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COLLEGE OF PHARMACY

UNIVERSITY OF MICHIGAN

Research Experiences for Undergraduates

Please review the REU projects and research interests of the REU faculty mentors listed below. Select <u>five faculty members</u> with whom you would like to work. There is no guarantee that you will be matched with your top choice, if selected for participation in the program, but every attempt will be made to accommodate your interests.

Ryan Baldridge | Lab Website

Project Title: Understanding substrate selection by protein quality control systems

Project Description: Nearly one-third of eukaryotic proteins are imported into the endoplasmic reticulum (ER) for folding, including both integral membrane and soluble proteins. When these proteins fail to fold correctly, they are removed through ER-associated degradation (ERAD).

Our research focuses on understanding the protein quality control systems at cellular membranes. We investigate how these systems select and process protein substrates, identify the molecular networks that define substrate specificity, and explore potential therapeutic applications of these mechanisms. A key component of our work involves identifying the degrons—specific sequence features that target proteins for degradation—and understanding how these molecular markers guide the cell's protein disposal mechanisms. Our current work aims to understand the molecular principles governing protein selection and the decision-making processes at cellular membranes using yeast and mammalian tissue culture systems. By mapping these complex cellular quality control mechanisms, we seek to provide insights into protein folding, misfolding, and cellular stress responses.

Brandon Bordeau

Project Title: Discovery and Development of Antibody-Based Therapies

Project Description: The Bordeau laboratory focuses on developing innovative antibody-based therapies. One of the significant advantages of antibodies is their remarkable adaptability to engineering, with >100 distinct antibody formats, including intact antibodies, antibody fragments, and bi- and tri-specific antibodies. We employ pharmacokinetic modeling and simulation to identify key antibody attributes including target binding affinity, clearance rates, valency, and molecular size. Simulation results inform antibody engineering campaigns to develop lead antibody therapies for experimental testing.

Students joining the lab can expect to learn how antibodies are selected through panning and screening of phage display libraries. Following phage screening, several unique antibodies are identified that are evaluated in a range of binding and activity assays. Students will learn recombinant expression and purification techniques, and analytical methods to evaluate purified protein quality. Once a lead antibody is identified, additional engineering work is completed to develop a lead therapy for further testing.

Charles L. Brooks III | Lab Website

Project Title: In Silico Drug Discovery and Development

Project Description: Our laboratory is focused on the application of statistical mechanics, quantum chemistry and computational methods to chemically and physically oriented problems in biology. Key questions of current interest involve free energy-based methods for inhibitor screening and optimization, including lambda-dynamics and multi-site lambda dynamics – novel statistical mechanical methods to enable the high throughput in silico screening of large databases of small molecule inhibitors, and ligand docking and discovery methods.

Students joining the project would work with a team of graduate students and postdocs to assist in large-scale screening benchmark studies that are currently underway in the laboratory. These studies involve the application of computing infrastructure, hardware with significant GPU acceleration and novel free energy software that is part of the CHARMM biomolecular simulation package, to explore ligand – protein receptor binding free energies. Additional projects could involve work with a team of graduate students on docking benchmarks using developing methods for protein – ligand docking to test and evaluate evolving methodologies in the group. Some comfort with using computers is suggested, but not required, as students will learn how to work in our environment from other team members through structured mentoring.

Timothy Cernak | Lab Website

Project Title: Chemical synthesis at the interface of data science

Project Description: Chemical synthesis is a primary tool in the invention of medicines and biochemical probes. A large amount of data must be collected and interpreted in the chemical synthesis step and in the product characterization step. Our lab uses data science and high-throughput chemical experimentation techniques to navigate this near-infinite reaction space and chemical space in the hunt for new drugs. We look for unanticipated patterns and trends in reaction data, and use our findings to develop new reactions of importance to medicinal chemists. The Cernak Lab is outfitted with robotics and other tools for organic synthesis, high-throughput experimentation, high-throughput analysis and data analysis. Students typically learn cutting-edge techniques in these areas and should expect to run both wet chemistry experiments and computational informatics studies. Talented undergraduates hone their skills in modern chemical synthesis, high-throughput experimentation, automation and data science. REU students typically work towards the invention of a new chemical reaction that would be impactful in drug discovery.

