

**Dr. Corey Berkland**

Nanoparticles for the delivery of proteins and DNA

The fragile nature of proteins and DNA require new strategies to deliver these molecules to a disease target. Currently, most administrations require invasive injections or sustained infusions of therapeutic proteins and DNA with minimal ability to target the drug to the point of interest. Designing multifunction nanoparticles with the ability to target delivery, stabilize the drug, and produce feedback as to the location of the nanoparticle/drug in the body is highly desirable. Therefore, work on this project will be to design and functionalize nanoparticles with peptides for targeting molecular sites in the body and include contrast-enhancing agents for imaging with MRI.

**Dr. Jeff Krise**

Mechanistic Analysis of Intracellular Drug Sequestration

Most drugs are designed to interact with receptors that are located inside cells. The intracellular location of most drug targets are well characterized and are often housed within a specific population of organelles. Unlike drug targets, little is known about the intracellular disposition of drugs. Considering the fundamental importance in maximizing interactions between drugs and their respective targets, we have initiated research aimed at elucidating the mechanisms important in intracellular drug localization. The specific focus of this research project will be to investigate the mechanism(s) by which a class of anticancer drugs is sequestered into organelles contained within cancer cells. Such information will aid in the design/selection of new anticancer drugs with improved interactions with their targets and may also be useful in overcoming drug resistance mechanisms associated with these cells.

**Dr. Jennifer Laurence**

Protein Production and Structural Stability Analysis

Structural integrity belies the biochemical and biological function of proteins and is essential to maintain prior to and during delivery, as unfolding abrogates therapeutic value. The increasing importance and need for employing biological macromolecules as therapeutic agents demands the production of large quantities of pure, homogeneous proteins and, moreover, comprehension of how to preserve the integrity of their three-dimensional structure and avoid aggregation. The project begins with the use of recombinant expression systems to produce proteins for analysis. High-field solution NMR as well as other biophysical, spectroscopic, enzymatic and cellular assays are used to characterize the protein's structure, dynamics and stability. Screening is performed to identify interactions between the protein and potentially stabilizing partner molecules, including drug compounds, excipients, lipid bilayers, peptides and other proteins.

**Dr. Sue Lunte**

Project and Description TBA

**Dr. Russ Middaugh****STABILIZATION OF PROTEINS, DNA, VIRUSES AND VACCINES**

The stability of proteins, DNA, viruses and vaccines is often a key to their use as pharmaceutical agents. Projects in this area involve the biophysical characterization of various macromolecules and their complexes, the development of high-throughput assays that detect stability changes and the screening of libraries of compounds and polymers for agents that enhance the stability of a wide variety of biotechnology derived products.

**Dr. Eric Munson****STRUCTURE AND STABILITY OF DRUGS IN FORMULATIONS**

Formulating a drug often involves grinding, milling, spray drying, lyophilization, and other processes which can dramatically affect the dissolution and stability of a drug in the formulation by promoting drug-excipient (diluent) interactions, causing amorphous/crystalline transitions, and changing particle size and morphology. Our goal is to identify and follow the state of the drug in the formulated product when it is exposed to different environments such as increased temperature, humidity, and pressure. A variety of analytical techniques will be used to follow changes in drug structure and dynamics over time, including spectroscopic techniques (solid-state NMR, IR, Raman), X-ray diffraction, and calorimetric techniques.

**SOLID-STATE NMR STUDIES OF PHARMACEUTICALS**

Solid-state NMR spectroscopy is emerging as one of the most powerful techniques for the characterization of pharmaceutical solids. Projects in this area will focus on the unique capabilities of solid-state NMR to study the structure and dynamics of bulk drugs and drug formulations. Specific projects include: (1) correlating solid-state NMR spectral information with thermodynamic properties such as solubility and dissolution rate; (2) using isotopic labels to follow amorphous to crystalline transitions in solid drugs; (3) developing new techniques to increase the sensitivity and to control the relative humidity and temperature of solid-state NMR experiments. -state NMR, IR, Raman), X-ray diffraction, and calorimetric techniques.

**Dr. John Stobaugh****CHEMICAL MODIFICATION OF BIOLOGICAL IMPORTANT STRUCTURES FOR HIGH SENSITIVITY DETECTION**

Often one encounters substances inherently having important biological activity where analytical methodology is needed for their measurement in very low levels ( $\leq$  nM concentrations). Other times chemical modification of substances occurs in biological systems to produce products that may be referred to as the result of oxidative stress. Two classes of molecules are of interest in these laboratories that fall into these categories, catechols (including catecholamines) and various 5-hydroxyindoles. In each case, previous reports and our own work has shown that benzylamine, or the dimeric analog diphenylethylenediamine (DPE), reacts with such substances to form highly fluorescent benzoxazoles. While being useful for the trace determination of such substances when used in conjunction with liquid chromatography, the detailed kinetic aspects of these

reactions are as yet to be defined. Such information would be useful in the optimization of the reaction chemistry for use as a step within a multi-step operation leading to the bioanalysis of the aforementioned compound classes. The research in this area will focus on comparative kinetic studies of these reactions with a variety of biologically important analytes to gain a further understanding of these reactions.