2021-2022

UNDERGRADUATE RESEARCH PROGRAM

Brigham Young University
Department of Chemistry and Biochemistry
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The Department of Chemistry and Biochemistry has a long tradition of undergraduate involvement in research with our faculty. Students gain valuable experience as they join graduates and undergraduates in ongoing programs.

For more information about the research described in this booklet, talk directly to the professor or visit chem.byu.edu/faculty.
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  Joshua L. Andersen, PhD  
  Merritt B. Andrus, PhD  
  Matthew C. Asplund, PhD  
  Daniel E. Austin, PhD  
  Steven L. Castle, PhD  
  Kenneth A. Christensen, PhD  
  Daniel H. Ess, PhD  
  David V. Hansen, PhD  
  Jaron C. Hansen, PhD  
  James K. Harper, PhD  
  Roger G. Harrison, PhD  
  Jeremy A. Johnson, PhD  
  Ryan T. Kelly, PhD  
  Matthew R. Linford, PhD  
  David J. Michaels, PhD  
  James D. Moody, PhD  
  James E. Patterson, PhD  
  Matt A. Peterson, PhD  
  J.C. Price, PhD  
  Joshua L. Price, PhD  
  Paul B. Savage, PhD  
  Eric T. Sevy, PhD  
  Kara J. Stowers, PhD  
  Richard K. Watt, PhD  
  Barry M. Willardson, PhD  
  Brian F. Woodfield, PhD  
  Adam T. Woolley, PhD
Undergraduate Research Awards (URA)

The Department of Chemistry and Biochemistry has a long tradition of undergraduate involvement in research. Students gain valuable experience as they join graduates and undergraduates in ongoing research programs. Any student currently working in a research group has the opportunity to apply for an Undergraduate Research Award. A student may apply for an Undergraduate Research Award for Fall and/or Winter Semester and for Spring/Summer Terms.

How to Apply

- Be currently working in a research group.
- Attend a grant writing workshop
  - First time applicants are required to attend the workshop; other applicants are also welcome. Faculty will be available to lead a discussion on how to write a high-impact aims page and how to incorporate any preliminary data into the proposal. You are expected to have a rough draft of your proposal by the time of this meeting. The day/time for the workshop will be advertised.
- Prepare a grant proposal aims page
  - The URA application process will teach students to write a one-page overview of an NIH-style grant. This overview is called an “aims” page.
  - Why write a grant proposal? Prior to performing research, an investigator must secure funding. Funding covers the cost of research associates (postdocs, graduate students, and undergraduate students), supplies, and all other necessary items. Generally, funding is secured through a grant application to a foundation or a government agency such as the National Institutes of Health (NIH), National Science Foundation (NSF), or Department of Energy (DOE). Because funding has become increasingly competitive to secure, it is critical to learn excellent grantsmanship—the art of writing a grant.
  - Application Process: Follow the instructions on the Chemistry and Biochemistry Website (www.chem.byu.edu) On the top ribbon, go to Undergraduates, then Undergraduate Research Awards. There you will find the three step process to apply for a URA.
    1. Complete "My Profile" (Includes uploading a photo, preferably of you working in your lab) at http://mentoring.byu.edu
2. Complete "Application" (found on the dashboard) for each semester/term you apply at http://mentoring.byu.edu

3. Complete “URA Cover Page” and upload your proposal at https://goo.gl/forms/lPW0reZP5YqT2ryh2

Proposals will be read and evaluated by the Undergraduate Research Award Committee. Students will be notified of the outcome by email. If you have questions, please see the Administrative Assistant in C104 BNSN.
Y-Chem Society

Y-Chem is the student chapter of the Central Utah Section of the American Chemical Society and is designed to help BYU students succeed in a challenging scientific environment. Though the focus is on chemistry and biochemistry, students of every major are welcome.

Y-Chem is run by a group of students who are passionate about chemistry. They strive to share their love of science with others, while helping them with challenges they may encounter along the way. In addition to their efforts in planning events, they are good resources for questions that students may have. They also work closely with several professors.

One of Y-Chem’s main purposes is to help students succeed in their chosen discipline. Accordingly, many of the activities are directed to this end. Some examples of past activities include fundraising to sponsor students attending national meetings, graduate school preparation, and tours of academic and industrial science laboratories.

Another important purpose of the club is community outreach. The students are passionate about science and want to help kindle that flame in others. Y-Chem members receive the opportunity to be trained to perform chemistry “magic shows.” Once trained, these members perform dazzling chemistry demonstrations both on and off campus for a variety of audiences. They also participate in judging science fairs, as well as Undergraduate Research Night and the BYU major fair. In addition to these activities, Y-Chem also puts on an annual community outreach event called Open Lab Day. During Open Lab Day, Y-Chem members engage with junior high and high school students by helping them perform exciting science experiments.

The international chemistry community is relatively tight-knit. It is quite possible that today’s classmates will become tomorrow’s colleagues and employers. Y-Chem sponsors several social activities each year in order to promote networking amongst peers. In addition to meeting and associating with people on similar career paths, Y-Chem offers its members opportunities to interact with professors. These professors often become valuable contacts and can offer excellent career advice.
However, Y-Chem’s activities aren’t all business. Y-Chem also seeks to have activities that are just plain fun—like the annual Nerd Dance.

You are invited to join Y-Chem. It provides a great opportunity to associate with peers and professors as well as to learn, grow, and serve. Y-Chem strives to be as beneficial as possible and they are always excited to hear what suggestions members have so that they can better serve them.

To join or to find more information, please visit ychem.byu.edu or contact me at byuychem@gmail.com.

Sincerely,

The Y-Chem President
Research Facilities

Research activities occupy more than 50 percent of a 192,000-square-foot building. The university library, where the science collection includes more than 500,000 volumes and about 9,000 journal subscriptions, is located about 150 yards away.

Major equipment available in the department includes NMR (200, 300, and 500 MHz); mass spectrometry (high-resolution, quadrupole, ion cyclotron resonance, ToF-SIMS, and MALDI); X-ray diffraction (powder and single crystal); spectrophotometry (IR, visible, UV); lasers (YAG, gas, excimer, Ti-sapphire and dye); separations—including capillary column GC/MS, ion, and supercritical fluid chromatography; capillary electrophoresis; particle size analyzers; environmental chambers; ICP; thermodynamics (calorimeters of all types, including temperature and pressure scanning, titration, flow, heat conduction, power compensation, combustion, and metabolic); and molecular biology (DNA synthesizer and sequencer, phosphorimager, tissue culture facility, recombinant DNA facility, fluorescence activated cell sorter, and ultracentrifuges).

All computing facilities are fully networked, including computational chemistry and laboratory workstations as well as personal office computers, with convenient connection to supercomputing facilities and the internet. Fully staffed shops for glassblowing, machining, and electronics also serve research needs.
FACULTY RESEARCH PROFILES
Mechanisms of Cancer

Nearly half of us will have cancer in our lifetime and for the majority of patients, cytotoxic chemotherapy is the primary treatment option. The goal of these treatments is to induce tumor cell death. However, these therapies are often ineffective because tumor cells possess the dynamic ability to subvert cell death and become chemoresistant. With this in mind, our research combines molecular and proteomics approaches to understand the mechanisms by which tumor cells proliferate and gain resistance to cell death. Based on this research, we aim to devise therapeutic strategies to overcome chemoresistance and improve clinical outcomes for cancer patients.

Our recent work has focused on the dynamic phospho-binding protein 14-3-3ζ, which interacts with a large network of proteins to reprogram a nascent tumor cell toward proliferation and resistance to stress. As part of this effort, we have harnessed 14-3-3ζ proteomics as a tool to identify novel cell survival mechanisms. This work has led to a variety of projects in our lab, including 1) a mechanism by which tumor cells ‘switch on’ a catabolic process called autophagy, which allows tumor cells to survive through periods of stress (e.g., chemotherapy); 2) an unusual mechanism of tyrosine kinase activation through non-covalent interaction with poly-ubiquitin; and 3) a mechanism that controls the nuclear-cytoplasmic shuttling and proteasomal turnover of a protein regulator of prostate cancer growth.

Research in my laboratory will expose you to current research topics in the cancer field and will teach you the molecular and biochemical tools to solve pressing molecular mechanism-oriented research questions. Dedicated and productive students will also get the chance to be a part of the larger scientific community through research presentations at international meetings and publication of data in peer-reviewed journals.
**Natural Product Synthesis**

Efforts in our lab are focused on methods for the synthesis of biologically-active natural products that possess unique structures and potential for combinatorial library construction and screening. New methods include metal-catalyzed couplings and condensations to assemble key intermediates. Libraries of structural variants are then made and used to probe receptor binding and improve activity.

Recent work includes the synthesis of the polyene stipiamide, a new agent to treat multidrug resistance (MDR); geldanamycin A, a large anticancer macrocycle; englerin A, a terpene based anticancer agent; and resveratrol, a small disease preventative stilbene.
Resveratrol, a simple, yet very important target, is the suspected causative agent of the “French Paradox.” Diets rich in foods that contain this material, grapes in particular, lead to lower rates of cancer and heart disease. New coupling methods and strategies developed to produce this material will now be used to produce structural variants for various screens. New targets now include F4-4, an antiviral lignin natural product that inhibits herpes and shingles infections, and simplified analogs of englerin A. General synthetic methods with broad application are also under development using new ligands for asymmetric styryl Diels-Alder and aldol transformations.

Dedicated undergraduate students, including beginning students, are welcome to participate in all aspects of the work.

References


Organometallic Photochemistry

The development of short-pulsed lasers, from 10 femtoseconds \((10 \times 10^{-15} \text{ s})\) to nanoseconds \((10^{-9} \text{ s})\), has allowed for unprecedented information into the dynamics of chemical reactions. With pulses of light this short, we can easily measure the spectra of chemical intermediates in condensed phase (primarily liquid solution) chemical reactions. A first photon (usually in the visible or UV region of the spectrum) begins the reaction, and the intermediates can be monitored on a number of time scales in the infrared to give structural detail. We have used this instrumentation to study a class of organometallic intermediates important in chemical catalysis. The reaction begins when a photon of UV light causes one ligand to dissociate from a metal center to form a metallic radical. On a very short time-scale, this unsaturated metal center forms a complex with a neighboring solvent molecule. Over time, this complex exchanges with other solvent molecules until it finally decomposes after 5-10 seconds. By following the infrared spectrum of the complex, we can measure the dynamics and binding energy of these weak complexes and compare them with quantum chemical calculations.