Mara Duncan | Lab Website

Project Title: Understanding the proteins important for Membrane traffic

Project Description: Membrane traffic is essential for the normal functioning of our bodies, because maintains the proper functioning of many membrane bounded organelles, including the plasma membrane, Golgi, ER, and lysosome. Importantly, it is the mechanism by which cells can control the content of their plasma membrane, which is important for many processes including cell communication, adhesion, and migration. The Duncan lab studies the proteins that are important for membrane traffic using a combination of genetic, biochemical, and cell biological approaches. One currently available REU project looks at components of a conserved complex that is required for membrane traffic. This project will include structure-function analyses in vivo and in vitro to map functionally important regions of the protein and physical interactions between the complex subunits. A second project looks at a novel protein inhibitor of type V myosins. Students will be involved in testing specific protein-protein interactions using recombinant proteins. Techniques learned will include yeast and bacterial culturing techniques, molecular genetics including generating mutant alleles and fluorescently tagged proteins, recombinant protein purification, and fluorescence microscopy.

Lydia Freddolino | Lab Website

Project Title: Modeling Bacterial Regulatory Networks for Therapeutics and Synthetic Biology

Project Description: Dr. Freddolino's laboratory investigates the intricate regulatory networks of bacteria, emphasizing their pivotal role in information processing and environmental interactions. The lab is dedicated to developing predictive models of these networks, with implications ranging from advancing antimicrobial therapies to deepening our understanding of bacterial evolution. Through high-throughput experimental methods, the team measures biomolecular interactions, assesses cellular regulatory states, and profiles the phenotypic consequences of regulatory changes. Complementing these experiments, molecular simulation and mathematical modeling provide high-resolution insights into biomolecular interactions and systems-level effects.

REU students who join Dr. Freddolino's lab will learn a wide variety of high-throughput experimental methods and computational bioinformatic approaches to investigate this bacterial decision-making in health/biotech-relevant microbes like Escherichia coli, Vibrio cholerae, and others.

Amanda Garner | Lab Website

Project Title: Decoding Druggable RNA Biology Using Chemical Biology

Project Description: Following completion of the human genome project, it was revealed that only ~2% of our genome encodes for proteins, and the overwhelming majority is comprised of often highly conserved non-coding RNAs. Since that time, RNA has been shown to significantly impact nearly all of human biology from transcriptional regulation to splicing, translation, RNA function, and catalysis. These efforts are carried out by a pantheon of RNA molecules ranging in size and structure, from small ~22 nucleotide (nt) microRNAs (miRNAs) to >200 nt long non-coding RNAs (lncRNAs) to highly structured RNA catalysts, or ribozymes. Accordingly, we have witnessed an explosion in discoveries connecting these RNAs with human diseases, making the search for RNA-targeted therapeutics ever more pressing. The Garner Laboratory uses chemical biology, medicinal chemistry and molecular and cellular biology approaches to investigate new strategies for affecting coding and non-coding RNA biology for chemical probe and drug discovery efforts. An REU student can expect to be exposed to techniques drawing from organic chemistry, biochemistry, and molecular and cellular biology to contribute to our efforts in decoding druggable areas of RNA biology.

James Moon | Lab Website

Project Title: ImmuoEngineering

Project Description: The Moon Laboratory at the University of Michigan is developing new immunotherapies and vaccines at the interface of immunology and engineering. We design new drug delivery systems for improving immune functions in the context of cancer, infectious pathogens, and autoimmunity. Students will use a variety of methods including nanomaterials, polymer and scaffold synthesis, organic chemistry, analytical chemistry, biochemistry, advanced microscopy, and whole animal in vivo imaging for the design and development of new immunomodulatory drugs.

Alison Narayan | Lab Website

Project Title: Developing Biocatalytic Reactions and Elucidating Enzyme Mechanisms

Project Description: In this project undergraduate researchers will get the opportunity to learn skills across organic synthesis and biochemistry through developing novel biocatalytic reactions.

Rachel Niederer | Lab Website

Project Title: How does mRNA sequence impact protein output?

Project Description: We are interested in uncovering what determines the translational output of an mRNA. What are the mechanisms? How do these processes change in stress and disease? And can we use this information to engineer output for mRNA therapeutics?

Patrick O'Brien | Lab Website

Project Title: Molecular Mechanisms of DNA Repair

Project Description: Our genomes are under constant attack from endogenous and exogenous sources of chemical damage. Fortunately, many pathways exist to survey genomic DNA, remove chemical lesions, and restore the original sequence. Failures in DNA repair can cause a wide variety of diseases, including cancer and neurodegeneration. Therefore, a molecular understanding of DNA repair pathways is critical for understanding disease risk and recent progress is leading to novel strategies to treating diseases such as cancer. REU students have the opportunity to learn biochemical and biophysical approaches to studying enzyme mechanisms and specificity in protein-protein and protein-DNA interactions. Specific projects are designed based on the interests of the student and on the feasibility in relationship to current research in the lab. Past student projects have developed new biochemical assays, characterized new small molecule inhibitors, and determined catalytic specificity and chemical mechanism.

