VERMONT GENETICS NETWORK (VGN)
UNDERGRADUATE STUDENT SUMMER RESEARCH SUPPORT 2019

INTERNSHIP LOCATION DESCRIPTIONS

Albany College of Pharmacy and Health Sciences (Colchester, VT)

Lab 1: Dr. Karen Glass (https://www.acphs.edu/glass-lab)

The human genome is compacted into chromatin, allowing nearly three meters of DNA to fit into the small volume of the nucleus. Chromatin is composed of DNA and proteins, and this DNA-protein complex is the template for a number of essential cell processes including transcription and replication. Understanding the role of chromatin's higher order structure in transcriptional control is important as loss of this regulation underlies many disease processes.

My research focuses on understanding the molecular mechanisms underlying chromatin dynamics and its role in the regulation of diverse cellular process including gene transcription and replication. High field Nuclear Magnetic Resonance (NMR) spectroscopy, X-ray crystallography, and biochemical and molecular biology approaches are utilized determine the three-dimensional structures and functions of chromatin binding proteins implicated in heart disease, cancer and other human diseases.

Lab 2: Dr. Yana Cen (https://www.acphs.edu/yana-cen)

My research group aims to understand the roles of mammalian enzymes play in physiological and pathological processes and to use this knowledge to identify novel therapeutic targets for the treatment of human diseases. To achieve these goals, we develop and apply new technologies that bridge the fields of chemistry and biology. Our technological innovations address fundamental challenges in biology that are beyond the scope of contemporary methods. We complement these efforts in technology development with focused studies on individual enzymes.

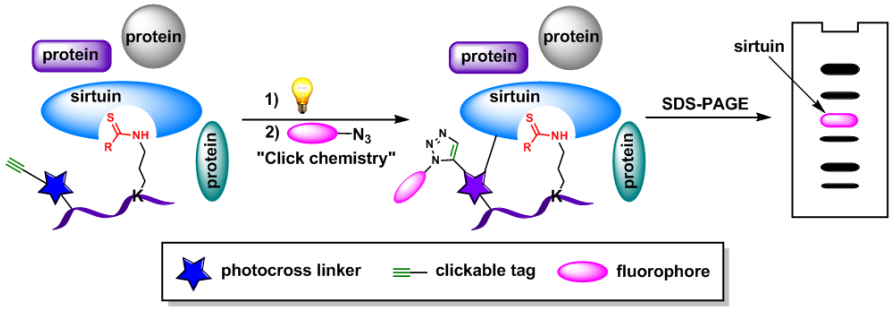
Novel Chemical Probes for Mammalian Sirtuins

My research interest has been focused on a class of epigenetic modification enzymes called sirtuins. Sirtuins are NAD^+-dependent deacetylases that are found in 7 distinct sequences (SIRT1-7) in mammalian cells, and are compartmentalized into nuclear, cytosolic and mitochondrial loci. Sirtuin activities are thought to mediate the beneficial effects of calorie restriction (CR), which increase lifespan in a variety of organisms from yeast to mammals. In addition to being the "master regulator" of metabolic programming, sirtuins have also been implicated in various pathological conditions and have been shown to be forceful potentiators and sustainers of diseases such as cancer.

Despite the intense pursuit of sirtuins as therapeutic targets, there is a clear lack of knowledge of the exact mechanism of actions of these proteins. Currently available methods fall short on one aspect or another. The urgent need of a novel chemical tool to detect the activity of these

