MONTANA STATE UNIVERSITY
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY
FACULTY RESEARCH

The graduate recruiting and admission committee, as well as the entire research active faculty of the Department of Chemistry and Biochemistry at Montana State University, would like to thank for your interest in this booklet. We are continuously looking for motivated graduate students with strong academic backgrounds in chemistry, biochemistry, or materials science, who are looking for cutting-edge research opportunities while pursuing a Ph.D. degree in our department.

Please join us as the leading department at Montana State University in scientific discovery, research innovations, and research funding. Our department is proud to emphasize innovative, externally funded research programs that engage students in small research group settings with personal mentoring and individualized graduate programs of study. Students customize their coursework and quickly begin their independent scholarly research projects under the guidance of a research active faculty member. Many faculty are involved in collaborative research projects which offer students the unique opportunity to become simultaneously trained in chemical synthesis, characterization, instrumentation, theory, and modeling. We currently have a graduate student body of ~70 students, with an average time to degree of less than 6 years. All graduate students are appointed on either research or teaching assistantships and both appointments offer a tuition waiver and a competitive monthly stipend.

Our community in Bozeman, Montana, is culturally rich and offers numerous recreational opportunities, while providing historically what only "The West" can offer. Undoubtedly, Bozeman's location presents unparalleled natural beauty. We encourage all our students to take advantage of all the best that Montana can offer, while staying engaged in our laboratories and remaining competitive nationally and internationally.

If a research program of any faculty in our department catches your interest, please do not hesitate to directly contact them or send a general inquiry to the graduate program director, whose contact information is located at the back of this booklet.

BRIAN BOTHNER

Professor, Biochemistry

111 Chemistry and Biochemistry Building

bbothner@chemistry.montana.edu

(406) 994-5270

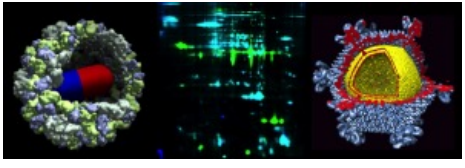
Proteomics

Chemical Biology

Structure

Systems Biology

RESEARCH OVERVIEW



Research in the Bothner lab has two main foci: (1) Investigation of cellular response to stress using chemical biology, proteomics, and metabolomics. (2) Assembly, stability, and dynamics of multi-subunit enzymes and nucleoprotein complexes. This research takes us from the atomic scale provided by high-resolution structural models of viruses and enzymes to complex interaction networks of nucleic acids, metabolites, and proteins that make up a living system. The Bothner lab is part of the Biological Electron Transfer and Catalysis (BETCy) Energy Frontiers Research Center (EFRC), the Thermal Biology Institute, and MSU's new Keck program in Extreme Microbiology of Yellowstone. (1) Cellular response to stress involves numerous networks and signaling pathways. We use changes in protein abundance and activity along with metabolomics to elucidate the pathways and networks that control biology. Leading edge mass spectrometry and more recently NMR are the pillar of our omics investigations. A wide range of projects spanning extremophiles in Yellowstone National Park, response of human the microbiome to arsenic, and hemorrhagic shock are ongoing. (2) Protein function is intimately connected to dynamics; therefore, knowledge of the frequency, range, and coordination of motion in large complexes is critical to understanding biological mechanisms. On going projects include use of adeno-associated virus (AAV) in gene therapy, electron transfer in hydrogenases, and small molecule inhibitors of Hepatitis B virus.

REPRESENTATIVE PUBLICATIONS

1: Tokmina-Lukaszewska M, Shi Z, Tripet B, McDermott TR, Copié V, Bothner B, Wang G. Metabolic response of Agrobacterium tumefaciens 5A to arsenite. ***Environ Microbiol.*** *2017 19(2) 710-721.*

2: Lubner CE, Jennings DP, Mulder DW, Schut GJ, Zadvornyy OA, Hoben JP, Tokmina-Lukaszewska M, Berry L, Nguyen DM, Lipscomb GL, Bothner B, Jones AK, Miller AF, King PW, Adams MWW, Peters JW. Mechanistic insights into energy conservation by flavin-based electron bifurcation. ***Nat Chem Biol.*** *2017 13(6):655-659*

3: Hamerly T, Bothner B. Investigations into the Use of a Protein Sensor Assay for Metabolite Analysis. ***Appl Biochem Biotechnol.*** *2016 Jan;178(1):101-13.*