Stephen Ragsdale | Lab Website

Project Title: Role of Metal-Containing Cofactors in Biochemistry

Project Description: The efforts of the Ragsdale laboratory focus on studying the roles of metallocofactors in the structure and function of proteins. In several projects, we are studying the catalytic role of metal-containing cofactors (vitamin B12, heme, a nickel-tetrapyrrole, iron-sulfur clusters). The processes that we study involve key microbial reactions in the global carbon cycle (carbon dioxide fixation, methane synthesis, carbon monoxide metabolism). We also are determining the mechanism of mercury methylation. In another project we are determining how heme is used to regulate metabolism and the circadian rhythm in mammals. REU students have the opportunity for training in a wide array of biological and biochemical skills involving the culture of diverse microbes or human cells; performing protein purification; measuring enzyme activity and spectroscopic analyses; making and characterizing site-directed variants of proteins.

Les Satin | Lab Website

Project Title: Role of Metabolism in Insulin Secretion Oscillations

Project Description: The Satin lab is interested in understanding the cellular and molecular basis of insulin secretion from pancreatic beta cells in both healthy and diabetic animals, and islets from humans. Our unique focus are interactions between ion channels of the beta cell plasma membrane and fuel metabolism of the beta cell. Our work on interactions of metabolism and ion channels includes the development of novel genetically encoded metabolic sensors for glucose metabolites, intracellular ion measurements, metabolomic analysis, and studies of genetically modified mice, as well as human islets. We have new work underway that seeks to understand how the function of beta cells in response to insulin resistance may in turn alter the mass of beta cells capable of secreting insulin.

We are also interested in understanding how abnormalities in endoplasmic reticulum calcium levels contribute to ER stress, and the impact of ER Ca changes on various protein folding diseases, of which diabetes is one example. We are also studying gap junctions and their role in beta cell to beta cell communication within the islet. Our overall goal is to improve our understanding of the cellular mechanisms controlling oscillatory insulin secretion, and to improve the treatment of diabetes through the development of new drugs targeting the stimulus-secretion coupling pathway.

Emily Scott | Lab Website

Project Title: Structure/function of human drug targets in the cytochrome P450 enzyme superfamily.

Project Description: The Scott lab uses multiple structural and analytical techniques to determine the relationships between cytochrome P450 protein active sites and potential new drugs for a wide variety of disease states: cancer, Cushing's, obesity, non-alcoholic fatty liver disease, spastic parapalegia, etc. In our laboratory you would learn recombinant protein expression and purification (red heme proteins make this easier than usual), be exposed to X-ray crystallography, and enzymology bioassays employing UV/vis spectroscopy, HPLC, plate reader assays and/or liquid chromatography-mass spectrometry (LS-MS). We've a highly interactive, team-based learning environment composed of grad students and postdocs from five different UM graduate programs, so also provide a cross-section of perspectives on grad school at UM. Check out our website, especially our events page to see what we're up to currently.

Jonathan Sexton | Lab Website

Project Title: Phenotypic Drug Discovery for Metabolic Disorders

Project Description: The Sexton lab focuses primarily on phenotypic-based drug discovery and development for the interrelated set of disorders involving diabetes, obesity, metabolic syndrome, and associated complications. This means that we use functional outcomes of tissues and cells to guide our drug discovery around metabolic endpoints. Our current strategy for drug development uses a combination of phenotypic and molecular target-driven approaches with core competencies in pancreatic islet technologies, fatty liver disease, and metabolic regulation in muscle tissue coupled with in vivo models of diabetes and obesity. Our main technology focus is high content screening - an automated epifluorescence microscopy approach to biological imaging coupled with image analysis to yield quantitative and clinically relevant endpoints in cellular models of disease.

