UNDERGRAD RESEARCH BOOKLET

2026-2027

2025-2026

BYU DEPARTMENT OF CHEMISTRY & BIOCHEMISTRY

UNDERGRADUATE

RESEARCH PROGRAM

Department of Chemistry and Biochemistry

Brigham Young University

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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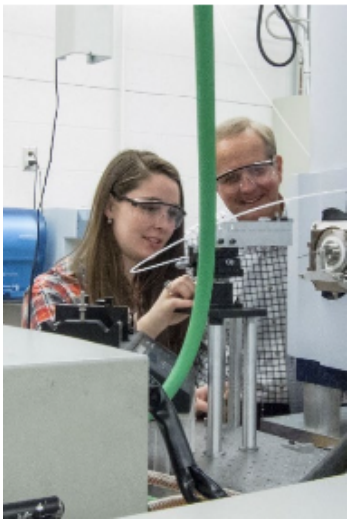
Undergraduate Research Awards (URA)



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 **Academics**, then **Undergraduate Research Awards**. There you will find the process to apply for a URA.
    1. Applications open at the beginning of Fall and Winter semesters. The form will not be reopened once the application period has closed.

2. If renewing for a URA, follow the process outlined on the department's website. (https://www.chem.byu.edu/academics/undergraduate-research-awards/)

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 a club for chemistry and biochemistry students designed to help them success in their classes, make friends in their major, and prepare for a future career with a degree in chemistry or biochemistry. Y-CHEM is also the student chapter of the Central Utah Section of the American Chemical Society. 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. We strive to share our love of science with others, while helping them with challenges they may encounter along the way. We work closely with the department professors and administration staff to plan events and provide our club members with useful resources. One of our main goals is to help students succeed in their chosen discipline, and many of our activities are directed to this end. Some examples of past activities include fundraising to sponsor students attending national meetings, graduate school preparation, fun club events designed to foster friendships, 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. Many Y-CHEM members are trained to perform chemistry "magic shows", which are 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. We also put on an annual community outreach event called Open Lab Day. During Open Lab Day, our club members engage with junior high and high school students by helping them perform exciting science experiments in the Benson Building.

The international chemistry community is relatively tight knit. It is quite possible that today's classmates will become tomorrow's colleagues and employers. We are passionate about promoting networking amongst peers. Y-CHEM also offers its members opportunities to interact with professors and these professors often become valuable contacts and can offer excellent career advice.

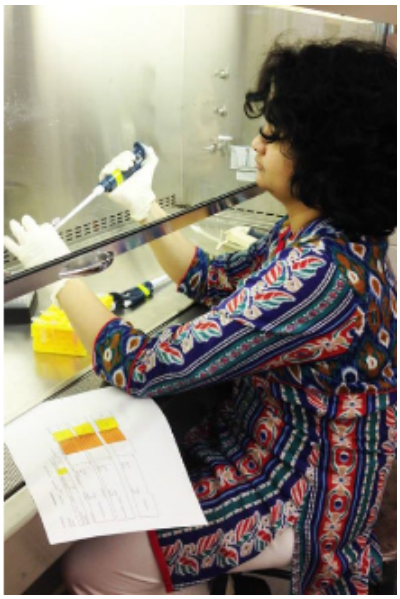
Y-CHEM provides a great opportunity to learn, grow, serve, and associate with fellow chemists. We are always excited to hear what suggestions members have, helping us grow and improve our club!

Sincerely,

Y-CHEM Presidency

To join or to find more information, please visit our website at https://ychem.prod.brigham-young.psdops.com/ or contact us at ychem@byu.edu.

Research Facilities



Research activities occupy more than 50 percent of our 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.

For more information on the Chemistry and Biochemistry's facilities, visit our department website at: https://www.chem.byu.edu/department/research-facilities-and-instruments/.

FACULTY RESEARCH PROFILES

MERRITT B. ANDRUS, PHD

Organic & Biomolecular Chemistry

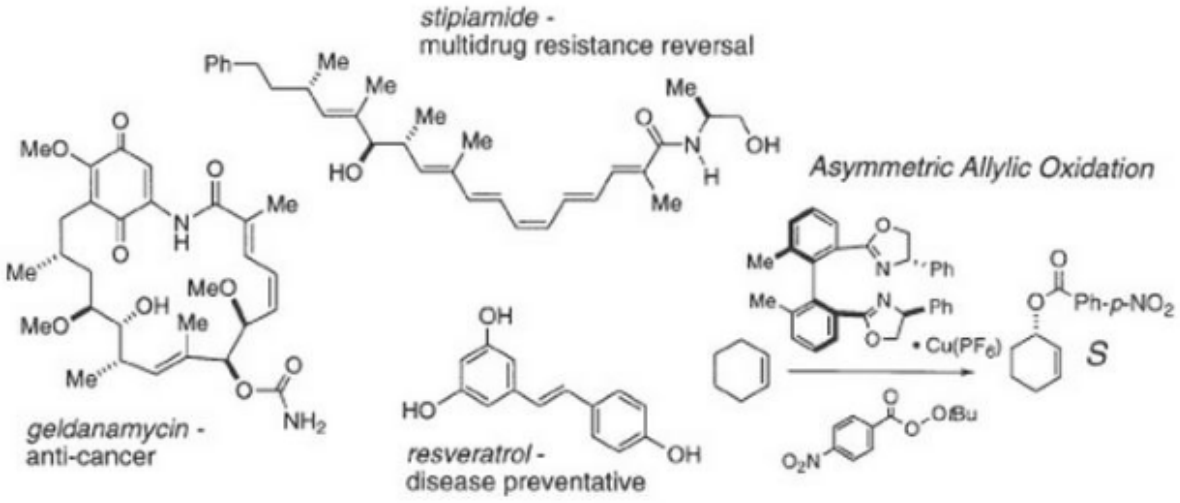
C410 BNSN, 422-8171

Email: mbandrus@chem.byu.edu

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 prevatative 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

1. Acerson, M. J.; Bingham, B. S.; Allred, C. A.; Andrus, M. B. Design and Synthesis of Terpene Based Englerin A Mimics Using Chromium Oxide Mediated Remote CH2 Oxidation. *Tetrahedron Lett.* **2015**, *56*, 3277-3280.

2. Acerson, M. J.; Andrus, M. A. Selective Esterification of the Polyphenol Resveratrol at the 4'-Position. *Tetrahedron Lett.* **2014**, *55*, 757–760.

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Matthew C. Asplund, PhD

Physical Chemistry

C309 BNSN, 422-5275

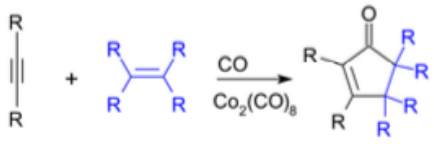
Email: asplund@chem.byu.edu

Organometallic Photochemistry

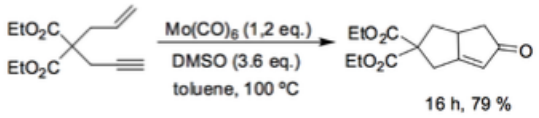
The development of short-pulsed lasers, from 10 femtoseconds (10 x 10^{-15} s) to nanoseconds (10^{-9} s), has allowed for unprecedented information into the dynamics of chemical reactions. With pulses of light this short, we can easily measure the spectra of chemical intermediates in condensed phase (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.



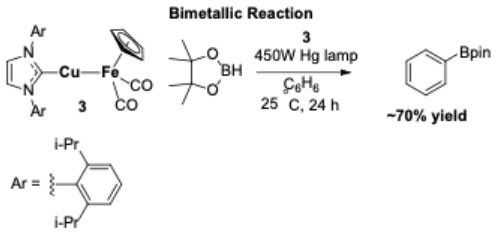
The reaction proceeds thermally, and in order to follow the reaction with time-resolved spectroscopic methods, we use a variant of the reactant that combines the alkene and alkyne in the same molecule.



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.



Daniel E. Austin, PhD

Analytical Chemistry, Planetary Science

C311A BNSN, 422-1551

Email: austin@chem.byu.edu

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

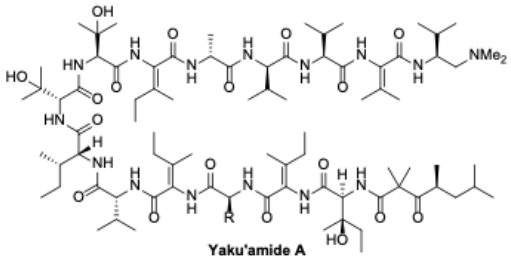
C411 BNSN, 422-1780

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. One of our recent synthetic targets, the anticancer peptide yaku'amide A, is 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.