4: Hamerly T, Tripet BP, Tigges M, Giannone RJ, Wurch L, Hettich RL, Podar M, Copié V, Bothner B. Untargeted metabolomics studies employing NMR and LC-MS reveal metabolic coupling between Nanoarcheum equitans and its archaeal host Ignicoccus hospitalis. ***Metabolomics****. 2015 Aug 1;11(4):895-907.*

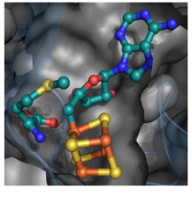
JOAN B. BRODERICK

Distinguished Professor-Women in Science,
Biological and Inorganic Chemistry
219 Chemistry and Biochemistry Building
jbroderick@montana.edu
(406) 994-6160

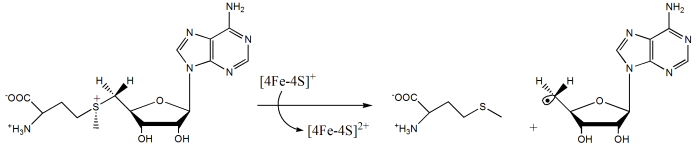
Radical SAM Enzymes
Biological Iron-Sulfur Clusters
Biological Radical Reactions, DNA Repair
Hydrogenase H-Cluster Assembly

RESEARCH OVERVIEW

Our research program is focused on understanding the detailed molecular mechanisms by which iron-sulfur clusters participate in biological radical reactions. Thousands of enzymes spanning all branches of life are now known to use iron-sulfur clusters to initiate difficult and diverse chemical reactions by radical mechanisms, yet few of these enzymes have been studied. Further, the fundamental chemical basis for these reactions is not well understood. We utilize a broad multidisciplinary approach to elucidate mechanism in these enzymes, including molecular biology, biochemistry, spectroscopy, synthesis, and structure.



Students obtain broad interdisciplinary training and have the opportunity to interact with collaborators at MSU and elsewhere. Systems on which we are currently focused include a DNA repair enzyme, an antiviral protein, a tRNA-modifying enzyme, several enzymes involved in the biosynthesis of the H-cluster of hydrogenase, and two enzymes that catalyze the formation of protein radicals.



REPRESENTATIVE PUBLICATIONS

B. R. Duffus, S. Ghose, J. W. Peters, and J. B. Broderick, "Reversible H Atom Abstraction by the Radical SAM Enzyme HydG," *J. Am. Chem. Soc.* **2014**, *136(38)*, 13086-13089.

A. S. Byer, E. M. Shepard, J. W. Peters, and J. B. Broderick, "Radical S-Adenosyl-L-methionine Chemistry in the Synthesis of Hydrogenase and Nitrogenase Metal Cofactors," *J. Biol. Chem.* **2015**, *290(7)*, 3987-3994.

J. N. Betz, N. W. Boswell, C. J. Fugate, G. L. Holliday, E. Akiva, A. G. Scott, P. C. Babbitt, J. W. Peters, E. M. Shepard, and J. B. Broderick, "[FeFe]-Hydrogenase Maturation: Insights into the role HydE plays in dithiomethylamine biosynthesis," *Biochemistry* **2015**, *54(9)*, 1807 – 1818.

M. Horitani, A. S. Byer, K. A. Shisler, T. Chandra, J. B. Broderick, Brian M. Hoffman, "Why Nature uses radical SAM enzymes so widely: ENDOR studies of lysine 2,3-aminomutase shows the 5'-dAdo• 'Free Radical' is never free," *J. Am. Chem. Soc.* **2015**, *137(22)* , 7111 - 7121.

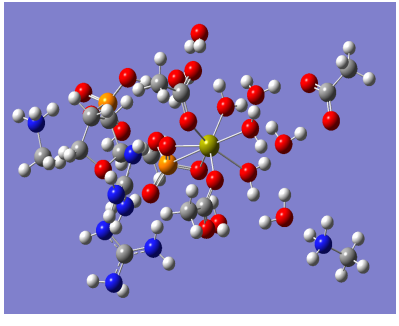
M. Horitani, K. Shisler, W. E. Broderick, R. U. Hutcheson, K. S. Duschene, A. R. Marts, B. M. Hoffman, and J. B. Broderick, "Radical SAM catalysis via an organometallic intermediate with an Fe-[5'-C]-deoxyadenosyl bond," *Science* **2016**, *352(6287)*, 822-825.