David H. Sherman | Lab Website

Project Title: Marine Microbial Discovery and Analysis

Project Description: The efforts of the Sherman laboratory to isolate novel marine bacteria involve field collection of sediments, sponges, and other invertebrates (bryozoans, ascidians, soft corals, tunicates) from the Indo-Pacific and eastern Pacific regions. Sediments provide a rich source of diverse actinomycetes that are yielding new biological activities and natural products. Based on our findings that novel classes of microorganisms that produce important secondary metabolites are being discovered from marine sources, there is exciting new information to be learned from these novel organisms at the genetic, biochemical and metabolomic levels. Talented undergraduate students are trained to acquire a diverse set of microbiology skills that include developing new conditions and media for growing diverse forms of marine bacteria. As pure cultures are obtained, their research experience develops to include phylogenetic analysis of the microorganisms using 16S rRNA gene sequence analysis, total genome sequencing, biosynthetic gene cluster mining, and bioinformatics analysis. In addition, students that are interested in chemical aspects of microbiology participate in large scale culture, extraction, fractionation and purification of biologically active natural products. We also have an active program in biocatalysis discovery, characterization and enzyme characterization.

Duxin Sun | Lab Website

Project Title: Advancing Therapeutics through Innovations in Drug Development, Nanomedicines, Cancer Vaccines and GI Tract Variations

Project Description: The Sun lab has 4 major ongoing projects.

- **Why does 90% of drug development fail and how to improve it?**
  This project aims to improve drug development success through the integrated STAR system (structure-tissue/cell selectivity-activity-relationship) by addressing the 90% failure rate for immuno-oncology drugs.

- **Why most anticancer nanomedicines do not enhance clinical efficacy and how to improve it?**
  This project develops a drug/nanocarrier-specific anticancer nanomedicines to enhance their clinical efficacy and improve clinical success for cancer immunotherapy

- **Why do most cancer vaccines only achieve short-term efficacy and how to improve it?**
  This project is focused on developing a cancer vaccine to achieve long-term tumor remission.

- **What are the differences in the microbiome, bile salts, and drug release in different regions of the human GI tract?**
  This project investigates the variations in the microbiome, bile salts, and drug release within the human stomach, small intestine, and colon, and studies how these differences influence drug product development and disease states.

Peter Tessier | Lab Website

Project Title: Bioinformatics and computational methods for improving antibody discovery

Project Description: The success of therapeutic antibodies depends not only on their specific bioactivities but also on their highly variable and difficult-to-predict physicochemical properties (solubility, specificity and biodistribution). The goals of this project are to develop predictive computational and bioinformatics methods for designing, optimizing and identifying drug-like monoclonal antibodies for therapeutic and diagnostic applications. Interested candidates should have experience in programming, and an interest in biotechnology.

Alternate Project Title: Novel methods for discovering antibodies and antibody-like molecules

Project Description: In vitro methods such as phage and yeast surface display are commonly used for screening large antibody libraries to identify rare variants with high affinity and specificity. However, there are several key challenges related to in vitro antibody discovery that must be solved to improve the utility and robustness of these methods. The goals of this project are to i) generate novel antibody libraries that closely resemble those generated by the natural immune system, ii) develop novel screening methods for identifying drug-like antibodies with high specificity and solubility, iii) identify conformation-specific antibodies specific for several complex target molecules, and iii) identify agonist antibodies that activate cellular receptors. Interested candidates should have an interest in biotechnology.

Peter Toogood | Lab Website

Project Title: Synthesis of Compounds for Treating Pancreatic Cancer

Project Description: Approximately 60,000 people in the U.S. are diagnosed with pancreatic ductal adenocarcinoma (PDA) each year and most will die within 5 years (data from the American Cancer Society). Current treatments for PDA depend upon the stage of disease when it is first detected. For early stage and locally advanced disease, when the tumor is in the pancreas, surgical resection is typically employed to remove the primary tumor. Depending on the medical center, patients may also be treated before/after surgery with chemotherapy or radiation for tumor debulking and to reduce the risk of recurrence. The five-year survival rate for these patients is ~25%. Unfortunately, most patients with PDA are not diagnosed until their disease is well advanced and has spread to other organs in the body. For these cases, chemotherapy is the only option and in many cases, treatment is largely palliative: the 5 year survival rate for patients with advanced disease is ~2%.

In this project our goal is to discover a new approach to treating PDA. We are testing inhibitors of a novel cancer metabolism target that data show is particularly sensitive in some pancreatic tumors due to deletions of a related protein. Of note, this genetic context will also enable precision-medicine based patient selection. We are currently working to optimize two classes of compounds that were identified as inhibitors of this target using a high throughput screen.

The student on this project will work in the lab to synthesize small organic molecules that our collaborator will test for activity against the target in biochemical assays. Potent and selective compounds will be further tested for their ability to inhibit the proliferation of pancreatic cancer cell lines.