Yaku'amide A

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). On occasion, exceptions can be made for highly motivated students who have not yet taken organic chemistry courses.

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Kenneth A. Christensen, PhD

Kenneth A. Christensen, PhD

Biochemistry, Analytical Chemistry

E205 BNSN, 422-0249

Email: ken.christensen@byu.edu

Website: https://christensenlab.byu.edu

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

The first project arose from our discovery that the anthrax toxin receptor capillary morphogenesis gene protein 2 (ANTRX2/CMG2) is involved in pathological blood vessel growth 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 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 to regulate its metabolism. Since glycolysis is key to parasite survival, inhibiting glycolysis could be an excellent targeted therapeutic approach for the 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 the biocompatibility of printed resins, and developing cell-based assays that leverage the small scale, both active and passive fluidic components, and the ability to multiplex analysis.

Note: I am willing to work with beginning students; however, I only accept a limited number of students each year, depending on the current planned graduation dates of students already working in my lab. Please contact me about the possibilities for joining the lab. Visit my website for the latest information and recent publications.

David V. Dearden, PhD

Analytical/Physical Chemistry

C107 BNSN, 801-422-2355

Email: dvd@chem.byu.edu

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 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 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 energy- and 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.

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, Gaussian, 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 resources. 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 an 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

1. Yang, F.; Voelkel, J. E.; Dearden, D. V. Collision Cross Sectional Areas from Analysis of Fourie Transform Ion Cyclotron Resonance Line Width: A New Method for Characterizing Molecular Structure. *Anal. Chem*. **2012**, *84*, 4851-4857.

2. Arslanian, A. J.; Dearden, D. V., Gas Phase Cucurbituril Chemistry. In *Monographs in Supramolecular Chemistry No. 28: Cucurbiturils and Related Macrocycles,* Kim, K., Ed. Royal Society of Chemistry: London, **2020**; pp 208-237.

3. Heravi, T.; Shen, J.; Johnson, S.; Asplund, M. C.; Dearden, D. V. Halide Size-Selective Binding by Cucurbit[5]uril—Alkali Cation Complexes in the Gas Phase. *J. Phys. Chem. A* **2021**, *125*, 7803-7812.

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5. Shrestha, J.; Porter, S. R.; Tinsley, C.; Arslanian, A. J.; Dearden, D. V. Prototypical Allosterism in a Simple Ditopic Ligand: Gas Phase Topologies of Cucurbit[n]uril•*n*-Alkylammonium Complexes Controlled by Binding in the Second Site. *J. Phys. Chem*. *A* **2022**, *126*, 2950-2958.

6. Heravi, T.; Arslanian, A. J.; Johnson, S. D.; Dearden, D. V. Ion Mobility and Fourier Transform Ion Cyclotron Resonance Collision Cross Section Techniques Yield Long-Range and Hard-Sphere Results, Respectively. *J. Am. Soc. Mass Spectrom.* **2022**, *33 (9)*, 1644–1652. DOI: 10.1021/jasms.2c00112.

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8. Mane, S. S.; Dearden, D. V.; Lee, K. W. Identifying and Quantifying Relative Concentrations of Epimers in Mixtures via Cyclic Ion Mobility Mass Spectrometry: Dexamethasone and Betamethasone as a Case Study. *J. Am. Soc. Mass Spectrom.* **2024**, *35 (10)*, 2458–2464. DOI: 10.1021/jasms.4c00258.

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Daniel H. Ess, PhD

Computational Chemistry

C403 BNSN, 422-9164

Email: dhe@chem.byu.edu

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).

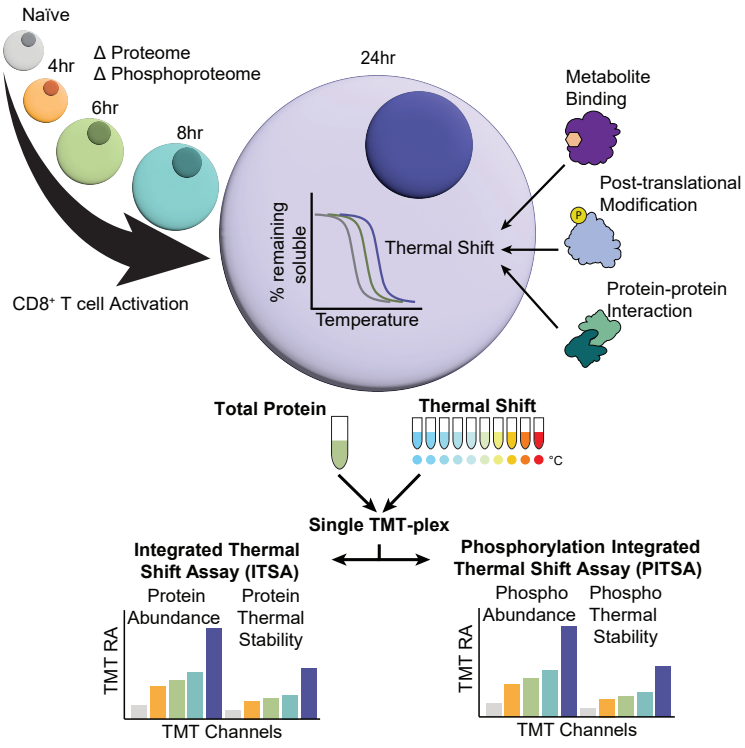
Brandon M. Gassaway, PhD

Biochemistry

E111 BNSN, 422-7193

Email: brandon.gassaway@gmail.com

With the advent of mass spectrometry-based proteomics and improved phosphopeptide enrichment, it is now feasible to detect thousands of phosphorylation events in a given experiment. However, the functional role for >94% of these events is completely unknown and those that do have some functional annotation are often inaccurate or incomplete despite the ubiquity and importance of this post-translational modification. I am dedicated to developing tools and methods to bridge this gap between phosphorylation site detection and functional understanding. To this end, I developed the Proteome Integrated Thermal Shift Assay (PITSA), which measures protein abundance, protein thermal stability, phosphorylation site abundance, and phosphorylation site thermal stability in the same assay. This assay has the potential to identify phosphorylation sites with altered biophysical states, which are presumably correlated with functional changes in the protein. In a model of T cell activation, PITSA identified phosphorylation sites on key TCR signaling regulators, such as LCK and CBLB, that are correlated with changes in abundance and thermal stability and are likely to play functional roles. We also determined that as a class, CDK kinase activity tends to thermally destabilize its substrates, presumably through dissociation of protein-protein complexes.



Additionally, we use phospho-amino acid orthogonal translation systems, where we genetically encode phosphorylated amino acids at precise positions in the genome, as well as traditional molecular biological and biochemical techniques to understand

how phosphorylation affects protein function. We are also interested in expanding PITSA to other post-translational modifications beyond phosphorylation, such as cysteine oxidation, as well as applying PITSA to a variety of interesting biological systems, such as models of cancer, neurodegeneration, and aging.

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David V. Hansen, PhD

Biochemistry

C212 BNSN, 422-7241

Email: dvhansen@chem.byu.edu

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 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 β-amyloid and tau pathologies (refs. 4-5).

Our research will help us better understand the relationship between AD-associated genes and AD pathogenic mechanisms. Through these efforts, we aim to identify new targets for pharmacological intervention to slow the progression of this debilitating and tragic illness.

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Jaron C. Hansen, PhD

Analytical Chemistry

C100B BNSN, 422-4066

Email: jhansen@chem.byu.edu

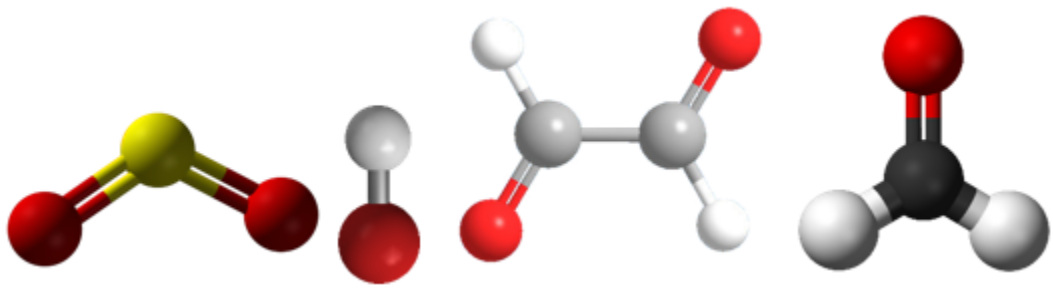
Atmospheric Chemistry and Renewable Energy

Research in the Hansen group is divided into three elements: (1) Kinetics and Spectroscopy of Atmospherically Important Reactions, (2) Air Sampling Campaigns and Human Exposure/Environmental Chamber, and (3) Biofuel/Alternative Energy. Our group combines computational and experimental studies to investigate the kinetics and mechanisms of important atmospheric reactions. Laboratory studies are complemented by air sampling campaigns designed to investigate the sources of air pollution. We utilize an environmental chamber to aid in the interpretation of air sampling campaign data. We also conduct research on the conversion of biomass into energy. Undergraduate students with at least two years of coursework are often engaged as research assistants. Interested students are encouraged to contact Dr. Hansen for more information.