Model Ring Formation Reactions

One area of particular interest in my lab is reactions involving organometallic species involved in the formation of new carbon-carbon bonds and the formation of rings. An interesting class of reactions is labeled Pauson-Khand reactions. In its most general form, it is the reaction of an alkene, and alkyne a carbonyl to form a 5-membered cyclopenteneone ring.
The reaction proceeds thermally, and in order to follow the reaction with time-resolved spectroscopic methods, we use a variant of the reactant that combines the alkene and alkyne in the same molecule.

The reaction mechanism shows that the first step is the removal of a CO from the Mo(CO)₆, followed by formation of a complex between the Mo(CO)₅ and the complex, followed by formation of the ring. We are trying to establish which part of the ligand attaches to the metal first.

**Bi-metal catalyst systems**

One of the difficulties in current catalytic systems is that they usually require use of a rare and expensive metal atom. There is tremendous interest in using bimetallic systems where the two atoms act cooperatively to give reactions that are similar to rare metals. While there are many catalytic reaction studies that have established the viability of this approach, there is little known about the details of the reactions. We are applying our transient infrared spectroscopy to these bi-metallic systems to try to understand how these cooperative systems drive chemistry. The initial proposed mechanism suggested that the UV light broke the Cu-Fe bond, which started the reaction. Current work in both time-resolved IR spectroscopy and DFT computations suggest that loss of CO from the Fe is the initial step in the reaction. More work is needed to understand this catalytic reaction.
Analyzing the dust on Mars

We are building a small instrument that will measure the size and electrical charge of dust in the Mars atmosphere. This instrument, based on charge detection mass spectrometry, will hopefully fly to Mars on a future lander. Information from this instrument will reduce the risk of a human mission to Mars, as well as improve our understanding of Mars’ atmosphere and surface.

Miniaturized mass spectrometers for portable chemical analysis

We are developing small, handheld chemical analyzers based on ion trap mass spectrometers. Conventional ion trap systems are too large for in-field applications such as tracking illicit drugs. Through novel ion trap designs and fabrication procedures we have already produced the world’s smallest working linear ion trap mass analyzer.

Chemistry and Biology of High-Velocity Impacts: Simulating Space Processes

We are developing several experimental and theoretical tools to explore high-velocity impacts of molecules, ions, and even intact microorganisms on surfaces. The understanding of the chemical and biological effects of impacts are relevant to spacecraft-atmosphere sampling and transport of biological material through space. As an example of a project in this area, we are building an ultra-fast rotor with molecular beam that allows molecule-surface impacts at 4 km/s, with the molecular fragments analyzed using mass spectrometry.

Undergraduate students work closely with graduate students and gain experience in building scientific equipment, particularly vacuum systems and mass spectrometers. Any chemistry, physics, or engineering students who have completed their first two years of undergraduate study are invited to join.
Steven L. Castle, PhD

*Organic & Biomolecular Chemistry*

C411 BNSN, 422-1780

Email: scastle@chem.byu.edu

**Synthetic Organic Chemistry, Peptide Chemistry**

Our research focuses on the total synthesis of complex bioactive natural products and peptides. The structures of such compounds serve as inspiration for the invention of new organic reactions and processes. Additionally, studies of their bioactivity can increase our understanding of their modes of action, potentially leading to the design and development of new therapeutic agents. Some of our recent synthetic targets are shown below.

The new reactions that we develop in the course of synthesizing a target compound are fully investigated with respect to scope and mechanism. It is our aim to develop widely applicable processes that deliver complex products from simple starting materials in a minimum number of steps. We also believe that it is important to understand how these processes operate.

We frequently synthesize structural analogues of the target natural products or peptides. This allows us to elucidate the modes of action of these compounds, often in collaboration with biological and biochemical research groups. We are also engaged in finding new ways to stabilize peptides to proteolytic degradation, thereby increasing their potential as drugs.

Students in our group receive rigorous training in the techniques of organic synthesis and structure determination. In addition, they learn the more general, widely applicable skills of strategic
planning and problem solving. Furthermore, in the course of presenting their research in verbal and written formats, they acquire valuable communications skills. Prior to joining our group, students should have completed Chem 351, 352, and 353/354 (concurrent enrollment in 352 and 353/354 is acceptable).

References


My lab works in the fields of biochemistry and bioanalytical chemistry. We develop methods that apply optical spectroscopy, flow cytometry, time-lapse microscopy, and microfluidics to questions in biochemistry, biophysics, cell biology, and microbiology. Currently, there are three main research areas in my laboratory that are described below.

The first project grew out of our discovery several years ago that the anthrax toxin receptor capillary morphogenesis gene protein 2 (ANTRX2/CMG2) is involved in pathological in the eye and in tumor models. Our current work focuses on identifying both intracellular and extracellular ligands of CMG2, which are thought to be extracellular matrix proteins, via proximity proteomics. The lab is trying to address a critical barrier to progress in this field by identifying the role these cell surface receptors play in angiogenesis and developing a model that can be tested using traditional biochemical approaches. This project is an active collaboration with Dr. Michael Rogers at Boston Children’s Hospital/Harvard Medical School.

Another project focuses on measuring and monitoring the dynamics of metabolism in eukaryotic parasites. For example, in *Trypanosoma brucei* (the causative agent of Human African Trypanosomiasis), the sole source for generating ATP during the infectious lifecycle stage of the African trypanosome occurs exclusively in a unique peroxisome-like compartment called the glycosome. We are developing and using recombinant protein-based FRET biosensors to quantitatively measure multiple metabolites (e.g., pH, glucose, ATP, AMPK activation, and redox potential) in live parasites. We are also investigating the biochemical mechanisms the organism uses for regulation of metabolism. Since glycolysis is key to parasite survival, inhibiting glycolysis could be an excellent targeted therapeutic approach for treatment of African Trypanosomiasis. Other parasites of interest are *Leishmania donovoni* and *Trypanosoma cruzi*.
This project is an active collaboration with Dr. James Morris at Clemson University as well as other collaborators at the University of Wisconsin-Madison and The Ohio State University.

Finally, the newest project in the lab is using 3D-printed microfluidic devices for cell-based analysis. Working together with Dr. Greg Nordin’s lab at BYU (Electrical and Computer Engineering), we are designing devices, optimizing biocompatibility of the printed resins, and developing cell-based assays that take advantage of the small scale, both active and passive fluidic components, and ability to multiplex analysis.

Note: I am willing to work with beginning students; however, I am accepting a limited number of students in the 2020-2021 academic year. Please contact about possibilities for joining the lab.

**Selected Recent Publications**


Our group uses one of the most powerful types of mass spectrometry, combined with molecular modeling using high-end supercomputers, to develop methods for characterizing molecule-sized devices. My goal is to give students a real taste of the kind of work done by researchers on the cutting edge of fundamental science, culminating in publication and/or presentation of the results. Our group has an excellent track record of placing undergraduates who desire additional training in some of the world’s top graduate programs. Projects will be selected based on the student’s level of preparation. All of our work includes strong possibilities for collaboration with other groups working in related areas.

**Tertiary Structure from Mass Spectrometry: A “CRAFTI” New Method**

Tertiary structure (the way a molecule is folded, resulting in its overall shape) is extremely important to molecular function in such diverse areas as biochemistry, catalysis, and the assembly and function of molecular nanomachines. Therefore, it is important to develop ways to determine tertiary structure, and to do so with very small samples. Although mass spectrometry is a powerful, sensitive technique for characterizing the atomic composition and connectivity of atoms within molecules, it usually yields no information about tertiary structure. We recently invented a new technique for obtaining tertiary structural information using Fourier transform ion cyclotron resonance mass spectrometry; we call the technique "CRAFTI" (from cross sectional areas by Fourier transform ion cyclotron resonance). We also use the accepted “gold standard” method for measuring collision cross sections, called ion mobility spectrometry, to make comparisons with our CRAFTI measurements. Most recently we have added the capability to make time-resolved measurements, so we can watch molecules as they fold/unfold. Interested students will explore the strengths and limitations of this new technique, and develop supramolecular chemistry applications for it, supported by funding from the
National Science Foundation. Chemistry or biochemistry majors who are at least concurrently registered for Chem 462, 467, or 468 will be most successful in these projects, although motivated students with less preparation (as little as Chem 111 or Chem 105) can also do excellent experimental work. Commitments of about 10 hours per week are generally required to make meaningful progress on experimental projects.

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**A Picture is Worth a Thousand Words: Molecular Modeling**

Visualization and modeling of molecular systems is an essential part of our research. Software packages such as SPARTAN, ECCE, NWChem, and IMoS will be used to model the same host-guest complexes we are studying experimentally. Most of these software packages have intuitive, graphical user interfaces that make them easy to operate. Goals of the modeling projects include determination of low-energy structures and energies for the complexes, dynamic simulation of the complexes, calculation of vibrational frequencies that can then be used as input to statistical mechanics programs, and calculation of collision cross sections for comparison with experiments. Much of this work is
computationally very demanding and will require use of campus supercomputers. No prior knowledge of either modeling methods or computer operating systems is needed, but students will need to learn to be comfortable with UNIX. Chemistry or biochemistry majors taking Chem 351/352 have sufficient background to carry out these projects successfully, and motivated students from other majors or who are at earlier stages of their preparation (as little as Chem 105 or Chem 111) will also be able to make important, significant contributions. Again, to make meaningful progress on these projects students will need to commit to about 10 hours per week.

The undergraduates involved in this work will have full access to our state-of-the-art equipment. We have a well-equipped research lab centered around a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer with a 4.7-Tesla superconducting magnet and an external ion source equipped with electrospray and sonic spray ionization modules (Bruker model APEX 47e). We also use a new Agilent 6560 ion mobility-time of flight mass spectrometer. All of this equipment is computer-interfaced and script-controllable, allowing very versatile experiments to be designed and performed. For students with good mechanical or programming skills interested in building instruments, we currently have ongoing needs for instrument control and data analysis software development.

**Selected Publications**

Theory and Simulation

If you like computers and chemistry, my group is the place to make discoveries. My group uses and develops quantum-chemistry, molecular dynamics, and data science (machine learning) methods to discover mechanisms, reactivity principles, and selectivity for experimentally important chemical reactions related to catalysis and energy. In practice, this means using supercomputers and software to accurately model chemical reactions. My group emphasizes making predictions and designing catalysts that are then realized in the laboratory. This naturally leads to close collaboration with experimental groups in academia and industry. My group publishes several top-tier publications each year and undergraduates are very often co-authors. Current areas of research involve: (1) Computational catalyst design with industrial application, (2) Chemical dynamics of organometallic reactions, (3) Computational studies of alkane C-H functionalization reactions, and (4) Developing software for dynamics simulations and machine learning. See my webpage for a video and project descriptions: https://www.chem.byu.edu/faculty/daniel-h-ess/.