Raymond Trievel

Project Title: Structure and Function of Histone Modifying Enzymes

Project Description: Genomic DNA in eukaryotes is organized in a hierarchical structure termed chromatin. Nucleosomes represent the basic repeating unit in chromatin and are composed of an octamer of the core histones H2A, H2B, H3, and H4, around which is wrapped DNA. Histones undergo a plethora of posttranslational modifications, such as methylation, phosphorylation, ubiquitination and various forms of acylation. These modifications have fundamental roles in governing a diverse array of nuclear processes, including transcription, epigenetic silencing, chromatin remodeling, DNA damage response, and maintenance of genome stability. Histone modifying enzymes catalyze the addition or removal of these modifications to dynamically regulate these processes. Dysregulation of the activities of histone modifying enzymes has been implicated in numerous types of cancer, neurogenerative disorders, bacterial pathogenesis, and other diseases. Our laboratory focuses on studying the substrate specificities, catalytic mechanisms, and regulation of histone lysine methyltransferases and demethylases employing biochemical and biophysical methods. Students engaged in research in our lab will receive training in techniques such as molecular biology, protein expression and purification, X-ray crystallography, enzyme kinetics, calorimetry, and fluorescence-based binding assays, providing an interdisciplinary research experience in chromatin biochemistry.

Ashootosh Tripathi | Lab Website

Project Title: Rational Data-Based Natural Product Drug Discovery

Project Description: The efforts of the Natural Products Discovery Core is to isolate novel marine bacteria from all over the world and develop a data-intensive NP drug discovery platform. Based on our findings that novel classes of microorganisms that produce important secondary metabolites are being discovered from marine sources, there is exciting new information to be learned from these novel organisms at the genetic, biochemical, and metabolomic levels. Talented undergraduate students are trained to acquire a diverse set of microbiology skills that include developing new conditions and media for growing diverse forms of marine bacteria. As pure cultures are obtained, their research experience develops to include chromatographic separation, mass spectrometry data collection, and analysis of microbial metabolites, phylogenetic analysis of the microorganisms using 16S rRNA gene sequence analysis, total genome sequencing, biosynthetic gene cluster mining, and bioinformatics analysis. In addition, students that are interested in chemical aspects of microbiology participate in large-scale culture, extraction, fractionation, and purification of biologically active natural products. We also have an active program in biocatalysis discovery, characterization, and enzyme characterization.

Chase Weidmann | Lab Website

Project Title: Mapping structural features of anti-oxidant noncoding RNA by live-cell chemical probing

Project Description: Our laboratory is interested in how noncoding RNAs (RNA transcripts that are not translated into proteins) fold and form macromolecular assemblies that govern biology and disease. We measure the formation of these assemblies using RNA-reactive chemical probes in human cell culture. Through a process called mutational profiling (MaP), we capture the locations of chemical reactivity on RNAs as mutations in a complementary DNA molecule, which can be read out by sequencing.

Our laboratory has identified a number of noncoding RNAs activated in response to oxidative stress, and we want to use MaP technology to characterize motifs important for their function. This project will focus on MaP of one such RNA target, with the ultimate goal being identification of motifs that might be targeted to treat lung cancers, many of which survive though overactivation of the anti-oxidant pathway. This project includes training in human cell culture, chemical probing, RNA structural biology, high-throughout sequencing, and bioinformatics.

Qiong Yang | Lab Website

Project Title: Biophysics of Living Systems

Project Description: Our lab employs interdisciplinary approaches (imaging, microfluidics, modeling) for a quantitative understanding of self-organizing behaviors of single cells and single molecules during early embryo development. By connecting the understanding at the molecule, cellular, and tissue levels, we pin down the physical mechanisms that give rise to collective spatiotemporal patterns that arise from complex interactive networks of cells and molecules through biochemical signals and mechanical forces.

Two potential REU projects this year:

For the ongoing tunability project: Understanding the tunability of oscillators through modeling. Certain biological oscillators like the cell cycle can vary their period over a large range. Others, such as the circadian oscillator, maintain a robust period against perturbations. This project combines differential equations, sensitivity analysis, bifurcation diagrams, and protein interaction networks to understand which biological circuits are more tunable in period and amplitude.

For the model discovery project: Data-driven discovery of dynamical models. Recent advances in machine learning and sparsity-promoting techniques such as SINDy, show promise as tools for the discovery of dynamical equations that govern biological systems. The quality and quantity of data generated in our lab present a unique opportunity to test these novel techniques with experimental data. This project aims to test these techniques and compare the results with well-established models of biological oscillators.