Spectroscopy of Atmospherically Important Molecules

In the Hansen Lab, we measure and quantify the concentration of key atmospheric molecules such as sulfur dioxide (SO_2), hydroxyl radical (OH), glyoxal (CHOCHO), and formaldehyde (CH_2O). These molecules play critical roles in understanding the sources and formation of ozone and particulate matter. Concentrations are measured using broadband cavity-enhanced absorption spectroscopy (BBCEAS).

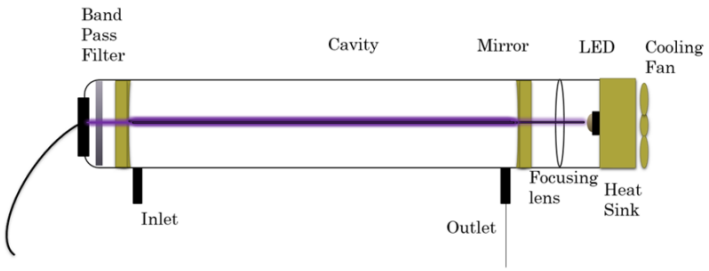
Figure 1: Structures (left to right) of SO_2, OH, CHOCHO, and CH_2O.



Broadband Cavity-Enhanced Absorption Spectroscopy (BBCEAS)

Absorption spectroscopy is an analytical technique used to analyze how molecules interact with light across different wavelengths. It measures the amount of light absorbed by a substance as it passes through or interacts with the molecule. By examining absorption at specific wavelengths, spectroscopy provides insights into the composition, structure, and concentration of substances. BBCEAS allows simultaneous measurement of multiple molecules with high accuracy.

Figure 2: Basic schematic of the BBCEAS cavity.



Selected Research Highlights

Detection of Sulfur Dioxide

Sulfur dioxide (SO_2) is a key precursor in atmospheric sulfate aerosol and acid rain formation. We developed a BBCEAS instrument capable of detecting SO_2 with a minimum detection limit of 0.75 ppbv (3σ) using a spectral range of 305.5–312 nm and a 5-minute averaging time. The system achieves a 610 m effective absorption path length and demonstrated excellent correlation with fluorescence standards (R^2 = 0.9998). No interference was observed with fluorescence methods, and ambient results were consistent with established techniques.

DOI: https://doi.org/10.3390/s22072626

BBCEAS Coupled with an Interferometer for Glyoxal Detection

Glyoxal (CHOCHO) is a trace gas used to indicate biogenic emissions. This study compared two BBCEAS detection methods: a spectrograph with CCD detector (10 ppt detection limit) and an interferometer with photomultiplier tube (600 ppt detection limit). While the spectrograph-CCD method achieved higher sensitivity, both provided valuable data for comparing detection performance.

DOI: https://doi.org/10.3390/toxics12010026

Detection and Sources of Formaldehyde in Bountiful, UT

The U.S. EPA's National Air Toxics Trends Stations Network has monitored hazardous air pollutants, including formaldehyde (HCHO), since 2003. Data from Bountiful, Utah revealed elevated HCHO levels exceeding risk thresholds. Positive Matrix Factorization (PMF) analysis identified biomass burning and biogenic emission conversion as primary sources. Back-trajectory analyses confirmed pollutant transport from industrial zones near North Salt Lake City.

DOI: https://doi.org/10.3390/atmos12030375

Detection of Glyoxal and Formaldehyde via BBCEAS

This study examined the relationship between volatile organic compounds (VOCs), nitrogen oxides (NO_x), and ozone formation. Simultaneous detection of glyoxal (biogenic indicator) and formaldehyde (anthropogenic indicator) helped identify emission sources along the Wasatch Front and supported the creation of ozone isopleths that map O_3-NO_x-VOC interactions.

Absorption Cross-Sections for Short-Chain Alcohols

Absorption cross-sections for OH overtones in methanol, ethanol, and isopropanol were measured using Incoherent BBCEAS. Findings matched computational predictions and provided accurate determinations of vibrational frequencies, anharmonicity constants, and OH vertical dissociation energies. The data support theoretical models of radical formation under atmospheric conditions.

DOI: https://doi.org/10.1016/j.jms.2023.111746

Biofuel and Alternative Energy

Renewable energy production via anaerobic digestion (AD) of waste streams requires cost-effective, scalable pretreatment methods to improve conversion efficiency. Traditional approaches such as mechanical, thermal, and chemical pretreatments often suffer from high energy costs. Thermal Hydrolysis (THP) remains the most effective method, increasing biogas yield by up to 50% while improving dewatering and sterilization. However, biological pre-digestion using thermophilic organisms may provide similar benefits at lower costs.

The Hansen Lab investigates hybrid systems that combine THP and biological pre-digestion to maximize methane yield and volatile solids destruction. This approach may optimize energy recovery from complex organic wastes while maintaining operational efficiency.

Roger G. Harrison, PhD

Inorganic and Analytic Chemistry

C104A BNSN, 422-8096

Email: rgharrison@chem.byu.edu

Nanomaterial Synthesis and Properties

Materials with subunits in the nanometer range are being studied for their catalytic and magnetic properties. Members of our group synthesize nanoparticles, nanoprisms, and nanoplates made of ZnO and Fe_3O_4 and investigate their gas adsorption, magnetism, and bacteria binding ability. 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 XPS. Students have found that silica coated magnetic nanoparticles effectively bind bacteria and remove them from solutions containing red blood cells (Figure 1). This will lead to better detection of infections.

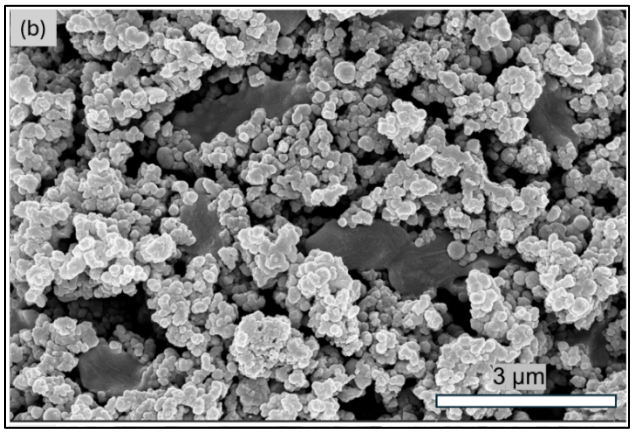


Figure 1. Bacteria trapped by magnetic nanomaterials.

Quantifying Contaminants in Water

Another area of research we are pursuing is separating and quantifying very low levels of water and air contaminants. Small quantities of some molecules are harmful and toxic to humans, plants, and animals. Students in our group use liquid chromatography mass spectrometry (LCMS) to detect and quantify

perfluorinated (PFAS) and pharmaceutical compounds (Figure 2). To do this, they extract the compounds from water or air and analyze them by mass spectrometry. Students become experts in separation techniques and use their skills to analyze molecules in river water, air, and biological fluids.

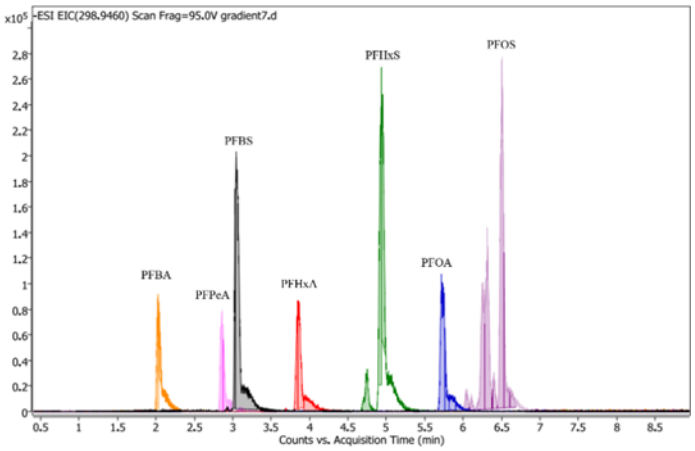


Figure 2. Chromatogram of perfluorinated compounds separated by LC-MS.