Undergraduate chemistry, biochemistry, engineering, physics, biology, and computer science students in my lab have a range in backgrounds, from a computer science minor to no programming experience. To be successful, you need to have a desire to learn inorganic and organic chemistry, develop computer skills, and work hard (15-20 hours per week in Fall/Winter and 30-40 hours per week in Spring/Summer).
Microglia and Alzheimer’s disease: Where immunology meets neuroscience

Like many other tissues and organs, the brain is populated with resident immune cells that operate as sentinels for injury and infection. In the central nervous system, these cells are known as microglia, and their macrophage-like properties are important for tissue maintenance and optimal nerve cell function.

Alzheimer’s disease (AD) develops in the aged brain when the protective functions of microglial cells, such as debris clearance and tissue maintenance, become compromised (ref. 1). Human genetic studies have revealed several genes and proteins expressed by microglia that influence the risk of developing Alzheimer’s disease (AD). One such gene is TREM2, which encodes an immunoreceptor expressed on the surface of microglia that activates tyrosine kinase signaling and is essential for the response to damaged neurons. The R47H point mutation, which reduces the interaction of TREM2 with its ligands and blunts microglial activation, confers triple the normal risk of developing AD, and also results in a faster rate of AD progression following diagnosis. Therefore, pharmacological approaches to augment TREM2-driven microglial activation may protect against AD, both in preventive and therapeutic settings.

Many other genes that contribute to AD risk are expressed by microglia, but the molecular functions of the proteins they encode are mostly unknown. Likewise, the cellular mechanisms by which microglial cells protect against AD in the brain are not well understood. My research program aims to unravel these complex physiological processes using three general approaches:

- We define the biochemical properties, molecular interactions, and cellular functions of AD-related microglial proteins. For example, PILRA is an inhibitory immunoreceptor that opposes tyrosine kinase signaling, and we recently showed that a single amino acid change in PILRA that associates with reduced AD risk also reduces interaction of PILRA with its ligands (ref. 2).
We use bioinformatic approaches to characterize microglial responses associated with neuroprotective or inflammatory signaling in order to better understand different microglial activation states in mouse models and in human tissues. For example, we recently purified microglial cells from frozen human samples and revealed that microglia in AD brains show an enhanced aging signature and fail to display the protective microglial response observed in mouse AD models (ref. 3).

We perform genetic or pharmacological manipulations in cellular or animal disease models to observe how our molecules and pathways of interest impact AD pathologies. For example, we recently showed that Trem2 deletion leads to increased neuronal damage and degeneration in the PS2APP and TauPS2APP models of b-amyloid and tau pathologies (refs. 4-5).

The field of Alzheimer’s disease research is strewn with failure after failure among clinical trials aiming to slow the progression of this debilitating and tragic illness. An enlightened understanding of how the functions of AD-associated genes translate into pathogenic disease mechanisms will identify new opportunities for pharmacological intervention.

References


Atmospheric Chemistry and Renewable Energy

Research in the Hansen group is divided into three elements: (1) Kinetics and Spectroscopy of Environmentally Important Reactions, (2) Air Sampling Campaigns and Human Exposure/Environmental Chamber, and (3) Biofuel/Alternative Energy. Our group couples computational and experimental studies to investigate the kinetics and mechanisms of important atmospheric reactions. Laboratory studies are complimented by air sampling campaigns designed to investigate the sources of air pollution. We utilize an environmental chamber to aid in the interpretation of our air sampling campaign studies. We also have an active research element in our group that studies the conversion of biomass into energy. Interested students are encouraged to contact Dr. Hansen with questions about his research. Details about two of our three research areas are described below. Undergraduate students with at least two years of classwork are often utilized as research assistants in his group.

Kinetics and Spectroscopy of Atmospherically Important Molecules

Aerosols are defined as solid or liquid particles suspended in air. Aerosols affect visibility, human health, and climate. Primary aerosols are released directly into the atmosphere from both biogenic and anthropogenic sources. Secondary aerosols form in the atmosphere as a result of physical and chemical processes. Formation of secondary aerosol particles is frequently modeled with classical nucleation theory (CNT). The first step in CNT is the nucleation step where molecular clusters form and grow in size until they reach the
critical cluster size. The critical cluster size is defined as the maximum in the Gibb’s free energy curve (Figure 1). The second step in CNT is growth of the critical cluster through coagulation or condensation. Using this model, current predictions of atmospheric aerosol content underestimate measured concentrations of aerosols in the atmosphere. This discrepancy highlights our lack of understanding of the sources and formation mechanisms for aerosol particles in the atmosphere.

In the Hansen lab, we expand on our previous computational and experimental work by using a variety of amines and carboxylic acids that are found in the atmosphere in the presence of water vapor to measure aerosol formation rates as a function of temperature, water vapor, amine, and carboxylic acid concentrations. These systems are explored both computationally and experimentally.

Experimentally, we use an in-house designed instrument to measure the kinetics of particle formation. Figure 2 shows a schematic of the instrument. The instrument is modeled after commonly used slow-flow reactor cell but with expanded capability. The heart of the instrument is a 180 cm long Pyrex slow-flow reactor cell (i.d. 5.1 cm) coupled to two scanning mobility particle sizer (SMPS) detectors on the downstream end of the cell. Gases are introduced at the top of the reaction cell as shown in Figure 2. Amines are introduced at varying points in the flow cell by use of a Teflon-coated shower ring attached to a stainless steel sliding rod. The shower ring (i.d. 4.5 cm) with pin holes allows for movement up and down the flow cell shown in Figure 3. This method of introducing amines allows for reaction times varying between 8 s to 48 s. The concentration of gases in the cell is varied by controlling the flow of gases using mass flow controllers. Their concentrations are measured by UV absorption spectroscopy to determine carboxylic acid and amine concentrations and NIR spectroscopy for detection of water vapor.

![Figure 2. Schematic of slow-flow reactor/SMPS aerosol generation and detection instrument](image)

![Figure 3. Teflon coated shower ring assembly for introduction of amines into the reaction cell](image)
At both ends of the tube, aluminum blocks serve to support the reaction tube and provide holders for CaF₂ windows to introduce UV and IR light coaxially with the flow of gases into the reaction cell. Optics collimate the light from a 100 W D₂ lamp and direct it through the reaction cell and into a temperature-regulated CCD detector. The concentration of particle precursors, like carboxylic acids and amines, in the cell is accomplished by UV absorption spectroscopy with published absorption cross-sections.

The carboxylic acid reacts with water vapor and an amine in the flow cell to form a carboxylic acid-water-amine complex (see figure 4) that serves as the first step in aerosol formation. This complex further reacts with water molecules and/or other complexes/clusters in the flow cell to form particles. The number of particles formed depends on the reaction time available and the concentration of precursors in the reaction cell. Both the size distribution and absolute number densities of particles is measured at the exit of the flow cell by two SMPSs.

Biofuel/Alternative Energy

Transformative advancement in renewable energy production by anaerobic digestion (AD) of waste streams requires an inexpensive, simple, and scalable pretreatment to increase the conversion of organic wastes into biogas. Production of biogas by AD offers a proven, readily-scalable, and well-understood mechanism for energy production and disposal of organic wastes. However, inefficient conversion of waste into biogas, typically 30-40% in mesophilic digesters without pretreatment makes it difficult for AD to be an economically viable source of renewable energy. Improving the economic viability of AD in the renewable energy market therefore requires a low-cost, efficient pretreatment that consistently and significantly increases the fraction of biomass converted into biogas.

Pretreatment of organic wastes prior to AD by physical (e.g., mechanical pulverization, cavitation, and limited pyrolysis), physicochemical (e.g., steam explosion and ammonia fiber explosion), chemical (e.g., acid hydrolysis, alkaline hydrolysis, high temperature organic solvent pretreatment, and oxidative delignification), biological (e.g., lignin degradation by white- and soft-rot fungi), and electrical...
methods, and various combinations thereof, have existed for several decades, but are energy inefficient and are often not economically viable. To date, the only economically successful pretreatment method for increasing degradation and biogas production is the thermal hydrolysis process (THP), in which the influent is heated to 130-180°C for 30-60 minutes. THP of sewage sludges increases biogas yield by 50%, decreases viscosity, allowing higher loading rates, decreases effluent chemical oxygen demand (COD) by 50%, improves dewatering, and provides sterilized, odor-free compost.

The optimum system for waste pretreatment depends on the physical and chemical characteristics of the waste being treated, and for some wastes, a pretreatment that uses a thermophilic biological component may provide many of the same advantages as THP at less cost. A biological pre-digestion process is more energy efficient than THP because it operates at lower temperature and pressure. However, for some wastes, the optimum pretreatment may be to add thermophilic biology post-THP, which could be done with no additional energy cost because the influent is already heated. Such a combination of compatible pretreatments may provide a significant increase in performance over THP or biological pre-digestion alone for some wastes.

Many wastes are recalcitrant for AD because the organic solids are large, polymeric molecules, e.g. lignocellulose, that are not directly accessible to methanogens. Hydrolysis of these polymeric materials into small, soluble molecules or ions makes them readily accessible for methanogenesis and improves the rate and efficiency of conversion of the substrate into biogas by AD.

Figure 5 shows a schematic diagram of how a biological pre-digestion would be implemented in a commercial plant for producing biogas from an organic waste stream.

**Figure 5:** The proposed commercial process occurs in three steps: First, feedstock is mixed and heated in a hydrolysis tank to drive off O₂ and reach the requisite temperature and pH for growth of *C. bescii*. Second, feedstock is pre-digested in an anaerobic secretome bioreactor (ASB). And third, the predigested feedstock is anaerobically digested to produce biogas in a conventional anaerobic digestion vessel.
In the first stage or tank, an organic waste containing polymeric organic materials is suspended in water in a mixing-hydrolysis tank at 75°C or higher where partial hydrolysis of the substrate occurs, O$_2$ is removed by decreased solubility and reaction with the organic material, and the suspension is pasteurized. Note that this hydrolysis tank could be a THP tank which may be advantageous for some wastes. Pre-digestion takes place in a second stage or tank (termed an anaerobic secretome bioreactor, ASB) at 75°C and pH 7-8. The temperature in the ASB is high enough to provide relatively fast reactions and short retention times, but not so high as to require special materials or designs for tanks, pumps and fittings or to incur excessive heating costs. In the last phase, AD takes place in a third vessel that could be thermophilic or mesophilic. Thermophilic digestion may be advantageous since the energy cost of heating the influent has already been incurred during the pre-digestion phase. The hypothesis being tested in the Hansen Lab in collaboration with Dr. Zach Aanderud (BYU) is that biological pre-digestion of will significantly increase the amount of VS destroyed and therefore increase the yield of biogas and methane.
Research in our laboratory focuses on three major areas: (1) NMR spectroscopy in solids and solutions, (2) Development of new computational/theoretical methods to support our NMR studies and (3) Discovery of endophytic fungi that produce novel products. A more detailed description on each of these areas of research are given below.