PATRIK R. CALLIS

Professor
Physical Chemistry
55 Chemistry and Biochemistry Building
E-mail: pcallis@montana.edu
Tel: (406) 994-5414

Quantum Chemistry
Protein Electric Fields
Enzyme Mechanisms
Molecular Dynamics
Protein Fluorescence
Tryptophan, GFPs, RFPs

RESEARCH OVERVIEW



Enzymes enormously accelerate the rates of chemical reactions over the rates of the same reactions in water (by 10^8-10^{15} fold), but the precise manner by which enzymes accomplish this in detail is still considered an open question.

We are making a seamless transition from obtaining a detailed understanding of how the intense internal electric fields in proteins profoundly affect the properties of tryptophan fluorescence, towards a better understanding and more detailed view of how enzymes attain their astronomical acceleration of biochemical reactions.

We are currently performing classical and quantum molecular dynamics computations on the active sites of many enzymes, with the goal of observing unbiased enzymatic reaction events.

REPRESENTATIVE PUBLICATIONS

Jianhua Xu, Binbin Chen, Patrik Callis, Pedro L. Muiño, Henriëtte Rozeboom, Jaap Broos, Dmitri Toptygin, Ludwig Brand, and Jay R. Knutson, Picosecond Fluorescence Dynamics of Tryptophan and 5-Fluorotryptophan in Monellin: Slow Water−Protein Relaxation Unmasked, J. Phys. Chem. B (2015) 119, 4230−4239.

P.R. Callis, Simulating Electrostatic Effects on Electronic Transitions in Proteins. Molecular Simulation, (2015) 41, 190–204.

P.R. Callis, Binding Phenomena and Fluorescence Quenching. I: Descriptive Quantum Principles of Fluorescence Quenching using a Supermolecule Approach, J. Mol. Struct. 1077 (2014) 14-21.

P.R. Callis, Binding Phenomena and Fluorescence Quenching. II: Photophysics of Aromatic Residues and Dependence of Fluorescence Spectra on Protein Conformation, J. Mol. Struct. 1077 (2014) 22–29.

P.R. Callis, J.R. Tusell, MD + QM Correlations with Tryptophan Fluorescence Spectral Shifts and Lifetimes, Methods Mol. Biol. (Clifton NJ) 1076 (2014), p. 171-214.

Biesso, J.H. Xu, P.L. Muiño, P.R. Callis, J.R. Knutson, Charge Invariant Protein-Water Relaxation in GB1 via Ultrafast Tryptophan Fluorescence, J. Am. Chem. Soc. 136 (2014), p. 2739-2747.

J.N. Scott, P.R. Callis, Insensitivity of Tryptophan Fluorescence to Local Charge Mutations, J. Phys. Chem. B 117 (2013), p. 9598-9605.

MARY CLONINGER

Professor, Bioorganic Chemistry

351 Chemistry and Biochemistry Building

mcloninger@chemistry.montana.edu

(406) 994-3051

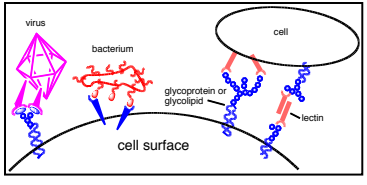
Chemical Biology

Multivalency

Dendrimers

Protein-Carbohydrate Interaction

RESEARCH OVERVIEW



The main focus of our research is on the use of dendrimers, which are highly branched synthetic macromolecules, to study multivalent biological interactions. For example, we have synthesized many carbohydrate-functionalized dendrimers for the study of protein-carbohydrate interactions. Protein-carbohydrate interactions have been implicated in a myriad of biological processes including the mounting of an immune response, cellular differentiation and growth, and cancer cellular processes such as tumor formation and metastasis.

One current area of interest is the use of carbohydrate-functionalized dendrimers to study galectin-3 mediated cancer cellular processes. Galectin-3 is a carbohydrate-binding protein that is known to play a role in cellular aggregation and metastasis. We recently reported that carbohydrate-functionalized dendrimers alter galectin-3 mediated cancer cellular aggregation for several cancer cell lines that over-express galectin-3. A second area of research emphasis is the development of antimicrobial dendrimers. Finally we needed to develop new techniques and new instrumentation, as well as to study fundamentals of polymer-nucleated protein aggregation.