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. Students working on this project learn to synthesize organic and inorganic compounds and characterize them with such instruments as NMR, MS, UV-vis, and XRD. They use these compounds to bind and encapsulate other molecules.

Recent student publications

A.D. Ojaide, M.J. Bradford, C.J. Tinsley, E.M. Stecher, N.G. Harrison, J.K. Harper, S.J. Smith, R.G. Harrison "Locations of Ca^{2+}, Zn^{2+}, and Sulfur in Zn-Modified LTA Zeolites During Sulfur Capture and Release" *Inorganic Chemistry*, **2026**, under review.

J.H. Chen, J. Riggs, C. N. Maruri, Z. Sandall, C. M. Tracy, J. C. Hansen, R. G. Harrison "Spatiotemporal Per- and Polyfluoroalkyl Substances Distribution in a Snowmelt Supplied River and Reservoir Water System" *Env. Chem. Ecotox.,* **2026**, under review.

R.P. Gautam, T.P. Okonkwo, J.B. Limburg, J.W. Colby, B.J. Houser, J.P. Talley, T.P. Green, S.J. Smith, W.G. Pitt, R.G. Harrison, K. Chesnel "Nanostructuring effects on the Verwey transition and associated magnetic properties in Fe_3O_4 nanoparticles" *JMMM*, **2026**, accepted.

T.P. Okonkwo, R.P. Gautam, J.B. Limburg, B.L. Forstrom, B.J. Houser, A. Rappleyea, T.P. Green, J.P. Talley, A.D. Daum, S.J. Smith, K. Chesnel, W.G. Pitt, R.G. Harrison. "Magnetic Nanoparticles Tethered with Zn-DPA for the Removal of Bacteria from Red Blood Cell Suspension" *RSC Adv.* **2025**, 15, 31402-31415.

B.J. Houser, A.N. Camacho, C.A. Bryner, M. Ziegler, J.B. Wood, A.J. Wilson, R.P. Gautam, V. Wagner, T.P. Okonkwo, K. Chesnel, R.G. Harrison, W.G. Pitt. "Bacterial Binding to Poly-Dopamine-Coated Magnetic Nanoparticles" ACS Appl Mater Interfaces, **2024**, 24, 58226-58240. https://doi.org/10.1021/acsami.4c1169.

C. Pang, B.T. Karlinsey, M. Ward, R.G. Harrison, R.C. Davis, and A.T. Woolley, "DNA-templated Nanofabrication of CdS-Au Nanoscale Schottky Contacts and Electrical Characterization" *Langmuir*, **2024**, *40*, 14076-14085. https://doi.org/10.1021/acs.langmuir.4c01554.

W.N. Chan, J. Daum, A. Daum, R.G. Harrison "Separation of perfluoroalkyl substances by ion chromatography with a resorcinarene stationary phase" *Sep Sci plus,* **2023**, *6*, 2200136.

Jeremy A. Johnson, PhD

Physical Chemistry

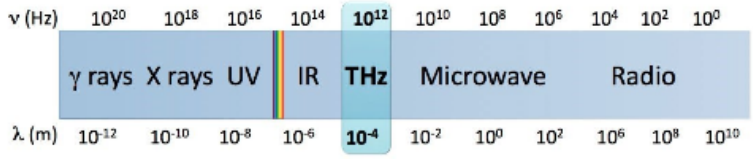
C312 BNSN, 422-0245

Email: jjohnson@chem.byu.edu

Note: I am willing to work with beginning students.

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 mm 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.

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Ryan T. Kelly, PhD

Analytical Chemistry

C267 BNSN, 422-1949

Email: ryan@chem.byu.edu

Mass spectrometry (MS)-based proteomics and metabolomics analyses enable the quantification of hundreds or thousands of biomolecules within biological system, 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 requiredtechnology.

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

1. Axtell, N. B.; Webber, K. G. I.; Truong, T.; Lin, H.-J. L.; Sandberg, A.; Martin, S.; Xie, X.; Wang, C.; Kelly, R. T. Modification of a low-cost pipetting robot for nanoliter liquid handling and autosampling for liquid chromatography-mass spectrometry. *J. Sep. Sci.*, **2025,** submitted.

2. Wang, C.; Lin, H.-J. L.; Huang, S., Haynie, G.; Triggs, K.; Chang, Y. J.; Hansen, D. V.; Truong, T.; Xie, X.; Kelly, R.T. High-Throughput Label-free Single-Cell Proteomics Enabled by Multicolumn NanoLC with a 5-min Cycle Time. *Nature Communications,* **2025,** submitted. Preprint at Research Square.

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Kenneth W. Lee

Analytical/Biophysical Chemistry

C305, 422-0429

Email: kenny.lee@byu.edu

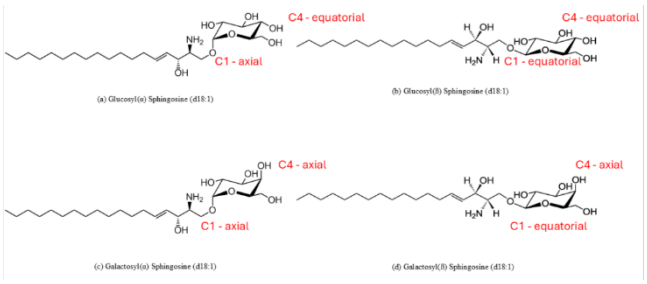
Overview

The Lee lab develops unique mass spectrometry-based tools and methods to characterize the structure and interactions of biomolecules. This focus intersects physics, biology, engineering, in addition to chemistry. Our research philosophy is to push mass spectrometry technology to address challenging molecular characterization. We leverage the unique vacuum environment to isolate and probe specific species. This approach allows us to separate and characterize different molecular forms of a species, including isomers and conformations.

Because of this philosophy, students work directly with our mass spectrometry instrumentation to develop new methods. This gives them the unique advantage of understanding mass spectrometry at the fundamental level. Students in my lab will have opportunities to build and modify instrumentation, develop analytical methods, and contribute to the fundamental understanding of biomolecular structure and function.

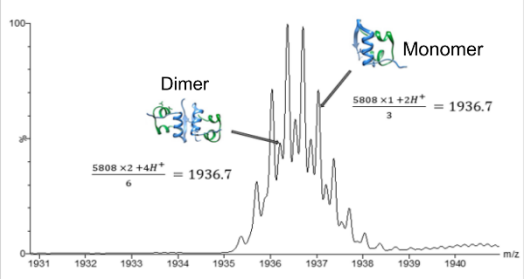
Applications

Pharmaceutical and biomolecular isomer characterization: New pharmaceuticals need to be thoroughly characterized including any potential isomers that result during synthesis. In addition, various biomolecules such as lipids contain multiple isomeric forms that are related to different cellular processes and medical conditions. Separating and characterizing isomers is therefore critical to understanding the biochemistry of pharmaceutical compounds and biomolecules. We address this challenge by developing custom ion mobility–mass spectrometry methods.



Small molecule binding effects on protein stability: Protein structure dictates their ability to perform intended functions. PFAS and other environmental toxins appear to have long-term effects on human health; however, little is understood about the biotoxicity mechanisms. We leverage ion mobility to measure the stability of isolate proteins when exposed to toxin molecules.

Protein aggregation: Aggregation at best inactivates protein function and at worst causes severe health challenges. Characterizing different oligomeric forms that are generated under different conditions helps us understand how to prevent these diseases. Using ion mobility and mass spectrometry, we can probe and characterize isolated protein oligomers formed in solution.



Methods

Nano-electrospray ionization: Electrospray ionization (ESI) provided the means to study a wide range of molecules in a mass spectrometer, including large biomolecules. Nano-ESI provides even greater enhancement of protein/protein and protein/ligand complex analysis.

Non-Covalent Derivatization: Strategic manipulation of chemical structures can lead to more information on structure and energetics. ESI facilitates the preservation of non-covalent structures for mass spectrometry analysis.

Ion Mobility: Ion mobility separates species based on their size, shape, and charge. This provides millisecond separations of species in the gas phase and allows for molecular shape measurements and isomer separations in mass spectrometry.

Instrumentation

Cyclic IMS Mass Spectrometer: The primary differentiator of this mass spectrometer is the embedded cyclic ion mobility spectrometer which allows us to separate ions based on size and shape at higher resolution than most other gas-phase separation techniques. Since we maintain the instrument in our lab, we have full access to modify it and develop new methods in collaboration with Waters Corporation.