NMR spectroscopy.

*NMR in solids – NMR crystallography.* NMR crystallography has the aim of developing NMR methods capable of providing structural information about crystalline solids including the ability to derive complete crystal structures. Our laboratory was among the first to demonstrate that complete crystal structures can be obtained using only NMR spectroscopy and computational methods. Other contributions to NMR crystallography include the development of methodology for obtaining thermal ellipsoids representing errors in atom positions based solely on NMR information. This can be achieved for all atoms within a structure of only atoms poorly defined by more conventional diffraction methods. More recently we have developed methods for refining crystal structures based only on NMR information. The resulting structures exhibit unusually high resolution that can even surpass the resolution that is theoretically achievable by diffraction methods (e.g. x-ray diffraction). These methods also have the unique ability to identifying exchanging hydrogen’s in hydrogen bonded atoms and to provide accurate positions for these hydrogens. We are currently applying these methods to structures that have historically been difficult or impossible to characterized by conventional crystallography.

*NMR in solution – complete structural analysis from a single experiment.* Our lab has recently developed methodology that provides complete structural characterization from a single NMR experiment. This analysis unambiguously establishes atomic connectivity, molecular conformation, identifies all
heteroatoms, hydrogen bonds and tautomeric forms. This characterization involves measurement of experimental one-bond carbon-carbon J-couplings ($1J_{CC}$) values using the INADEQUATE or $^1$H detected ADEQUATE. Dozens of structurally varied model structures are then created that encompass all feasible structural variations (e.g. conformations or hydrogen bonding arrangements). Computed $1J_{CC}$ values for each model structure are compared with experimental data to find where there is close agreement. This process has been demonstrated to successfully predict structure of the complex depsidone, perisalizinic acid, a novel structure recently isolated from a lichen.\textsuperscript{4}

**Theoretical/computational methods supporting NMR studies.** For over 20 years it has been possible to include lattice fields in NMR modeling computations by using methods that mimic periodicity in crystalline systems.\textsuperscript{5} One of the limitations of the most popular of these methods is that the functionals that are allowed are relatively inaccurate compared to more modern hybrid functionals. In collaboration with professor Joshua Hartman (San Jacinto College), we have been exploring the use of alternative methods that allow more accurate hybrid functionals to be included.\textsuperscript{6} At the present time, this process has been demonstrated to provide the most accurate $^{17}$O electric field gradient tensors than have yet been computed. Extending these methods to structurally challenging problems involving to more commonly encountered $^{13}$C and $^{15}$N chemical shift data is now underway.

**Natural products.** Another area of focus in our laboratory is the discovery of natural products from endophytic fungi. These fungi grow inside of higher plants and usually cause no detrimental symptoms in the plant. These microbes are thus less studied and a higher percentage of novel products can be obtained using this approach. Such organisms can be isolated by simple culturing methods and we have obtained endophytes from plants all over the world. Some of the products/fungi discovered include;

- Ambuic acid: a product that inhibits biofilm formation in gram-positive bacteria.\textsuperscript{7}
- Cryptocin: a molecule that that protects rice plants from rice blast disease.\textsuperscript{8}
- Pestacin/isopestacin: highly active antioxidants that function by a novel mechanism.\textsuperscript{9,10}
- Citrinin: Another antioxidant that functions by a novel mechanism.\textsuperscript{11}
- A novel fungus in the genus *Hypoxylon* that is able to convert cellulose into hydrocarbon fuels.\textsuperscript{12}

**Citations.**


Molecular Binding and Encapsulation

The supramolecular interactions between a host molecule and a guest molecule allow for selective binding, chiral recognition, and separation. Our introduction into the field of host-guest complexes came with the discovery in our group of a metal-assembled capsule, consisting of two synthesized cup-shaped molecules brought together by metal ions. Along with the capsules, we have formed metal-resorcinarene complexes with various metal ions such as iron, cobalt, and copper. We are now pursuing with interest host molecules that selectively bind one enantiomer preferentially over another. We are also exploring the synthesis and properties of larger host molecules and their ability to encapsulate water contaminants. Students working on this project learn to synthesize and characterize organic and inorganic compounds and use them to bind or encapsulate other molecules.

Separations of Contaminants Using Macroyclic Compounds

Another related area of research we are pursuing is the application of cavitands in separations. Small quantities of molecules are harmful to us as water contaminants or unwanted substances in our body. Students in our group use ion chromatography to detect and quantify anions, cations, pharmaceuticals, and biological compounds. To do this, they pack columns with cavitands and perform separations using an ion chromatography instrument. Students become experts in separation techniques and use their skills to analyze molecules in tap water, river water, and biological fluids.
**Nanomaterial Synthesis and Properties**

Materials with subunits in the nanometer range are being studied for their semiconductor and energy transfer properties. Members of our group synthesize nanoparticles, nanoprisms, and nanoplates made of ZnO and investigate their light absorption and emission properties, as well as gas adsorption. Students on this project synthesize new nanomaterials and, while characterizing them, learn to operate many instruments, such as XRD, SEM, TEM, ICP, UV-vis, and NMR.

**References**


Creating Ultrafast Spectroscopy

Light can be a wonderful tool to measure all sorts of fascinating material properties, but there is one important truth all spectroscopists keep in mind: light only cares about the optical properties of a material! In order to use light to learn about a whole host of material properties, the radiation must couple to the material property of interest. However, oftentimes, the optical properties are coupled to many material properties and understanding what we see can be difficult. Therefore, making measurements more “selective” to the property or dynamics of interest is crucial.

“Selectivity” in spectroscopy can be achieved in a number of ways. Perhaps the most straightforward is by simply changing the wavelength (color) of electromagnetic radiation we use, from x-rays to radio waves. In the Johnson Spectroscopy Lab, we focus on experiments using ultraviolet, visible, and infrared radiation. In addition, we have a strong emphasis on using terahertz (THz) radiation, an exciting region of the electromagnetic spectrum that lies just beyond the infrared, with wavelengths from 3 mm to 30 μm corresponding to frequencies from 0.1 to 10 THz (1 THz = 1012 Hz). These frequencies are associated with the time scales of atomic vibrations in solids, the lifetime of excited electronic carriers in some materials, electronic spin which gives rise to magnetism, and other dynamic properties we can study in solids, liquids, and gases. New high field THz sources are under development.

In typical “pump/probe” experiments to measure time-dependent laser-induced dynamics, thousands to even millions of laser shots are used to record the sample response. This requires the
sample to return to exactly the same state after every single laser shot. In the Johnson spectroscopy lab we are also developing what is called "single-shot probe" measurements, where all dynamics are recorded in a single laser shot. This opens up new possibilities to study irreversible dynamics central to laser processing of surfaces, light induced damage, and ultrafast phase transitions. Additionally, single-shot measurements can even expedite the collection of typical pump/probe data in normal, reversible measurements.

**Using Ultrafast Spectroscopy**

Ultimately, spectroscopy is a tool to study and control systems of interest. We study materials and processes that have promise to be used as ultrafast switches in the next generation of computing devices, as well as nanoparticles and layered hetero-structures with interesting properties relevant for energy production and catalysis.

We use high field THz pumping in tandem with single-shot probing to excite and control quantum mechanical modes coupled to macroscopic properties. We also use excitation light with wavelengths from the UV to IR to investigate and influence carrier dynamics, surface states, and energy flow in nanomaterials, which we can probe with optical light or THz radiation.

**References**


Mass spectrometry (MS)-based proteomics and metabolomics analyses enable the quantification of hundreds or thousands of biomolecules within biological systems, providing critical information for understanding cellular structure, function, and pathology. However, due to limitations in analytical sensitivity, samples comprising thousands or millions of cells are typically required for such in-depth biochemical measurements, which can lead to a blurry picture of the biological system that fails to differentiate multiple cell types, tissue structures, and their microenvironments. In addition, each measurement can take hours or days to complete, which leads to a high cost per analysis.

Our research group focuses on developing improved methods and instrumentation for MS-based biochemical measurements. Specifically, we strive to extract the maximum amount of biochemical information from the smallest samples possible to address questions in biology that cannot be answered using existing approaches. This requires overcoming shortcomings and minimizing sample losses across the entire workflow, including sample isolation, preparation, separation, ionization, and mass spectrometry.

**Tools of the trade**

Some of the instruments and techniques that we use and/or strive to improve are:

Sample isolation – Using laser capture microdissection, fluorescence-activated cell sorting, and microfluidics approaches to isolate tissues or cells of interest while excluding unwanted background material

Sample preparation – Developing microfluidic and robotic systems such as our recent Nanodroplet Processing in One Pot for Trace Samples (nanoPOTS) system to efficiently convert raw biological material from ultrasmall samples including single cells into ready-to-analyze biomolecules
Separations – Miniaturizing and improving nanoscale liquid chromatography and capillary electrophoresis separations to effectively deliver biomolecules to the mass spectrometer

Ionization – Optimizing nanoelectrospray ionization to efficiently convert solution-phase biomolecules into gas-phase ions for analysis by MS

Mass spectrometry – Ensuring optimal performance for commercial and custom MS instrumentation

Applications

We collaborate with researchers at a variety of institutions to address otherwise intractable problems in biology and biomedicine. For example, we are working with Professor Rosalie Sears, co-director of the Brendan-Colson Center for Pancreatic Care at Oregon Health & Science University, to understand what causes certain cells within pancreatic ductal adenocarcinoma tissues to undergo a transition from epithelial to neuroendocrine-like phenotype, and why these changes are associated with increased resistance to treatment. This requires us to map protein expression across tissues with high spatial resolution, and we are funded by the National Cancer Institute to develop the required technology.

We are also working to isolate and analyze extremely rare circulating tumor cells from the blood of cancer patients to track disease progression and responses to therapies with a minimally invasive assay.

Relevant Publications


Research in Synthetic and Analytical Chemistry on Surfaces

Students who work in my group have the opportunity to learn about many different areas of science while they focus on our primary interests: surface functionalization and characterization. We currently have projects that involve the development of new materials for chromatography (separation science) and chromatography sample preparation, i.e., new materials for solid phase microextraction (SPME), thin layer chromatography (TLC), and high performance liquid chromatography (HPLC). We are also doing advanced surface characterization of glass surfaces and developing new coatings for an industrial partner.