Our research is focused broadly in the area of chemical biology. Some of the students in the Cloninger group are organic chemists working in the area of carbohydrate synthesis and macromolecular functionalization. Other students are biochemists, working on biophysical techniques, assay development, and tissue culture work. Other students are microbiologists and analytical chemists. The multidisciplinary nature of the group provides a stimulating environment for students who wish to apply a variety of research approaches toward the study of complex problems.

REPRESENTATIVE PUBLICATIONS

Michel, A. K.; Nangia-Makker, P.; Raz, A.; Cloninger, M. J. "Lactose-functionalized dendrimers arbitrate the interaction of galectin-3/MUC1 mediated cancer cellular aggregation." ChemBioChem, 2014, 15, 2106-2112.

Ennist, J. H.; Gobrogge, E. A.; Schlick, K. H.; Walker, R. A.; Cloninger, M. J. Cyclodextrin-Functionalized Chromatographic Materials Tailored for Reversible Adsorption. ACS Appl. Mater. Interfaces 2014, 6, 18087–97

Cousin, J. M.; Cloninger, M. J. Glycodendrimers: tools to explore multivalent galectin-1 interactions. Beilstein J. Org. Chem. 2015, 11, 739–747.

Wolfenden, M.: Cousin, J.; Nangia-Makker, P.; Raz, A.; Cloninger, M. Glycodendrimers and Modified ELISAs: Tools to Elucidate Multivalent Interactions of Galectins 1 and 3. Molecules 2015, 20, 7059–7096.

VanKoten, H. W.; Dlakic, W. M.; Engel, R.; Cloninger, M. J. Synthesis and Biological Activity of Highly Cationic Dendrimer Antibiotics. Mol. Pharm. 2016, 13, 3827–3834.

Cousin, J. M.; Cloninger, M. J. The Role of Galectin-1 in Cancer Progression, and Synthetic Multivalent Systems for the Study of Galectin-1. Int. J. Mol. Sci. 2016 17(9). PMID: 27649167.

VALÉRIE COPIÉ

Professor of Biochemistry

111A Chemistry and Biochemistry Building

vcopie@montana.edu

(406) 994-7244

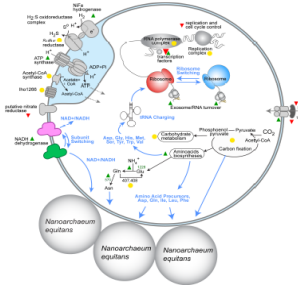
NMR Metabolomics and

Global Analyses of Cellular Metabolism

Protein Biochemistry

Structural Biology

RESEARCH OVERVIEW



We are interested in understanding the metabolome of complex systems using solution NMR and mass spectrometry and systems biology approaches, to analyze and identify metabolic pathways and cellular networks impacted as result of specific cellular and environmental conditions. Metabolite levels are closely related to cellular phenotypes. Further in cells, the number of metabolites is much lower than the number of genes or proteins. While metabolic changes are regulated by gene expression, they are widely influenced by environmental factors, such as stress. Our goals are to identify key biomarkers of cellular phenotypes and cellular responses to environmental stresses. The research in the Copié lab is highly inter-disciplinary, involving exciting research collaborations with multiple colleagues. The analytical approach integrates nuclear magnetic resonance (NMR), mass spectrometry (MS), including new LC-SPE-NMR-MS technology for the discovery of unknown small molecule metabolites, and to expand metabolome coverage. The spectroscopic analyses are coupled with bacterial/human cell culture work, robust metabolite extraction methods, cellular assays, and bioinformatics analysis of multi-omics data. Current research projects involve: (1) metabolic reprogramming of immune cells upon exposure to bacterial pathogens; (2) diagnostic metabolic markers of nutrient-induced non-alcoholic fatty liver disease (NAFLD); (3) the metabolic networks enabling microorganisms' adaptation to extreme environments and their ability to grow in arsenic-contaminated soils; (4) the interplay between neuronal cell death, microbiome dysbiosis, and metabolic dysregulation in animal models of Familial Dysautonomia (FD) neurodegenerative disease.