Custom Ion Trap/Soft-Landing: This modular instrument will perform gas-phase ion/ion reactions and ion soft-landing, which are not available on any commercial platforms. The combination of these unique capabilities will facilitate novel and unique experiments aimed at the characterization of structural and conformational heterogeneity present in complex biomolecular systems.

Matthew R. Linford, PhD

Analytical Chemistry

C306 BNSN, 422-1699

Email: mrlinford@chem.byu.edu

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.

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David J. Michaelis, PhD

Organic, Inorganic, Materials, & Biomolecular Chemistry

C409 BNSN, 422-9416

Email: dmichaelis@chem.byu.edu

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.

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 a 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 pancreatic 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.

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James D. Moody, PhD

Biochemistry

C206 BNSN, 801-422-6272

Email: james.moody@byu.edu

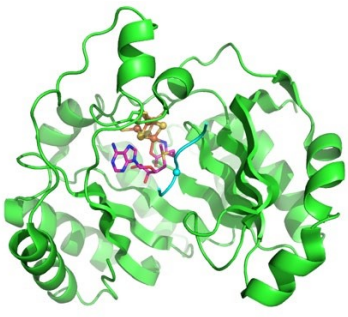
Protein engineering and structural biology to accelerate disease treatment

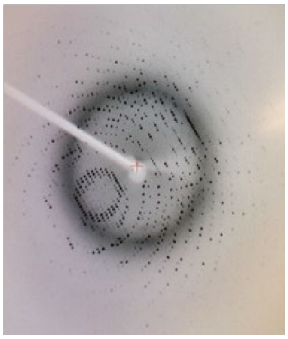
Like you and the entire biomedical enterprise, we want to help cure all the diseases that plague Heavenly Father's children! We use protein modeling, protein engineering, protein biochemistry, and protein structural biology to tackle bottlenecks in the drug and biologic development enterprise.

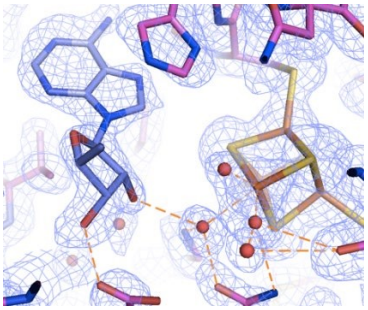
New tools to visualize protein structures at atomic resolution

If you're trying to engineer a new drug or biologic, it's best to start from an atomic level image of the protein the drug or biologic is intended to interact with. Once you have a drug or biologic candidate, it's essential to see an atomic level image of that drug or biologic interacting with its target protein. Cryo-electron microscopy is a powerful new technique, but it's not good for getting high resolution images of proteins smaller than 50–100 Å in size. X-ray crystallography is perfect for getting high resolution images of these smaller proteins. The only problem is that for X-ray crystallography to work, you must get your protein of interest to form a well-ordered crystal, which has about a 10% success rate!

Protein of interest □ Crystals □ X-ray Diffraction data □ Electron Density □ Protein structure

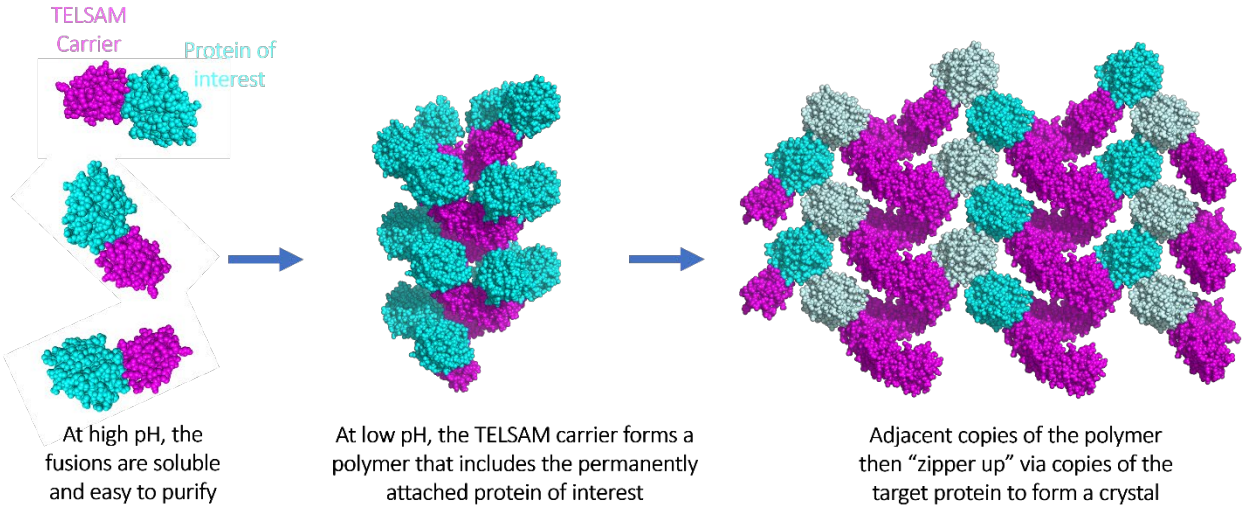




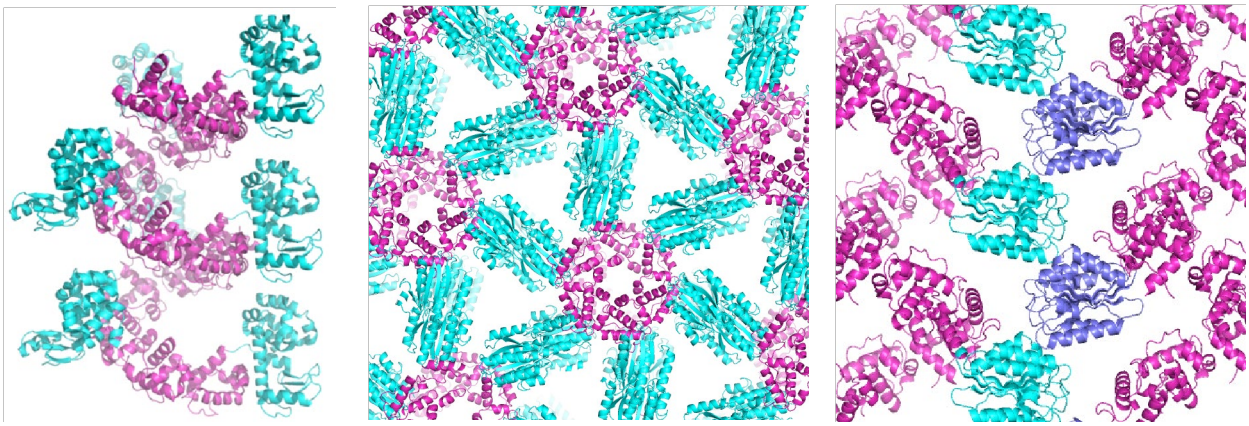


For the past several years we've been investigating and improving TELSAM fusion crystallization, a new tool to make disease proteins crystallize so we can get those precious atomic level images.

TELSAM, engineered from a normal human protein, is soluble at pH >8 but forms a helical polymer at pH <7. You simply genetically fuse TELSAM to your protein of interest, purify the fusion protein, and lower the pH to polymerize TELSAM. The TELSAM polymers (with your protein of interest in tow) readily form crystals, with a >90% success rate! In addition, researchers in different labs can be equally successful in crystallizing a given TELSAM fusion protein, unlike traditional protein crystallography. In addition, TELSAM fusions can reliably form crystals diffracting to 1.5 A resolution or better, also unlike traditional protein crystallography.



TELSAM polymer fused to target protein **Top and side views of TELSAM–target protein crystal lattice**



What else do we do?

We also do Cryo-electron microscopy of large, never-before-seen protein machines, we develop novel biologics, and we develop novel small molecule drugs.

Interested in joining?

In the Moody lab you can learn computational protein modeling and design, molecular biology techniques, protein biochemistry, protein X-ray crystallography and protein cryo-electron microscopy. If you're interested, I'd love to talk with you! We welcome dedicated, hardworking students with all levels of experience, Freshman through Senior. Please note that you must be able to spend at least 10 hours per week working in the lab during Fall and Winter semesters to be considered.

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James E. Patterson, PhD

Physical Chemistry

C310 BNSN, 422-1481

Email: jepatterson@chem.byu.edu

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.

