergraduate researchers input to this project would be the synthesis, purification and characterization of new phosphonic acids that will be send to Boston for testing in the zebrafish as well as human cell culture models.

Project 3) Treatments of Alzheimer's disease by targeting the α7 nicotinic acetylcholine receptor (nAChR). In this project, we are synthesizing small molecules, in collaboration with Dr. Todd Talley at Idaho State University College of Pharmacy to target the α7-nAChR, the only nicotinic receptor in the brain of Alzheimer's patients that is not down regulated. Meaning, if we can develop a molecule to stimulate this receptor, that is still available for stimulation in the brain, we hope to enhance the cognitive function of people with this disease. The undergraduate researcher in the lab would be synthesizing small molecules to be sent to the Talley lab for screening and potential X-ray crystallography using the acetylcholine binding proteins (ACHBO0Ps), soluble surrogates of the nAChRs in an effort to identify new leads compounds for future modification and testing at functional nAChRs.

Project 4) Development of a synthetic strategy and the preparation of biomarkers for human inborn errors of metabolism. In this project, we are developing both the synthesis, purification and characterization of biomarkers and isotopically labels biomarkers as well as developing the bioanalytical determination of these compounds in multiple biological sources including blood, brain and urine. The undergraduate researcher in the lab would be preparing 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.

There are other projects ongoing in the lab but the above listed projects should give you a taste of what we are actively doing in the Denton lab on the 3rd floor of HSB!

Liu Lab Research Opportunities

Our laboratory studies the molecular and cellular mechanisms that control cell proliferation, survival, genomic stability, and the organization of intracellular/subcellular structures. Our research has provided major insights into the mechanism that underlies the pathology of several human developmental diseases. Additional information can be accessed at http://www.pharmacy.wsu.edu/facultystaff/bios/liu.d.html. Our 3 research projects described below are available for PharmD students in Spokane. Interested students should contact the PI directly.

<u>Project 1: Production and regulation of white blood cells and inflammatory cytokines in ATF5 knock out mice</u>.
White blood cells (a.k.a. leukocytes) are part of the body's immune system. They are found throughout the body, including the blood and lymphatic system. Several different types of leukocytes exist, including lymphocytes, granulocytes, monocytes, phagocytes and macrophages, but they are all produced in the bone marrow and each has a particular function. They are normally maintained within preset normal ranges, but respond rapidly to immune challenges. Cytokines are produced by various types of cells including leukocytes and are part of the immune system. They exert their influence over various leukocytes. Abnormal production or function of any types of the leukocytes or cytokines can

have serious consequences such as chronic infection and high propensity of having cancer or autoimmune diseases and diabetes.
ATF5 is a transcription factor and a cell stress regulator. It was reported that ATF5 regulates the production of G-CSF (a kind of cytokine), which is a key regulator for neutrophil (a type of leukocyte). ATF5 is known to play a big role in the survival of the beta cells in the pancreas and of various cancer cells. We will use ATF5 knockout mice to investigate how ATF5 affects the production and regulation of the white blood cells and the inflammatory cytokines in animal model.

Project 2: Role of ATF5 in liver fibrosis/cirrhosis – A mouse model.
Nonalcoholic fatty liver disease (NAFLD) is a burgeoning health problem worldwide affecting between 25-30% of the general population. NAFLD refers to a spectrum ranging from non-inflammatory isolated steatosis to non-alcoholic steatohepatitis (NASH), which is characterized by steatosis, necroinflammatory changes and varying degrees of liver fibrosis. Patients with NAFLD exhibit an increased risk of death linked to type 2 diabetes mellitus (T2DM) and cardiovascular risk factors and those with NASH have also an increased liver-related mortality due to the progression to cirrhosis and hepatocellular carcinoma (HCC). Liver NAFLD/NASH development follows a defined course of liver injury response - starting with liver steatosis and mild fibrosis (liver scar) that are reversible, followed with steatohepatitis and cirrhosis, which may lead to HCC. ATF5 is expected to be upregulated during initial cell stress and downregulated upon persistent cell stress. ATF5 is hypothesized to have an essential role in carbon tetrachloride (CCl_4)-induced cirrhosis in mice. We will compare WT and ATF5 knockout mice in their response to CCl_4-induced liver damage, fibrosis, and cirrhosis. We also have research plan to determine how ATF5 affects liver regeneration in mouse hepatectomy model.

Project 3: Role of ATF5 in acute lung injury – A mouse model.
Acute respiratory distress syndrome (ARDS) is a devastating clinical syndrome, which causes 30%-50% in-hospital mortality. ARDS is believed to occur when a pulmonary or extrapulmonary insult, such as exposure to LPS, causes the release of inflammatory mediators, promoting neutrophil accumulation in the microcirculation of the lung. Neutrophils damage the vascular endothelium and alveolar epithelium, leading to pulmonary edema, hyaline membrane formation, decreased lung compliance, and difficult air exchange. Many approaches have been proposed for the prevention and management of ARDS, however, the results have been disappointing. A mouse ARDS model, in which LPS is installed into the lung, has been a valuable system to study the cause and treatment for ARDS.
It had been reported that ATF5 is upregulated in LPS-stimulated macrophage and that ATF5 activates the transcription of G-CSF. We therefore hypothesize that ATF5 plays a key role in neutrophil activation and ARDS pathology. We will explore the response of ATF5 knockout mice in LPS-ARDS model.