REPRESENTATIVE PUBLICATIONS

Tomina-Lukaszewska, M., Shi, Z, Tripet, B., McDermott, TR, **Copié, V.,** Bothner B., and Wang (2017) Metabolic Response of *Agrobacterium tumefaciens 5A* to arsenite. Environ. Microbiol, Vol 19(2) 710-721

Rawle, R., Hamerly, T., Tripet, B.P., Giannone, R.J., Wurch, L., Hettich, R.L., Podar, M., **Copié, V.,** Bothner, B. (2017) Integrated omics analysis provides insight to the *Ignicoccus hospitalis-Nanoarcheum equitans* association. Biochim. Biophys. Acta. Jun 4. pii: S0304-4165(17)30187-3

Fuchs, A., Tripet, B.P., Ammons, M.C., and **Copié V.** (2016) Optimization of metabolite extraction protocols for the identification and profiling of small molecule metabolites from planktonic and biofilm *Pseudomonas aeruginosa* cell cultures. Current Metabolomics Vol. 4 (1), pp 1-8

Ammons, M.C., Morrisey, K., Tripet, B.P., Van Leuven, J.Y., Han, A., Lazarus, G.S., Zenilman, J.M., Stewart, P.S., and **Copié, V.** (2015) Biochemical association of metabolic profile and microbiome in chronic pressure ulcer wounds. PLoS One, 2015 May 15;10(5):e0126735.

Hamerly, T., Tripet, B.P., Tigges, M., Giannone, R.J., Wurch, L., Hettich, R.L., Podar, M., **Copié, V.,** and Bothner, B. (2015) Untargeted metabolomics studies employing NMR and LC–MS reveal metabolic coupling between *Nanoarcheum equitans* and its archaeal host *Ignicoccus hospitalis*. Metabolomics. Vol 11(4), pp 895-907.

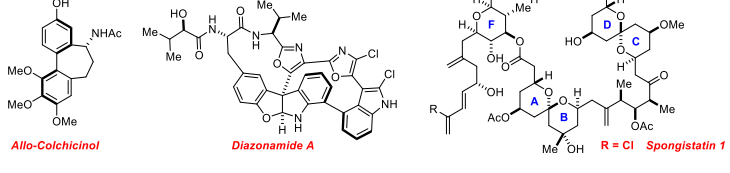
MATTHEW COOK

Assistant Professor, Organic Chemistry
317 Chemistry and Biochemistry Building
matthew.cook6@montana.edu
(406) 994-5625

Cascade Organic Reaction Pathways
Organic Synthesis
Natural Product Synthesis
Pharmaceutical Targets

RESEARCH OVERVIEW

We are actively developing new cascade reaction pathways to build molecular complexity in a step and atom efficient manner. We are focusing our efforts in three areas to develop transformations that can perform complex skeletal rearrangements that define multiple stereogenic centers in a single operation, these are: (1) using multiple pericyclic processes in a cascade; (2) using a single enantioselective transition metal catalyst to perform multiple reactions; (3) using synergistic (or cooperative) catalytic cycles to perform unique yet complementary functions. We are interested in both the unique molecular architectures these reactions can form alongside establishing a deep understanding the mechanisms being performed to aid us further in the development and improvement of them. The development of these processes will lead to new strategies for the synthesis of complex molecules, both natural products and pharmaceutical targets. Our aim is to develop truly useful methods that are general in their scope with good functional group tolerance negating the use of protecting groups and multiple oxidation state changes. We are currently investigating several natural product targets with a wide range of structural and biological features such diazonamide A, spongistatin and allo-colchicinol.



REPRESENTATIVE PUBLICATIONS

"**Palladium Catalyzed Oxidative Synthesis of Highly Functionalized Ortholactone**s" Kate L. Baddeley, Qun Cao, Mark J. Muldoon and Matthew J. Cook Chem. Eur. J. 2015, 21, 7726-7730.

"**Base Mediated Cascade Rearrangements of Aryl Substituted Diallyl Ethers**" Jolene P. Reid, Catherine A. McAdam, Adam, J. S. Johnston, Matthew N. Grayson, Jonathan M. Goodman and Matthew J. Cook* J. Org. Chem. 2015, 80, 1472-1498

"**MIDA Vinylsilanes: Selective Cross-Couplings and Applications to the Synthesis of Functionalized Stilbenes**" Mark G. McLaughlin, Catherine A. McAdam and Matthew J. Cook Org. Lett. 2015, 17, 10-13.