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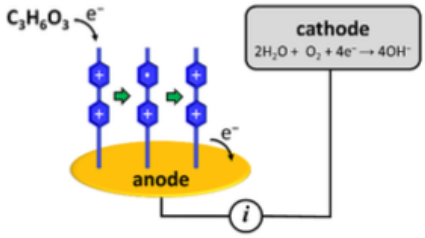
Walter F. Paxton, PhD

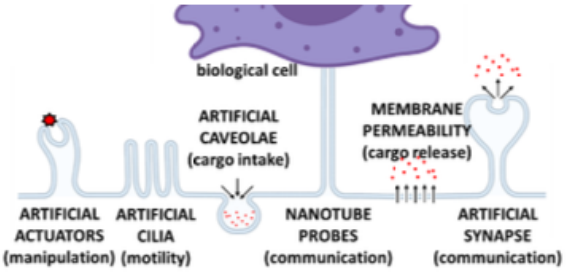
Analytical Chemistry

E111 BNSN, 422-4917

Email: paxton@chem.byu.edu

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.[1] 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.[2]





Desirable morphological transformations (shape changes) and related functions in biomimetic micro- and nanomachines (MNMs).

Electricity from Sugar. We are also developing a new kind of reusable electrode that can turn carbohydrates into electricity.[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.

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Matt A. Peterson, PhD

Organic & Biomolecular Chemistry

C463 BNSN, 422-6843

Email: mapeterson@chem.byu.edu

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. We have also performed research targeting inhibitors of VEGFR2 and BMPR1b. 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).

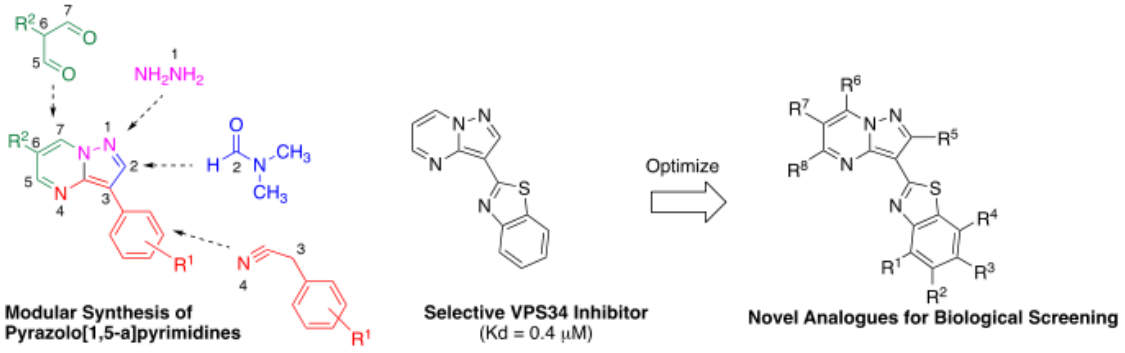
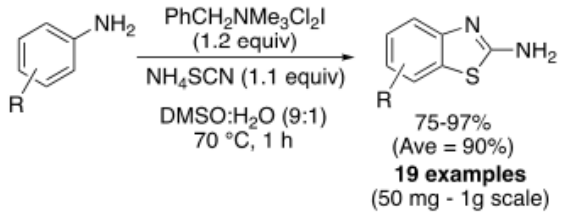


Figure 1.

An example of one of our recent methodologies is illustrated in Figure 2.



R. Dass, and M. A. Peterson "An Efficient One-pot Synthesis of 2-Aminobenzothiazoles from Substituted Anilines Using Benzyltrimethylammonium Dichloroiodate and Ammonium Thiocyanate in DMSO:H_2O" *Tetrahedron Lett.* **2021**, 153388

Figure 2.

We have also discovered N^6,5'-bis-ureidoadenosine 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_{50} = 9.7 nM). Other nucleoside derivatives synthesized in our lab include 6-[alkyl-heteroaryl)furo[2,3-d]pyrimidin-2(3H)-one antiviral nucleosides as well as 3-deaza-3-fluorouridine, a promising anticancer compound with mechanism of action unique from its parent 3-deazauridine (Figure 3).

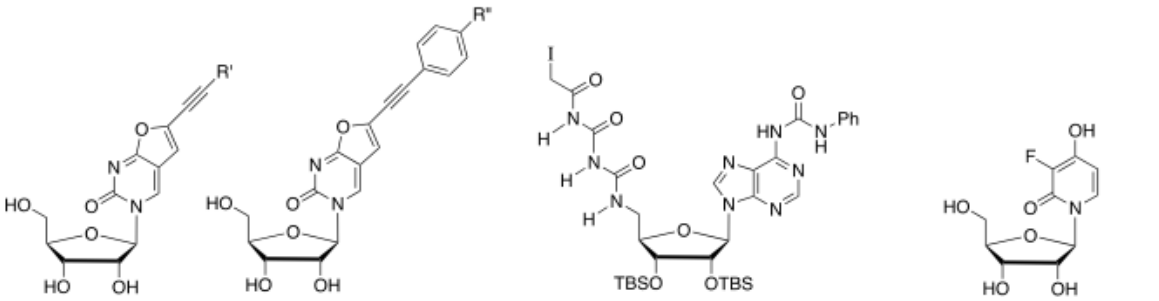


Figure 3.

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J.C. Price, PhD

Biochemistry

E113 BNSN, 422-6040

Email: jcprice@chem.byu.edu

My research focuses on the mechanisms that living cells use to control the quality and concentration of every molecule in the body. This regulation, known as molecular homeostasis, is remarkably complex. Each human cell contains about 20,000 different protein types, and the abundance and structure of each are carefully maintained at homeostasis. When this balance fails, the consequences are profound with disruptions in homeostasis of proteins, lipids, or metabolites contributing to diseases such as Alzheimer's, diabetes, and cancer.

A central goal of my lab is to develop and apply tools to study molecular homeostasis in vivo and to understand how it changes with aging and disease. We use stable isotope labeling to incorporate a time-dependent molecular "tag" into newly synthesized proteins and surface reactivity to test for structure changes. Combined with mass spectrometry, these approaches allows us to measure synthesis, degradation, and structural stabilities for thousands of proteins within complex mixtures. Combining data from proteins and lipids, we can create a holistic systems level model that reveals how cells dynamically regulate their molecular composition in response to stimuli.

We have successfully applied these techniques across a wide range of biological systems, from cell-free models to human studies.

Our current work focuses on three major research directions:

1. Regional control of metabolism

Cells regulate chemical reaction rates in part by compartmentalizing enzymes and substrates within specific cellular or tissue regions. We are integrating metabolic labeling, metabolomics, and proteomics with surface imaging mass spectrometry to map how the spatial organization of metabolism changes with disease and aging. These methods allow us to visualize how biochemical processes are coordinated within tissues, offering new insight into the regional regulation of metabolism.

2. Maintenance of proteome homeostasis through protein degradation

Many of today's most debilitating diseases—including Parkinson's, Alzheimer's, Huntington's, and diabetes—are disorders of protein homeostasis. A hallmark of these conditions is the buildup of aggregated proteins that resist degradation, suggesting dysfunction in the cell's catabolic machinery. Continuous protein turnover is essential to balance ongoing transcription and translation, yet the regulation of degradation remains poorly understood. Our research seeks to identify the natural substrates of cellular proteases and to determine how targeted proteolytic processing maintains proteome stability and allows cells to adapt to stress and aging.

3. Interventions to prevent loss of protein homeostasis

We have identified early, potentially causal changes in mitochondrial homeostasis that precede neurodegeneration and may contribute to aging itself. We are now investigating strategies to intervene and preserve proteostasis, which may ultimately provide a way to delay or prevent age-associated diseases such as Alzheimer's and cancer.

If these research questions interest you, I welcome you to reach out. I am always open to working with motivated students who are eager to explore how molecular homeostasis supports life and how its failure contributes to disease.

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Joshua L. Price, PhD

Organic Chemistry

C406 BNSN, 422-3689

Email: jlprice@chem.byu.edu

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.

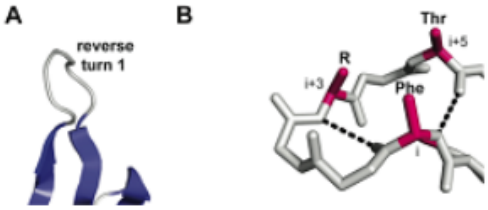

Figure 1. (A) Ribbon diagram of the WW domain from the human protein Pin 1 (PDB: 1PIN, ref. 22). β-strands are shown in blue, reverse turns in gray. (B) Stick representation of reverse turn 1 in the WW domain. Main-chain hydrogen bonds represented by black dashes; the *i*, *i*+3, and *i*+5 positions are highlighted in red. Protein **6-F,T**, and PEGylated protein **6PEG-F,T** differ in the group attached to Asn_{i+3}. These differences affect the melting temperature T_m of each protein as shown. T_m values are given as mean ± standard error for 10 μM protein in 20 mM sodium phosphate buffer, pH 7 (ref. 19). All structures were rendered in Pymol.