One of the reasons that students are exposed to many different ideas while they work in my group is because my work overlaps two different regions of chemistry: the synthetic side as well as the analytical side. On the synthetic end, we have prepared surfaces with different reactive functional groups, such as epoxides or carboxyl groups, and attached DNA to them. We are also using or are planning to use different polymerization methods, including ring opening metathesis polymerization, atom transfer radical polymerization, and conventional radical polymerization to grow polymers from surfaces. This polymer work should fit in nicely with the new methods we have developed for patterning silicon surfaces with micron and even nanometer sized features. It should allow us to create polymeric features on surfaces with these tiny dimensions for nanotechnology.

On the analytical end, my students use a number of instruments and methods to characterize our new materials and other materials we get by collaboration. Tools that we use include X-ray photoelectron spectroscopy (XPS), time-of-flight secondary ion mass spectrometry (ToF-SIMS), ellipsometry, wetting, scanning electron microscopy (SEM), and atomic force microscopy (AFM). While
most undergraduate students are not familiar with these methods before they join my group, within a few months they have usually developed a good sense for the type of information that these tools can provide and have become users of more than one of them. We have also developed an increasingly strong emphasis in chemometrics in my group. An important branch of chemometrics uses advanced data processing/statistical tools to extract information from large data sets. Two such tools we use are Principal Components Analysis (PCA) and Partial Least Squares (PLS). These tools are important for ToF-SIMS characterization of fuels (coal and biomass) and cancer tissue.

References


Bimetallic Catalysis with Homo- and Heterobimetallic Complexes

Nature often uses metals such as iron, copper, or cobalt in the active sites of enzymes to enable difficult reactions. In many instances, two or more metals are present that can cooperate to lower the barriers for reactions and enable faster reactivity. In organic synthesis, however, catalysts containing only a single transition metal are generally employed. In our laboratory, we are designing transition metal complexes containing two different metals as catalysts for organic synthesis. The second metal is specifically designed to interact with the catalytically active metal in such a way as to accelerate the overall rate of the reaction. Using this strategy, we are developing catalysts with unprecedented reactivity and exploring the development of new types of reactions that don’t work with traditional single-metal catalysts. Many of the complexes that we synthesize are air and water sensitive, and thus much of the chemistry performed for this project takes place in an inert atmosphere glove box. Students on this project learn organic and inorganic synthesis, air-free reaction techniques, and spectroscopic techniques such as NMR, mass spectrometry, and X-ray crystallography.

α-Helical Peptide Scaffolds as Modular, Tunable, Enzyme-Like Catalysts for Multistep Synthesis

The enormous breadth of chemical reactions performed in biological systems can be attributed to nature’s ability to construct highly ordered arrangements of catalytic functional groups, or enzyme active sites. In addition, many organisms have evolved the ability to assemble polyketide synthases (PKSs) or multienzyme complexes that are capable of performing multistep synthesis in a linear fashion. Chemists have tried to mimic nature’s efficiency by constructing multifunctional catalysts or by designing multicomponent reactions. In this project, we are investigating the use of short helical
peptides to scaffold multiple organic catalysts (transition metals, organocatalysts, Lewis acids) in close proximity in order to facilitate enzyme-like catalysis. This template approach will provide a new strategy for designing and optimizing catalysts that takes advantage of substrate preorganization and proximity to improve catalytic activity. The helical scaffold will also make possible the design and construction of multifunctional catalysts capable of performing multistep synthetic processes. Our catalysts are synthesized using microwave-accelerated solid phase peptide synthesis, and students on this project learn to analyze their catalysts and reactions using HPLC, NMR, mass spectrometry, and circular dichroism. We also perform kinetic experiments to quantify the reactivity of our enzyme-like catalysts.

**Design and Synthesis of Organic Crystals for THz Generation Applications**

THz spectroscopy has many applications in biological and medicinal sensing, in airport and national security, and in chemical detection and identification. The highest intensity THz sources for these applications are organic single crystals that generate THz waves via optical rectification with IR laser pulses. In a collaborative project between our group and the Johnson Spectroscopy lab, we are designing, synthesizing, and testing new THz-generating organic crystals. These efforts include computational design of new molecules, in-lab synthesis of new candidates, and the development and optimization of new methods for crystal growth and polishing. This collaborative research involves the efforts and expertise of students interested in physical and organic chemistry, as well as chemical engineering students. Students on this project learn organic synthesis and purification techniques, crystal growth techniques that include slow evaporation and slow cooling processes, and X-ray crystallography.

**Medicinal Chemistry with PROTAC-Based Cancer Therapeutics**

Protein-targeted Chimeras are bifunctional molecules that contain a binding ligand for a target cancer protein on one end and a ligand for an E3 ligase on the other. The cancer treatment strategy involves recruiting the E3 ligase into the vicinity of the up-regulated cancer-related protein to facilitate protein poly-ubiquitination and natural cellular degradation by the proteosome. In this manner, cancer-related proteins can be down-regulated with the cell’s natural machinery as a strategy for slowing cell growth and proliferation. With the JC Price laboratory, we are designing, synthesizing, and doing structure-activity-relationship (SAR) studies on new PROTACs aimed at studying and understanding protein regulation in prostate and brain cancer models. On this and other medicinal chemistry projects in the lab, students learn organic synthesis and purification techniques, and interface with the Price group to learn cell assay and biological mass spectrometry techniques.
References


**Protein engineering to accelerate scientific discovery**

Currently, we are working to develop generalizable protein engineering-based methods to facilitate protein structure determination by x-ray crystallography. We are also working to develop methods to re-engineer radical SAM enzymes to catalyze arbitrarily-chosen radical-mediated chemical reactions.

**Moody laboratory approach**

Novel protein crystallization chaperones:

X-ray crystallography allows us to determine the structure of proteins at the atomic level, helping us to understand how protein dysfunction causes disease, develop new treatments, and engineer new protein-based tools. Unfortunately, x-ray crystallography is only useful for those proteins that can be induced to form ordered crystals, about 10% of all known proteins.¹

**Protein → Crystals → Diffraction data → Electron Density → Protein structure**
Crystallization chaperones are an exciting new way to help difficult proteins crystallize. A crystallization chaperone is a helper protein that helps another protein to crystallize more easily. We are investigating a new paradigm in crystallization chaperones, multivalent crystallization chaperones (MVCCs). MVCCs display many copies of the target protein around the chaperone in a defined spacing and orientation. This helps to pre-program some of the crystal packing and lends avidity to strengthen any weak contacts made by the target protein.

One potential MVCC is TELSAM, based on the human translocation Ets leukemia protein (TEL) sterile alpha motif (SAM) domain. TELSAM spontaneously forms a 6-fold helical polymer, but only at low pH. Fusing proteins of unknown structure to TELSAM nearly always results in crystals, making TELSAM an exciting MVCC candidate. We are working to design and test new versions of TELSAM that will work better and for a larger set of protein targets.

**The TEL-SAM polymer (magenta) fused to lysozyme (cyan)**

Novel enzymes for radical-based chemistry:

While many other types of enzymes have been designed or re-designed through computational or experimental enzyme engineering, radical SAM enzymes have yet to be explored as rationally-engineered synthetic catalysts. We are computationally engineering radical SAM enzymes to accept novel substrates. Radical SAM enzymes create highly reactive organic radicals and use them to accomplish a huge variety of high-energy chemical transformations in substrate molecules, nucleic acids, and other proteins.

**Radical SAM activation mechanism**
Proposed enzyme-catalyzed radical cyclization reaction mechanism

In the Moody lab you will learn computational protein modeling and design, molecular biology techniques, protein biochemistry, and macromolecular X-ray crystallography. If you’re interested, I’d love to talk with you! We welcome dedicated, hardworking students with all levels of experience, Freshman through Senior. Be prepared to spend at least 10 hours per week during Fall and Winter semesters in the lab to make meaningful progress.

References

Materials Science is a very important area of current research. This interdisciplinary field involves aspects of chemistry, physics, and engineering. Our interest lies mainly in establishing the molecular basis for bulk properties of materials and how those properties are affected by external stresses. In many cases, the properties of the material that are the most important are the surface and interface properties. This is particularly important with composite materials, where two different materials are directly in contact with each other, and in mechanical processes such as lubrication and adhesion.

Response of Materials to Mechanical Stress

We are also interested in how materials respond to mechanical stress at the molecular level. We use nonlinear spectroscopy, specifically sum-frequency generation (SFG) and second harmonic generation (SHG), to probe the surfaces of materials before and after they are subjected to mechanical deformation. With these techniques, we are able to identify spectroscopic signatures of mechanical stress due to molecular-level changes at the surface of the material. These approaches have great potential for use in nondestructive testing and materials state awareness applications.

Molecular Basis for Adhesion

Because SFG can probe buried interfaces as well as free surfaces, we can investigate the molecular structure of bonded and composite materials. In a bonded system, two surfaces are held in mechanical contact by a layer of adhesive. Unfortunately, a full molecular basis for adhesive interactions has not been developed, primarily because of a lack of molecular level information on such systems. We want to systematically investigate bonded systems, such as polymers on solid substrates, industrial
adhesive materials, and composite materials, to understand how changes in the molecular structure affect the strength of the adhesive interactions and other material properties. This investigation includes both static and dynamic experiments.

We also want to understand the formation of adhesive bonds. Scientific questions we want to address are: What are the chemical and structural changes that take place as an adhesive cures? How do changes in the environment affect this bond formation? We also want to investigate aging phenomena. How does the structure of the adhesive interface change over time, leading to bond failure? The results of this research program will be applicable to other fields such as materials science and mechanical engineering.

*The Interface of Science*

Our research focuses on interfacial systems, but we are also interested in exploring interfaces of science. Other fields we could explore include mechanisms of chromatographic separation, biocompatible materials, interfacial properties of nanomaterials, heterogeneous atmospheric chemistry, lubrication, and others. Such projects will most likely involve collaboration with other members of the department and groups in other departments both on campus and at other universities. With the spectroscopic tools available to us, we are excited at the prospects of exploring a wide variety of interfacial systems. Our group is open to beginning students who have done well in their freshman courses, as well as more advanced students.