proteins becomes apparent. Since 2014 my lab has been developing chemical probes that can directly confer the functional state of a specific sirtuin isoform in complex biological samples. These activity-based probes target active sirtuins, mimicking the chemistry that occurs for standard acetyllysine groups on the active sites of the enzymes, ultimately causing mechanism-based inhibition. In addition, photoaffinity groups were incorporated to enhance the interaction between the probes and the enzyme. In order to provide signal readout, a terminal alkyne group was also appended to the probes to allow the conjugation of the probe-enzyme complex to a reporter (fluorescent dye or biotin) via copper(I) catalyzed “click chemistry”. The general scheme of the labeling strategy is shown in Figure 1. The strategy will selectively “highlight” the active sirtuin content in a complicated cellular context. Side-by-side comparison of functional sirtuin profiles under different physiological and pathological conditions, combined with proteomics analysis, should unwind the intricate interaction loops between human sirtuins and various cellular pathways and empower the better manipulation of these epigenetic enzymes for therapeutic purposes. Currently, this project is supported by a NIH R15 grant.

Figure 1. General scheme of sirtuin labeling using activity-based chemical probes



Allosteric Activation of Human SIRT6 by DNA

Among the seven mammalian sirtuins, SIRT6 is of special interest. It has been suggested to play critical roles in various cellular events such as DNA repair, genome stability, gene silencing as well as glucose metabolism. The study of SIRT6 biological functions has been hindered by the lack of knowledge on the direct cellular targets of this enzyme. Only a handful of endogenous substrates have been uncovered for SIRT6. This is partly due to the fact that the *in vitro* deacetylation activity of SIRT6 is very weak, making the identification of physiological substrates extremely challenging. However, SIRT6 has demonstrated robust cellular deacetylation activity. The discrepancy between *in vitro* and *in vivo* studies has led to the *hypothesis* that SIRT6 activity can be stimulated by endogenous activators. We propose, with strong preliminary data, that the cellular activity of SIRT6 can be stimulated by DNA strand breaks. Current understanding of sirtuin catalytic function and regulation within the cells fails to consider allostery as important. The need to dissect allosteric activation of SIRT6 on the molecular level becomes apparent. We will complement classical enzyme kinetics experiments with novel biochemical assays, activity-based protein profiling as well as live cell imaging to elucidate the molecular details with a high level of spatial and temporal resolution

Bia Diagnostics (Colchester, VT)

http://www.biadiagnostics.com/

Bia Diagnostics, an ISO 17025 accredited laboratory, is a world leader in food allergen analysis. In this internship, the student will gain experience working in a fast-paced contract testing laboratory, assisting in processing samples and lab cleaning, while also learning the science behind ELISA and PCR based food testing methodology. During the course of this internship the student will be expected to complete a research project that demonstrates practical hands-on knowledge of these technologies, for example by validating a test kit to industry standards or by testing a variety of store-bought foods for unlabeled allergens or GMOs.

Delaware State University (Dover, DE)

As part of an agreement between VGN and DSU, we exchange students via our summer undergraduate research programs. The DSU program description and FAQs can be found here: http://de-inbre.org/dissp-faq/.

After students have submitted their application to VGN and are selected for this opportunity, they will be directed to submit their materials a second time through DSU's application site. At that point students will be asked to list their top 3 mentor choices. Mentor research descriptions can be found here: http://de-inbre.org/mentor-search/

White River Junction Veterans Affairs Medical Center (White River Junction, VT)

https://www.whiteriver.va.gov/

We have four active laboratory science investigators, two who are studying HIV, HSV and Hepatitis B. The third is studying Sjogrens Disease and the role of VISTA in Arthritis. We have a Veterinary Medical Unit that houses rodents for the use in research. We are fully accredited by AAALAC and have a functioning Institutional Animal Care and Use Committee (IACUC).

We have approximately 42 active investigators with approximately 100 active human subjects research which encompasses the fields of Oncology, Cardiology, GI, Mental Health, Nephrology and Rheumatology. We also do a variety of health policy research, clinical epidemiology, research on the development of informed decision making instruments, and research that specifically targets rural patients (to improve their health care delivery). We are closely aligned with both the University of Vermont and Geisel Medical School.

We are fortunate to host two national programs at our facility. The National Center for PTSD and the National Center for Patient Safety both do an incredible amount of research in the area.