Increasing protein thermodynamic stability could address these problems because 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!

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Paul B. Savage, PhD

Organic & Biomolecular Chemistry

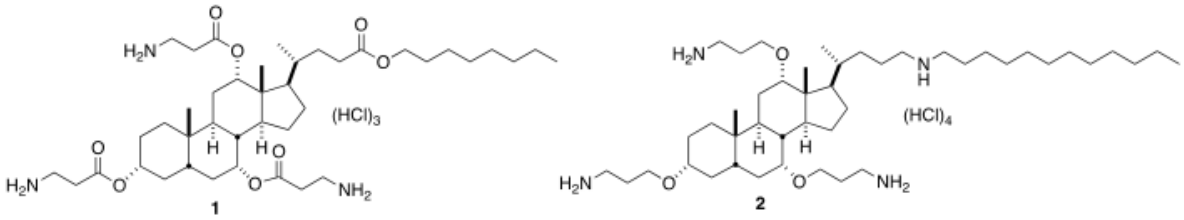
C404A BNSN, 422-4020

Email: pbsavage@chem.byu.edu

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).



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

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Eric T. Sevy, PhD

Physical Chemistry

C361 BNSN, 422-7235

Email: esevy@chem.byu.edu

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.

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Kara J. Stowers, PhD

Inorganic Chemistry, Organic Chemistry, Physical Chemistry

C405 BNSN, 422-0835

Email: kstowers@chem.byu.edu

Welcome to the Stowers Laboratory!

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.

General Considerations

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.

Sample publications

1. Nguyen-Sorenson, A. H. T.; Wu, Y.; Orcutt, E. K.; Kent, R. V.; Anderson, H. C.; Matzger, A. J.; Stowers, K. J.* “Energetic decomposition yields efficient bimetallic Cu MOF-derived catalysts.” *J. Mater. Chem. A*, **2020**, *8*, 15066-15073

2. Park, J. L.; Canizales, K. A.; Argyle, M. A.; Woodfield, B. F.; Stowers, K. J.* "The effects of doping alumina with silica in alumina-supported NiO catalysts for oxidative dehydrogenation of ethane." *Micro. Meso. Mater*. **2019**, *293*. 109799.

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5. Park, J. L.; Balijepalli, S. K.; Argyle, M. A.; Stowers, K. J.* Low Temperature Oxidative Dehydrogenation of Ethane by Ce-Modified NiNb Catalysts *Ind. Eng. Chem. Res*., **2018**, *57*, 5234-5240 *(Invited article)*

Pam M. Van Ry, PhD

Biochemistry

E221 BNSN, 422-1540

Email: pvanry@chem.byu.edu

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 basement membrane and extracellular matrix (ECM) in lung 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 versus traditional culture plates. Aside from this, we also developed a novel 3D culture technique allowing organ formation while cells are suspended in non-soluable concentrations of basement membrane. 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 patients suffering from pulmonary fibrosis. Our long-term goal for this project is to produce patient derived organoids for diagnostic and individualized treatment plans.

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 thosewho suffer from IPF.

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Richard K. Watt, PhD

Biochemistry, Inorganic Chemistry

C210 BNSN, 422-1923

Email: rwatt@chem.byu.edu

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, while the lack of iron results in conditions like anemia.

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.

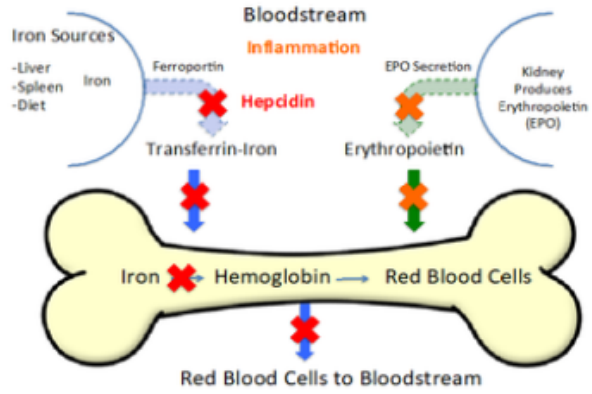

Figure 1. Inflammation produces hepcidin that binds to and degrades ferroportin. This stops iron delivery to the bone marrow. Inflammation also blocks EPO production and secretion from the kidneys. Combined these effects decrease red blood cell synthesis.

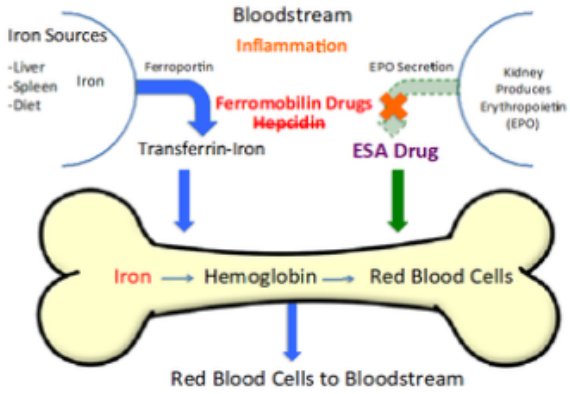

Figure 2. FerroMobilin Drug effect: FerroMobilin drugs block hepcidin production so ferroportin is not degraded. Iron is released from the liver and loads transferrin for iron delivery to the bone marrow. Depending on the cytokines that triggered the inflammatory process EPO may be present or ESA drugs may be required to stimulate red blood cell synthesis.

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

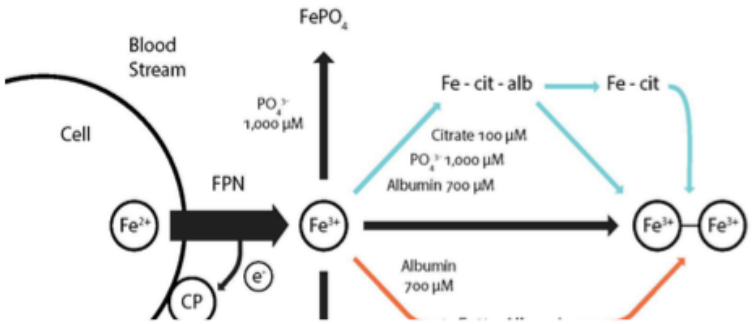

Figure 3. As Fe3+ is exported from the cell into the bloodstream it encounters a variety of serum molecules that can react with Fe3+ and form complexes that are not substrates for loading into apo transferrin. This work shows that citrate and albumin can prevent these dangerous side reactions and mediate iron delivery to apo transferrin to prevent the formation of non-transferrin bound iron.

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.

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 biomarkers that give diagnostic information to aid clinical practitioners identify the most beneficial and effective treatment.

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Barry M. Willardson, PhD

Biochemistry

C204A, 104C BNSN, 422-2785

Email: bmwillardson@chem.byu.edu

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.

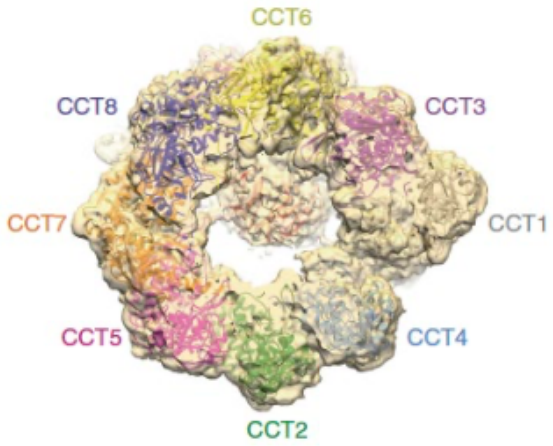

Figure 1. Structure of the mLST8-CCT complex. The 3D reconstructions of mLST8-CCT reveals the locations of the mLST8 β-propeller between the CCT rings associated with CCT subunits 3,6 and 8.

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 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 mLST8 β-propeller binds between the two rings of CCT and is held in a condensed, but not fully folded state (Fig. 1). This positioning between the CCT rings has not been previously seen with any CCT substrate. 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.