*References*

Soft Nanotechnology. One longstanding goal in nanotechnology is to create active matter and life-like artificial cells that exhibit autonomous behavior in response to environmental cues and programmed instructions. Mastering the physicochemical principles that govern the organization, reconfiguration, and actuation of soft matter would usher in a new era of soft micro- and nanomachines (MNMs). However, many of the mechanisms that would enable desired actuation in artificial cells and soft machines are not fully understood, and biomimetic membranes that controllably change their shape do not yet exist.

Toward this end, we aim to theoretically model and experimentally create minimal artificial cells with membranes that change their shape and other properties in response to a wide range of chemical stimuli. We are focusing our efforts on coupling i) pH-responsive supramolecular vesicle membranes to ii) catalysts that change pH. We target pH-responsive membranes because they can be activated not only by direct pH changes, but also indirectly by a wide range of chemical signals translated into pH changes via catalysis. We are using these materials to create smart containers for drug delivery and change the properties of interfaces in new kinds of biosensors.

Desirable morphological transformations (shape changes) and related functions in biomimetic micro- and nanomachines (MNMs).
Electricity from Sugar. We are also developing a new kinds of reusable electrode that can turn carbohydrates into electricity.\textsuperscript{3} Early results are promising for developing a new kind of reusable fuel cell that can turn wasted carbohydrates from food production (like the 2 million metric tons of whey permeate produced in the US each year from the Greek yogurt industry) into energy, turning food WASTE into electrical WATTS.

References


Research in our lab focuses on the design, synthesis, and biological evaluation of anticancer and/or antiviral compounds. Target molecules include medicinally important nucleosides and/or non-nucleoside small molecules with druglike properties. We also have an interest in the development of new synthetic methodologies, generally inspired by modeling results or other Computer Assisted Drug Design elements. Recent research focuses on optimization of kinase inhibitors, especially inhibitors of VPS34.\textsuperscript{1} We have also performed research targeting inhibitors of VEGFR2 and BMPR1b.\textsuperscript{ii} Inhibitors of these kinases effectively block cell signaling events that are involved in a variety of cancers including melanoma, lung, breast, ovarian, colon, and prostate cancers. Many of our targets have also been screened for antiviral activities, with some showing promising (low micromolar) activities against several viruses of emerging concern (e.g. Ebola).

A unifying feature in recent research has been application of a modular approach to preparing libraries of pyrazolo[1,5-a]pyrimidine derivatives for biological screening. We have developed an efficient microwave assisted synthetic method that allows rapid preparation of novel members of this class of compounds in as little as one hour total reaction time, with most compounds yielding readily to one-step recrystallization (Figure 1).
An example of one of our recent methodologies is illustrated in Figure 2.iii

\[
\begin{align*}
\text{PhCH}_2\text{NMe}_2\text{Cl}_2 (1.2 \text{ equiv}) & \quad \text{NH}_4\text{SCN (1.1 equiv)} \\
\text{S} & \quad \text{NH}_2 \\
\text{DMSO}:\text{H}_2\text{O} (9:1) & \quad 70 \, ^\circ\text{C}, 1 \text{ h} \\
75-97\% & \quad (\text{Ave} = 90\%) \\
19 \text{ examples} & \quad (50 \text{ mg} \cdot \text{g scale})
\end{align*}
\]


Figure 2.

We have also discovered N\text{\text{\textsuperscript{6}},5\text{\text{\textsuperscript{i}}}}-\text{bis}-\text{ureido}-\text{adenosine} derivatives that exhibited potent and selective activities against a broad range of human cancers, with our top analogue in this series inhibiting Lung Adenocarcinoma with low nanomolar activity (IC\textsubscript{50} = 9.7 nM).iv Other nucleoside derivatives synthesized in our lab include 6-[alkyl-heteroaryl)furo[2,3-d]pyrimidin-2(3H)-one antiviral nucleosidesv as well as 3-deaza-3-fluorouridine,vi a promising anticancer compound with mechanism of action unique from its parent 3-deazauridine (Figure 3).

Figure 3.
References


My research explores mechanisms used by living cells to control the quality and concentration of each molecule of our body. The complexity of this task is really astounding. For example, there are ~20,000 different protein types in each cell of your body. The quality and concentration of each one is carefully controlled in a condition generally referred to as protein homeostasis. When protein homeostasis fails, we quickly develop diseases like Alzheimer’s, diabetes, and cancer. Similar problems occur when the homeostasis of lipids or other metabolites fails. A big effort in our lab is developing the tools to study the processes supporting homeostasis in vivo and understand what changes as homeostasis is lost. Specifically, we use stable isotopes to label newly-synthesized molecules with a time-dependent tag. With a mass spectrometer, the time-dependent stable isotope enrichment and relative concentration of many molecules can be measured even within a complex mixture. This allows us to calculate synthesis and degradation rates simultaneously for many molecules in the body as it responds to stimuli. This allows us to perform experiments that survey broad sections of the proteome, and compare against DNA, RNA, or small molecules produced by enzymes within the cell. We have successfully used this technique in many different biosynthetic systems from "cell free" environments to humans. Currently, we are focused on understanding post-transcriptional control of the proteome composition within cells, especially on the changes associated with aging or disease as well as how protein degradation is regulated to maintain homeostasis. If you find these research questions interesting, then please come talk to me. I am always open to working with motivated students.

*Regional control of metabolism*

One method of controlling chemical reaction rates is to compartmentalizes enzymes and substrates inside of the tissue or the cell. We are incorporating metabolic labeling, metabolomics, and
proteomics with surface imaging mass spectrometry to understand how regional regulation of metabolism within a tissue changes with disease and aging.

**Maintenance of proteome homeostasis through protein degradation**

Many of today’s most devastating diseases can be identified as diseases of protein homeostasis. Parkinson’s, Alzheimer’s, Huntington’s, diabetes, and other diseases all exhibit cellular deposits of aggregated protein. These aggregates are often highly resistant to degradation and may indicate a dysfunction within the catabolic machinery of the cell. Continuous protein catabolism is critical in the presence of constitutive transcription and translation, yet these processes are poorly understood. The cell employs thousands of proteins (ubiquitin ligases, targeted proteases, proteasome, etc.) to guide the process of protein degradation. Thus, the complexity of the regulatory structure for removing a protein from the cell may be comparable to producing the protein in the first place. Our current work is focused on identifying the substrates for cellular proteases and understanding how targeted proteolytic processing is used by the cell.

**References**


Chemical Biology, Protein Folding and Structure

We are broadly interested in how proteins and polypeptides fold and adopt the beautiful three-dimensional conformations that ultimately give rise to their diverse functions. We want to understand noncovalent interactions along with the impact of modifying protein side chains (via glycosylation, phosphorylation, or with unnatural polymers like polyethylene glycol) on the stability and folding of the modified protein.

Our motivation for this work derives from the increasing promise of therapeutic proteins as treatments for conditions that are difficult to address with conventional small molecule therapies (cancer, chronic inflammatory and auto-immune disorders, anemia, neutropenia, etc.). Despite many recent successes, several problems continue to limit the usefulness of proteins as drugs: (1) they must be injected to avoid digestion by gastrointestinal proteases; (2) they are quickly cleared from blood via kidney filtration and proteolysis by serum proteases; and (3) they can adopt non-functional unfolded or misfolded conformations, which can then self-associate to form aggregates, sometimes leading to undesired side effects, including immune responses.

Increasing protein thermodynamic stability could address these problems because

![Figure 1](image-url)
thermodynamic stabilization increases the population of the pharmacologically-active folded state, while decreasing the populations of the protease-sensitive unfolded ensemble and/or aggregation-prone misfolded states. My research group is interested in developing reliable strategies for increasing protein stability.

One potentially useful strategy is to attach an ethylene oxide oligomer (i.e. polyethylene glycol or PEG) to a protein, typically by reacting a functionalized PEG electrophile with one or more nucleophilic side chain groups on the protein surface (this approach is hereafter called PEGylation). The bulky size of the attached PEG can block proteins from self-associating to form aggregates, can shield immunogenic epitopes on the protein surface, and can prevent the PEGylated protein from being filtered out of the bloodstream by the kidneys. We believe these beneficial effects could be further enhanced if PEGylation consistently led to increases in protein thermodynamic stability. However, little is known about the conditions under which PEGylation of a protein is energetically favorable.

We are currently working on uncovering the fundamental principles that allow PEGylation to increase protein thermodynamic stability; to understand which secondary structures (sheets, turn, or helices) are most amenable to PEG-based stabilization; and whether favorable interactions between PEG and nearby protein side chains can increase this stabilizing effect. We are always willing to talk about research with undergraduate students; beginning students are welcome to apply!

References


4. Xiao, Q.; Bécar, N.A.; Brown, N.P.; Smith, M.S.; Stern, K.L.; Draper, S.R.E.; Thompson, K.P.; Price, J.L.*

The ability to synthesize complex molecules enables organic chemists to influence, and in some cases control, biological processes. Our research group prepares new compounds and studies their interactions in multiple biological settings.

**Development of Antibacterial Agents, Control of Their Cell Selectivity**

Continuing emergence of drug-resistant bacteria has become a major health concern and may lead to untreatable infections in a vast number of people and animals. As a means of controlling bacterial growth without causing bacterial resistance, organisms ranging from bacteria to mammals produce peptide antibiotics that disrupt bacterial membranes. We have been interested in mimicking the antibacterial activities of these peptides using cationic steroid antibiotics developed in our laboratory. This research has led to preparation of multiple series of new potent antibiotics (e.g. structures 1 and 2).

![Chemical structures 1 and 2](image)

These compounds rapidly kill a broad spectrum of bacteria (both Gram-negative and -positive), demonstrate selectivity for prokaryotic cells, and are unlikely to induce formation of resistant strains. We are currently using these compounds to study how small molecules can be used to disrupt bacterial membranes. We are also working to improve the potency and cell selectivity of the antibiotics. Research on this project spans a number of disciplines. Studies involving titrations to determine binding constants are performed, new compounds are synthesized, and bacterial susceptibilities are measured.
Stimulation of Natural Killer T Cells and Generation of Conjugate Vaccines

As the immune systems of higher organisms become better understood, the abilities of relatively small molecules to cause potent immunological responses become clear. An aspect of innate immunity in mammals governed by interactions with glycolipids is currently being elucidated. Association of glycolipids with a protein, termed CD1d, on antigen presenting cells is followed by binding of the glycolipid-CD1d complex with a T cell receptor on natural killer T (NKT) cells. Depending upon the structure of the glycolipid, the NKT cells can release a variety of potent chemical messengers. Release of these chemical messengers, called cytokines, can cause a strong up-regulation of the immune system (T helper 1 mediated). Responses from stimulation of NKT cells can be harnessed to improve the effectiveness of vaccines. We are preparing carbohydrate-based vaccines containing bacterial antigens, conjugating these on self-assembling protein nanoparticles and using NKT cell responses to give strong memory responses to the bacterial antigens.