"**Silicon-Directed Rhenium Catalyzed Allylic Substitutions with N-Hydroxycarbamates, N-Hydroxysulfonamides and Hydroxamic Acids**" Sanjay W. Chavhan, Catherine A. McAdam and Matthew J. Cook J. Org. Chem. 2014, 79, 11234-11240.

"**Palladium Catalyzed Decarboxylative Rearrangement of N-Alloc Indoles**" Jun Chen and Matthew J. Cook* Org. Lett. 2013, 15, 1088-1091.

EDWARD A. DRATZ

Professor, Biochemistry
251 Chemistry and Biochemistry Building
dratz@chemistry.montana.edu
(406) 579-3399

Metabolomics, Systems Biology
Type 2 Diabetes, Alzheimer's Disease, Adult Stem Cells
Biochemistry, Proteomic Analysis

RESEARCH OVERVIEW

The Dratz lab uses metabolomics and proteomics to investigate signaling and metabolic networks in cells and tissues. The genome of an organism is quite static, whereas the proteins expressed or modified by cells often change rapidly in response to stimuli and metabolite levels typically respond even faster.

Metabolites are close to the phenotype of cells in health and disease. We have found and are studying new, previously uncharacterized lipid metabolites, which change drastically in Type 2 diabetes and have evidence that these metabolites have deeply functional roles in insulin resistance, characteristic of T2D. These novel metabolites promise to provide powerful and very early warning biomarkers of T2D and appear to point the way to nutritional supplementation to prevent and reverse T2D. Metabolic and proteomic changes in Alzheimer's disease promise to provide new insights into mechanisms, potentials for prevention, and provide early warning 10 years in advance of clinical symptoms

The long-term health of the body depends on replacement of cells with stem cells in a "stem cell supply chain". The propagation of adult stem cells in culture depends on several key nutrients, and we are pursuing the hypothesis that optimizing nutrition in culture reflects distinct needs of the stem cells in the bodies of different individuals, and can be used to prevent disease. Prof. Dratz has a long-standing interest in biochemical nutrition and is applying metabolomic methods in a multidisciplinary team effort for developing crops with improved nutritional content for disease prevention, in collaboration with researchers in Plant Sciences and Health and Human Development. Emerging efforts are working with nutritional supplementation of school children to assess and improve school performance and mood.

REPRESENTATIVE PUBLICATIONS

Tanaka N, Ashour D, Dratz E, Halonen S., Use of human induced pluripotent stem cell-derived neurons as a model for Cerebral Toxoplasmosis, Microbes Infect. 2016 Jul-Aug;18(7-8):496-504.

Usselman RJ, Chavarriaga C, Castello PR, Procopio M, Ritz T, Dratz EA, Singel DJ, Martino CF, The Quantum Biology of Reactive Oxygen Species Partitioning Impacts Cellular Bioenergetics, Sci Rep. 2016 Dec 20;6:38543.

Dachet F, Bagla S, Keren-Aviram G, Morton A, Balan K, Saadat L, Valyi-Nagy T, Kupsky W, Song F, Dratz E, Loeb JA. Predicting novel histopathological microlesions in human epileptic brain through transcriptional clustering. Brain. 2015 Feb;138(Pt 2):356-70.

Reeves BD, Joshi N, Campanello GC, Hilmer JK, Chetia L, Vance JA, Reinschmidt JN, Miller CG, Giedroc DP, Dratz EA, Singel DJ, Grieco PA Conversion of S-phenyl sulfonylcysteine residues to mixed disulfides at pH 4.0: utility in protein thiol blocking and in protein-S-nitrosothiol detection. Org Biomol Chem. 2014 Oct 28;12(40):7942-56.