Mechanism of assembly of SARS-CoV-2 RNA polymerase complex

Several viruses hijack CCT to fold viral proteins and assemble them into complexes. As a result, we investigated the role of CCT in SARS-CoV-2 replication and found that CCT contributes substantially to SARS-CoV-2 propagation by assisting in the folding of the RNA polymerase (Nsp12) that replicates the viral RNA. We have determined the structure of Nsp12 bound to CCT, which shows that the large Nsp12 protein extends from between the CCT rings through the folding chamber and out one end of the CCT barrel (Fig. 2). This structure was the first to show how CCT folds large proteins. Further refinement of the structure will show the key interaction sites between Nsp12 and CCT that can be therapeutically targeted to block SARS-CoV-2 replication.

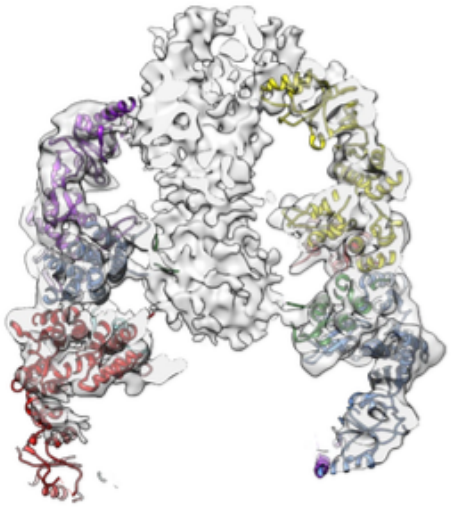

Figure 2. Structure of the Nsp12-CCT complex. Cut-away side view of Nsp12-CCT with Nsp12 in light gray and CCT subunits in various colors.

My lab typically brings on undergraduates at the beginning of their sophomore biochemistry courses, but talented freshmen 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.

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Brian F. Woodfield, PhD

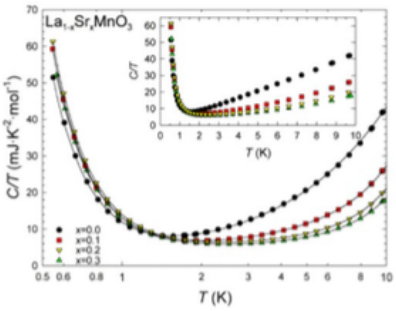
Physical Chemistry

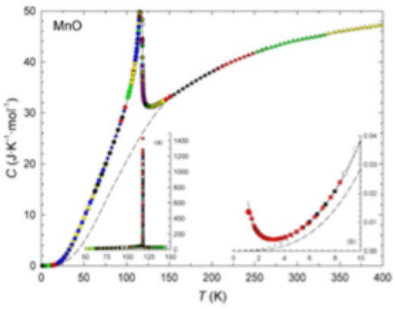
C304A BNSN, 422-2093

Email: brian_woodfield@chem.byu.edu

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-xSrxMnO3.





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

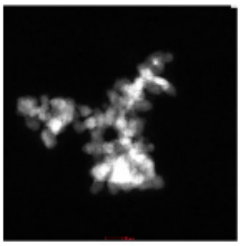
synthesize a series of industrial viable and state-of-the-art alumina catalyst supports and Fe and Co Fisher Tropsch catalysts. These supports and catalysts have tunable properties and perform better than any catalysts currently reported in the literature. We continue to focus our work on innovating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

Table 1

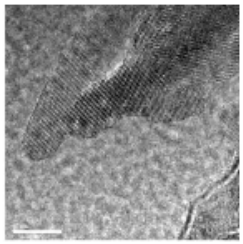
Material	Size (nm)
CoO	8 ± 1
Co_3O_4	8 ± 1
NiO	3 ± 0.5, 9 ± 1
CuO	8 ± 1
ZnO	8 ± 1, 16 ± 1
Al_2O_3	2 ± 0.5, 8 ± 1
In_2O_3	12 ± 1
SnO_2	4 ± 1
$LiCoO_2$	13 ± 1
$NiFe_2O_4$	7 ± 1
$Zn_{0.4}Co_{0.6}Fe_2O_4$	8 ± 1
$Li_{0.15}Zn_{0.3}Ni_{0.4}Fe_{2.15}O_4$	8 ± 1
Y_2O_3	1 ± 0.5, 13 ± 1
Nd_2O_3	9 ± 1
Ag_2O	65 nm
Ni	40 nm

Synthesis of Nanoparticles

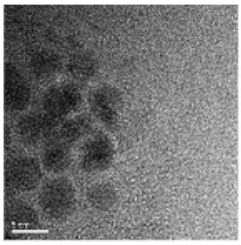
We have recently developed an elegantly simple process that allows us to make a nearly unlimited array of well-defined inorganic nanoparticles that have controlled sizes from 1 nm to bulk. The particles are highly crystalline with well-defined shapes (usually spherical but also rods). We can synthesize 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.



TEM image of 8 nm CoO. Magnetic properties are equivalent to bulk materials. Bar 50 nm



High resolution TEM image of 13 nm Y_2O_3. Notice the rods are crystalline to the edge. Bar 10 nm



TEM image of 3 nm NiO powders. Bar 5 nm

Adam T. Woolley, PhD

Analytical/Materials Chemistry

C205 BNSN, 801-422-1701

Email: atw33@byu.edu

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 medically relevant biomolecules, and we are also applying DNA in assembling nanoscale materials.

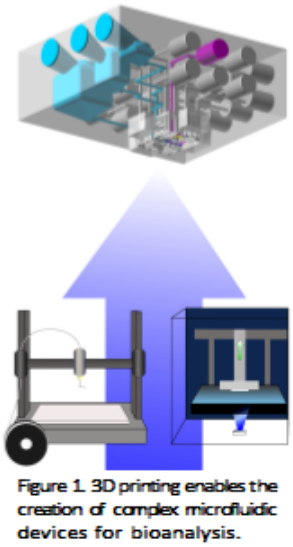


Figure 1. 3D printing enables the creation of complex microfluidic devices for bioanalysis.

3D Printed Integrated Microfluidic Analysis Systems

We are developing 3D printed microfluidic systems that integrate multiple analytical processes in a single miniaturized device (Figure 1). We use 3D printed microfluidics to analyze for maternal serum biomarkers related to preterm birth risk, to determine mosquito-borne viral infections, and to improve chromatographic separations. Iterative optimization processes possible with rapid 3D printing times enable creative design to solve bioanalytical problems.

Antibiotic Susceptibility Testing on Small Ensembles of Individual Bacteria

We are developing methods for studying the effects of antibiotics using individual *E. coli* cells. We use droplet microfluidics as shown in Figure 2 to encapsulate single bacterial cells into water-in-oil droplets, where we can assess their growth via a fluorescent probe for metabolic activity. We are developing methods for dosing individual cells with different concentrations of antibiotics, allowing susceptibility testing and determination of the minimum inhibitory

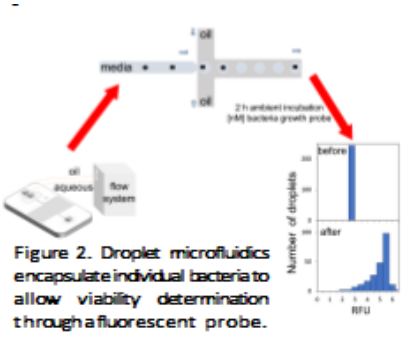


Figure 2. Droplet microfluidics encapsulate individual bacteria to allow viability determination through a fluorescent probe.

concentration, starting from low initial bacteria counts. This experimental platform provides a promising route for answering novel questions about single-bacteria response to antibiotic challenge.

Biotemplated Nanofabrication of Electronics

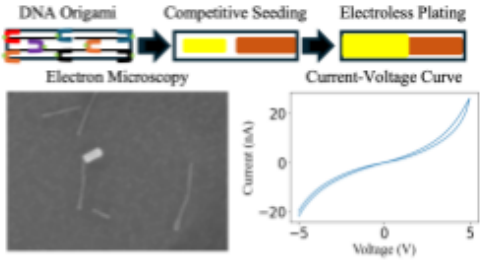


Figure 3. DNA origami offers a platform for self-assembly of nanomaterials; after electroless plating, metal-semiconductor junctions are created, and their electrical properties can be studied.

We are developing methods for self-assembling inorganic nanomaterials onto designed DNA nanostructures (Figure 3). DNA-coated Au and CdS nanorods can be localized onto a DNA origami nanostructure that has protruding complementary sequences, resulting in placement of Au and CdS in close proximity. After electroless plating of Au, metal-semiconductor junctions are formed. We have carried out structural and electrical characterization of these biotemplated nanomaterials. This process shows promise for creating nanoscale electronic circuitry from the bottom up.

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