Recent Papers


We are interested in studying events involving highly excited molecules with a “chemically significant” amount of energy. Highly excited molecules are of great importance, due to their reactivity; however, they are often extremely difficult to study as a result of their complexity. Reactants are produced using laser pumping techniques after which we observe the outcome of either a bimolecular collisional energy transfer event, or a unimolecular or bimolecular reaction. The goal of our studies is to understand these chemically significant events in a quantum state resolved fashion with detail that was, until recently, only dreamed of. We use novel high resolution spectroscopic techniques (~0.0003 cm⁻¹) to study the amount of energy distributed in the various energy states (vibration, rotation, and translation) of molecules after a reaction or collision. Current projects can be divided into three general categories:

**Collisional Energy Transfer**

Collisional Energy Transfer is one of the key steps in the Lindemann mechanism for unimolecular reactions. Collisional deactivation competes with chemical reaction by removing enough energy to bring the reactant species below threshold. By studying the final rotational and vibrational quantum states as well as the translational energy distributions of simple collision partners, we can establish the probability of transferring a specific amount and type of energy. The results from this quantum state picture can be converted into a probability distribution function, which provides information about the transition state and potential energy surface of the interaction.

**Photo-Induced Chemical Reaction Dynamic and Kinetics**
Using similar techniques, it is possible to track the products of a photodissociation process with quantum state resolution. Because the molecules used to study collisional energy transfer have such a large amount of energy (~5 eV), they are literally ready to explode into molecular and atomic fragments when the collision event takes place. Unimolecular decomposition is thus in competition with collisional energy transfer. By probing the molecular fragments, it is possible to follow the course of these photo-induced chemical reactions with detail never before observed. It is possible to extract not only the reaction rate, but also learn a great deal about fundamental properties of chemical reactions.

**Combustion Chemistry**

The combustion of methane is of considerable importance in the generation of energy; thus, it has received considerable attention. This apparently simple chemical reaction is actually not so simple. The kinetics of the reaction of methyl radicals with oxygen atoms, the key step in the overall combustion process, has been studied extensively; however, a consensus has yet to be reached in our understanding of this important reaction. Some of the controversy is potentially tied to methyl radical production. Understanding the photodissociation dynamics of methyl radical precursors, particularly the partitioning of energy among the various quantum states, is of utmost importance if a completely clear picture is to be obtained for the reaction of CH3 with O (3P). It is highly improbable that various methods of CH3 production produce radicals with the same characteristics; thus, the outcome of subsequent reactions will also, most likely, be different. In addition to performing a detailed quantum state resolved study of methyl radical formation, we are also interested in studying the subsequent chemical reactions.

**References**


Welcome to the Stowers Laboratory!

We expect students to be hardworking and dependable, committed to learning to do hard things, and enthusiastic about research. It's okay if you feel like you don't know enough about chemistry to work with us - many students felt the same way when they got started. It would be great if you could attend group meetings in order to get to know the lab and the projects. Because students are so much more productive when not also juggling a full course load, we prefer to have students join who are willing to commit to working over the spring/summer term. Chemistry students are preferred, but we've had other majors who have worked with us. The following are three active areas of research in the group:

1) Inorganic Synthesis of Heterogeneous Catalysts

We have found that many catalysts are sensitive to the types of preparations and additives to be highly active for a particular reaction. Synthesizing and characterizing catalysts with precision will allow us to determine how reacting molecules interact with the surface. Understanding the interactions of molecules and the active sites of the catalyst ultimately lead to designing even better catalysts. Students on this project will synthesize inorganic catalysts and determine the catalyst structure by a variety of techniques including microscopy and spectroscopy. We use these catalysts in a flow reactor where molecules in the gas phase react to form new products, which are detected by an online spectrometer.

2) Mechanistic Studies on Catalyst Surfaces

We use a stainless steel chamber at ultra-high vacuum in order to probe how organic molecules react at a metal surface without the competition of air or water molecules that usually cover surfaces. By using X-ray photoelectron spectroscopy, we can find out information regarding concentration, oxidation state, and elemental composition of intermediates on the surface. A heating ramp allows us to find out how
the reactants react and desorb from the surfaces. We use many model catalysts as a means for designing new catalysts, designing new reactions, or better understanding known reactions at a metal surface. Students working on this project will operate and become familiar with an ultra-high vacuum chamber, in-situ XPS, and temperature-programmed reaction spectroscopy, as well as computational analysis.

3) Fine Chemical Synthesis using Heterogeneous Catalysts

The interface between solids and liquids are interesting and can be tuned with the inclusion of heterogeneous surfaces that can act as acids or bases. We are interested in what kinds of chemical bonds can be broken or formed at the liquid solid interface in the context of fine chemicals. Catalysts that we have currently used include silver and copper nanoparticles and molybdenum-based metal oxides. Students working on this project will learn bench-top isolation techniques and characterize products using NMR or gas chromatography coupled with a flame ionization detector or a mass spectrometer.

Sample publications:


Investigation and treatment of Fibrotic Diseases including: muscular dystrophy, pulmonary fibrosis and cancer.

Identification of Protein Therapies for Muscular Dystrophy

The muscular dystrophies are a group of degenerative muscle wasting diseases that vary in age of onset, phenotype, cause, severity, and life span. Many of the treatment options for these diseases do not have substantial quality of life treatment options desperately needed for patients and families. The goal of my lab is to identify protein therapies for several different types of muscular dystrophies. We are currently using a protein called galectin-1 as a possible treatment in a subtype of muscular dystrophy called Limb Girdle Muscular Dystrophy 2B or Dysferlinopathy. It is caused by mutations in the DYSF gene (encoding dysferlin protein) and is characterized by the following: delayed removal of necrotic muscle fibers, loss of calcium sensitivity leading to signaling mis-regulation, increased inflammatory infiltrate, muscle atrophy, malformation of transverse tubule structure, and defective membrane repair. Research shows that models of Duchene muscular dystrophy treated with recombinant Galectin-1 display improved sarcolemma stability, reduced muscle pathology, improved muscle repair, and increased angiogenesis. Using several mouse and human dysferlinopathy models, we have defined the optimal dose of recombinant Galectin-1 protein to use to increase myogenesis, injury repair and decrease inflammation. We are currently conducting a long-term study and working to define the mechanism of therapeutic action.

Tissue engineering Team

We create 3D culture technologies (spheroids, organoids, microfluidic chips) to study the effects of the extracellular matrix (ECM) in organ formation. The technologies that we developed are applicable in developmental biology research, disease modeling, regenerative medicine, and drug development. Previously, we created a 3D culture plate which increases the efficiency of 3D suspension culture by
three times versus traditional culture plates. Aside from this, we also developed a novel 3D culture technique allowing organ formation while cells are suspended in ECM solution. We used this technology to create tiny lungs (called lung organoids) which are useful in modeling lung diseases including fibrosis, cancer, and hypertension. Currently, we are working with pulmonologists across the country to develop lung organoids from fibrosis patients and hopefully test pre-clinical drugs on them. These will give us robust information on patient-specific effects of the drugs.

**Idiopathic Pulmonary Fibrosis Team**

The Idiopathic Pulmonary Fibrosis Team is dedicated to uncovering new therapeutic strategies to combat the chronic, progressive, and fatal nature of IPF through clinically translatable methods. We test different therapeutics to provide novel drugs for future patient use and to find out more about the underlying condition causing IPF which is currently unknown. IPF is a lethal disease with a 5-year life expectancy after diagnosis and the two current FDA approved drugs for IPF do not improve the mortality rate. This poor prognosis for patients is what drives our lab to understand more about IPF and develop potential therapeutics. We use translatable methods to test delivery of experimentally designed drugs to measure their clinical relevance. We accomplish this through using the established animal model for IPF. We have found one of these designed drugs to show significant improvement in lung function and decreased disease biomarkers. We continue to refine drug delivery methods and doses to provide a starting point for potential human clinical trials. Our research is rooted in making a difference for those who suffer from IPF.

**References**


Bioinorganic Chemistry

Biological systems require trace amounts of transition metal ions to sustain life. Transition metal ions are required at the active sites of many enzymes for catalytic activity. In fact, transition metals catalyze some of the most energetically demanding reactions in biology. Unfortunately, these highly reactive metal ions also catalyze reactions that are dangerous for biological systems, especially if the metal ion is free in solution. For this purpose, biology has evolved elaborate transition metal ion handling systems to bind and sequester transition metal ions in non-reactive environments to prevent these dangerous reactions from occurring. The Watt lab focuses on how iron is properly moved throughout the body.

A healthy individual possesses iron trafficking systems to absorb iron from the diet, transport iron in the bloodstream, and deliver iron to cells that require iron. The failure or inhibition of these iron trafficking systems results in free iron that is a potent catalyst to form reactive oxygen species or oxidative stress.

The Watt lab studies diseases where iron trafficking is disrupted and oxidative stress is elevated. Such conditions include Alzheimer’s disease, Parkinson’s disease, kidney disease, and diabetes, along with other conditions.

Anemia of Chronic Inflammation Caused by Hepcidin

Hepcidin is an iron regulatory hormone induced by inflammation that degrades the iron transport protein ferroportin. Hepcidin causes a condition known as anemia of chronic inflammation. Ferroportin is required to transport iron into the bloodstream from the intestinal cells that absorb iron from the
diet. Ferroportin also exports iron from the liver and spleen into the bloodstream where transferrin binds iron and delivers iron to the bone marrow for red blood cell synthesis. The Watt lab has identified hepcidin inhibitors that prevent hepcidin production and stabilize ferroportin. Studies in rats show that iron delivery to the bone marrow is restored using these hepcidin inhibitors.

**Inhibitors of Iron Binding Proteins**

The Watt lab has focused on metabolites that build up in diseases with oxidative stress. We identified metabolites that disrupt iron loading into ferritin and transferrin. In chronic kidney disease, serum phosphate levels increase because the kidneys are not properly filtering phosphate from the bloodstream. We demonstrated that elevated phosphate inhibits iron loading into ferritin and transferrin by forming insoluble iron phosphate complexes. We are now focusing on other
elevated metabolites to determine if they also disrupt normal iron loading or release of iron from ferritin or transferrin.

**Alzheimer’s Disease**

Iron dysregulation is intimately connected to Alzheimer’s disease (AD) but the direct connections are not clear. A new hypothesis relating to homocysteine disrupting iron loading into ferritin might explain the elevated cytosolic iron and oxidative stress. The inability to load iron into ferritin results in elevated cytosolic iron which upregulates expression of the Amyloid Precursor Protein (APP). Homocysteine also inhibits the phosphatase that dephosphorylates tau leading to elevated hyper-phosphorylated tau and tau tangles. We are testing this hypothesis in collaboration with Dr. Jonathan Wisco in the BYU PDBio department.

**Diagnostics**

For each of the situations outlined above, we are developing point of care diagnostic methods to evaluate known biomarkers. The goals of the diagnostics research are two-fold. First, we are modifying and developing new methods related to antibody detection methods to provide increased sensitivity for this type of analysis. We also focus on particular biomarkers that give diagnostic information to aid clinical practitioners identify the most beneficial and effective treatment.

**Selected Publications**


Mechanisms of Assembly of Signaling Complexes

Most cellular functions are performed by proteins associated together into complexes. In fact, many proteins cannot exist in the cell without their binding partners. These protein complexes often require the help of other proteins, called chaperones, to bring the complexes together. This is certainly the case for protein complexes involved in cell signaling processes. Our work has focused on the mechanism of assembly of two types of signaling complexes, the G protein heterotrimer and the mTOR kinase complexes. It is through the G protein complex and its associated receptors and effectors that cells detect hormones, neurotransmitters, chemokines, and sensory signals, such as odorants, taste molecules, and even photons of light. G proteins regulate almost every aspect of cellular physiology, and as a result, more than a third of current therapeutic drugs target G protein signaling pathways. The two mTOR complexes, mTORC1 and mTORC2, are also high-value drug targets because of their role in orchestrating cell survival, growth, and metabolism in response to growth hormones and nutrient levels.

Both G protein and mTOR complexes are assembled with the help of the cytosolic chaperonin CCT (also called TRiC), a large protein folding machine with a double-ring structure of eight different chaperonin subunits in each ring. The center of each ring creates a protein folding chamber in which nascent proteins with intricate folding trajectories bind and are assisted in the folding process. One such protein fold is the β-propeller, which commonly has seven β-sheets that form the blades of a propeller-like circular structure. β-propellers have a unique folding trajectory that requires the C-terminus to interact with the N-terminus to make the last β-sheet that closes the β-propeller. CCT is believed to facilitate this process. We have found that the β-propellers of the G protein β subunit (Gβ) and the mLST8 and Raptor subunits of mTOR complexes are folded by CCT prior to their assembly into complexes.
The process of G protein heterotrimer assembly begins with the association of the G protein β subunit (Gβ) with the G protein γ subunit (Gγ) into the Gβγ dimer. Gβγ is an obligate dimer, meaning that neither subunit is stable in the cell without the other. As a result, Gβ and Gγ must be brought together by chaperones. At some point during or after translation, the nascent Gβ subunit binds CCT and is folded into its β-propeller structure. However, the β-propeller is not stable in the absence of the Gγ subunit, and Gβ cannot associate with Gγ until it is released from CCT. This conundrum is resolved by the CCT co-chaperone, phosducin-like protein 1 (PhLP1). PhLP1 binds Gβ in the CCT folding cavity and initiates the release of Gβ from CCT. Once released, Gγ is able to bind Gβ in the PhLP1-Gβ complex and form the stable Gβγ dimer. The G protein α subunit then associates with Gβγ, forming the active Gαβγ heterotrimer and simultaneously releasing PhLP1. All four of the typical Gβ subunits are assembled with their 12 associated Gγ subunits by this same mechanism involving CCT and PhLP1.

The atypical Gβ5 subunit forms a dimer with regulators of G protein signaling (RGS) proteins of the RGS7 subfamily. These dimers have a different function than Gβγ dimers. They turn off G protein signaling in neurons by accelerating the rate of GTP hydrolysis on the Gα subunit. We have found that CCT and PhLP1 also assist in the assembly of these Gβ5-RGS complexes. In fact, the conditional deletion of the PhLP1 gene in the rod photoreceptor cells of mice results in the loss of the Gβ5-RGS9 dimer from these cells in addition to the loss of Gβγ dimers. Consequently, G protein-dependent responses to light by rod photoreceptors were diminished and their recovery was slow. These findings have confirmed the importance of PhLP1 in Gβγ and Gβ5-RGS dimer formation in vivo.

In the case of mLST8 and Raptor, both of their β-propeller domains are folded by CCT. They then release from CCT independently of PhLP1 to associate with mTOR. Cryo-EM structural studies of the Gβ-CCT and mLST8-CCT complexes, done in collaboration with the lab of Jose M. Valpuesta at the Centro National de Biotecnologia in Madrid Spain, show that the β-propellers of both proteins have reached a near-native state while bound to CCT, but they associate with CCT very differently.
Despite their structural similarity (Figure 1), Gβ binds the CCT apical domains at the top of the CCT folding chamber similar to actin, another CCT substrate, while mLST8 binds CCT at the bottom of the folding chamber between the CCT rings, which has not been previously seen with any CCT substrate. These positions explain the effects of PhLP1, which can interact with Gβ at the top of the chamber and mediate its release, but it cannot access mLST8 between the rings. These structural studies provide the molecular details needed for structure-based therapeutic design to control the folding and thereby the function of these important CCT folding substrates.

My lab typically brings on undergraduates at the beginning of their junior biochemistry courses, but talented sophomores have occasionally joined in the lab as well. Successful students can expect to co-author a top-tier publication and compete for acceptance in the best graduate or medical schools.

References


G protein assembly and signaling in retinal rod photoreceptors.” *J. Neurosci.* 33, 7941-7951.

*Selected in Faculty of 1000*
Chemical Thermodynamics

While commercial specific heat apparatuses using relaxation methods exist, our custom designed and built instruments are capable of accuracies and precisions approaching, and even exceeding, 0.1%. This type of accuracy and precision allows us to study a wide range of interesting and relevant topics in solid-state physics and chemical thermodynamics. Shown below is an example of our measurements on a bulk sample of MnO and a sample of the collosal magnetoresister La1-xSrxF3.

Currently, our primary research interest is in the energetics of nanomaterials, which is funded by the Department of Energy. Our focus in this research project is to understand the fundamental driving forces governing the stability of materials as their particle sizes reach the nanoscale. We have done extensive work on high quality samples of the TiO2 polymorphs of anatase and rutile with sizes of 7 nm and on the magnetic material CoO.

Fisher-Tropsch Catalysis
We have created a Fisher Tropsch research focus in collaboration with the Catalysis Group in Chemical Engineering. We have applied our proprietary solvent deficient precipitation method to synthesize a series of industrial viable and state-of-the-art alumina catalyst supports and Fe and Co Fisher Tropsch catalysts. These supports and catalysts have tunable properties and perform better than any catalysts currently reported in the literature. We continue to focus our work on innovating in the catalysis area using our proprietary solvent deficient method.

**Synthesis of Nanoparticles**

We have recently developed an elegantly simple process that allows us to make a nearly unlimited array of well-defined inorganic nanoparticles that have controlled sizes from 1 nm to bulk. The particles are highly crystalline with well-defined shapes (usually spherical but also rods). We can synthesize them with chemical and phase purities as high as 99.9999%, we can control the particle size distribution to approximately ±10%, and we project with confidence that we can make industrial size quantities with manufacturing costs significantly less than any other current technique. The types of particles we can make are, in general, metal oxides, but the process allows us to control the oxidation state so we can make high, medium, and low oxidation state oxides and metals. We can make oxides of all of the transition metals, lanthanides, and actinides, and any stoichiometric combination of any number of these metals. We can include group I and group II metals in combination with the transition metals. Consequently, we have the ability to make an almost innumerable array of nanomaterials (single metal and multi-metal) with well-controlled physical properties, purity, oxidation state, size and size distribution using a process that is fast, reliable, and inexpensive. Table 1 gives examples of some of the materials we have synthesized, and below are some representative TEM images for NiO, Y2O3, and CoO powders.

<table>
<thead>
<tr>
<th>Material</th>
<th>Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoO</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Co₃O₄</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>NiO</td>
<td>3 ± 0.5, 9 ± 1</td>
</tr>
<tr>
<td>CuO</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>ZnO</td>
<td>8 ± 1, 16 ± 1</td>
</tr>
<tr>
<td>Al₂O₃</td>
<td>2 ± 0.5, 8 ± 1</td>
</tr>
<tr>
<td>In₂O₃</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>SnO₂</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>LiCoO₂</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>NiFe₂O₄</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Zn₄₋₃Co₆₋₃Fe₂O₈</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Li₀.₇₅Zn₀.₃Ni₀.₃Fe₂₀.₇₅O₄</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Y₂O₃</td>
<td>1 ± 0.5, 13 ± 1</td>
</tr>
<tr>
<td>Nd₂O₃</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>Ag₂O</td>
<td>65 nm</td>
</tr>
<tr>
<td>Ni</td>
<td>40 nm</td>
</tr>
</tbody>
</table>
My group works at the interface between chemistry, engineering, and biology. Thus, students receive broad technical training and are well positioned to contribute in these key research fields. A common theme in my research is the interrelationship between biological molecules and miniaturization. We are utilizing miniaturization tools to analyze for clinically relevant biomolecules, and we are also applying DNA in forming nanoscale materials.

**3D Printed Integrated Microfluidic Systems for Preterm Birth Risk Assessment**

Preterm birth (PTB) is a serious issue, with approximately 10% of pregnancies resulting in a preterm delivery, frequently coupled with complications that lead to poor outcomes and increased medical costs. We are developing 3D printed microfluidic systems that integrate various analytical processes in a single microchip (Figure 1). These devices will provide high-throughput, point-of-care screening from a finger prick quantity of blood to assess risk of a preterm delivery, weeks before contractions begin.
Biotemplated Nanofabrication of Electronics

My group is leading an interdisciplinary team whose objective is to explore bottom-up methods for the fabrication of nanoscale electronic systems. We fold DNA into controlled nanoscale designs that can be converted into functional electronic elements after metallization (Figure 2). We are presently applying these methods in making conductive metal nanowires and metal-semiconductor junctions with linewidths as small as 10 nm.

Rapid Blood Infection Determination

We are developing methods for rapid determination of bacterial infections in blood, including antibiotic susceptibility testing on single bacteria, in collaboration with a group of biologists and engineers. A schematic of the proposed approach is shown in Figure 3. In this multidisciplinary effort, we are creating microfluidic systems with solid supports designed to selectively capture and fluorescently label nucleic acid sequences from pathogenic organisms in blood. We are also working with microfluidic devices to encapsulate individual bacteria in droplets and then probe their susceptibility to common antibiotics.

References


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