JENNIFER L. DUBOIS

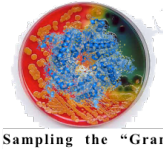
Associate Professor, Biological and Bioinorganic Chemistry

221 Chemistry and Biochemistry Building
Jennifer.dubois1@montana.edu
(406) 994-2844

Microbial Biochemistry of O_2, CO_2, and heme: Applications in Health, Energy, and the Environment

RESEARCH OVERVIEW

Modern science is tasked with solving many big problems. Some of the biggest may find their solutions in the smallest living things: the diverse microbial species that have conquered every niche on earth by molecular adaptation. In our lab, we ask: how do these molecules work? Can some of them be used to solve problems related to renewable energy generation, or improving human health? Inside a typical person, there are 10 times more bacterial than human cells. Some of these bacteria are friends and some are foes. By understanding how these bacteria work, on a molecular level, can we selectively eliminate the invaders? Can we understand and promote the collaborators? Our longstanding expertise is with biocatalytic processes exploiting atmospheric oxygen and its partners – iron, heme, organic cofactors, or sometimes just a protein environment alone. These reactions may be important for bacterial pathogenicity. Or, they may solve economically important problems, like the remodeling of renewable carbon sources in a chemically green way. Finally, the same kind of reactions carried out by bacteria in the human digestive tract appear to influence how well the human host derives nutrients from food, as well as the progression of diseases like colon cancer. Our lab is currently working on all three of these applications. We are a problem-based lab that uses many methodologies, often working as part of a team, with coworkers at the MSU Center for Biofilm Engineering, the National Renewable Energy Lab, and universities around the U.S.



Sampling the "Grand Prismatic Petri Plate". Microbial diversity, whether in the Yellowstone hot springs or the human gut, is reflected in the molecular diversity in vast genomic databases. Some of the most interesting molecules are enzymes, like the blue one in the image. Our lab focuses on identifying important molecules and pathways from microbial sources and understanding how they work on an atomic level.

REPRESENTATIVE PUBLICATIONS

Celis, A. I.; Gauss, G.H.; Streit, B. R.; Shisler, K.; Moraski, G. C.; Rodgers, K. R.; Lukat-Rodgers, G. S.; Peters, J. W.; DuBois, J. L. (2017) Structure-based mechanism for decarboxylation reactions mediated by amino acids and heme propionates in coproheme decarboxylase (HemQ). *J. Am. Chem. Soc., 139,* 1900-1911.

Prussia, G. A.; Gauss, G. H.; Mus, F.; Conner, L.; DuBois, J. L.; Peters, J. W. (2016) Substitution of a conserved catalytic dyad into 2-KPCC causes loss of carboxylation activity. *FEBS Lett., 590*, 2991-2996.

Streit, B.R., Kant, R., Tokmina-Lukaszewska, M., Celis, A.I., Machovina, M.M., Skaar, E.P., Bothner, B., DuBois, J.L. (2016) "Time-resolved Studies of IsdG Protein Identify Molecular Signposts along the Non-canonical Heme Oxygenase Pathway." *J. Biol. Chem.291:* 862-871.

Machovina, M.M., Usselman, R.J., DuBois, J.L. (2016) "Cofactorless Dioxygen Catalysis by an Antibiotic Biosynthesis Monooxygenase: Testing the Flavin Hypothesis." *J. Biol. Chem.* 291(34):17816-28

DuBois, J. L., Ojha, S. "Production of Dioxygen in the Dark: Dismutases of Oxyanions," (2015) *Metal Ions in Life Sciences*, Wiley and Sons, volume 15, Guest Editors: P.M. H. Kroneck and M.E. Sosa-Torres; Series editors: A.Sigel, H. Sigel, and R. K. O. Sigel, pp. 45-87.

ERIK GRUMSTRUP

Assistant Professor, Materials Science Program
047 Chemistry and Biochemistry Building
erik.grumstrup@montana.edu
https://www.mtmatsci.org
(406) 994-2988

Nonlinear Optical Microscopy
Nanoscience, Materials Synthesis and Spectroscopy
Chemical Imaging

RESEARCH OVERVIEW

Chemical and materials science research has long focused on well-defined systems: atoms, molecules, and pure crystals. While enormous insight can be gained from studies of these prototypical systems, practical devices we use every day, from solar cells to the transistors that make up a computer processor, are comprised of multiple materials whose performance is often determined not only by the properties of the pure bulk materials, but also (and sometimes primarily) by interfaces, defects, surfaces, and their specific geometry or structure.

Research in my group develops and uses nonlinear microscopies to study time-dependent electronic and chemical dynamics in the context of these "non-idealities". We are primarily interested in understanding photochemistry and charge-transport processes as they apply to next-generation photovoltaic materials, nanoscale (opto)electronics, and heterogeneous catalysis. With a variety of microscopy techniques, we watch non-equilibrium dynamics as they evolve in both space and time, on length scales between 10 nm and 10 μm and on time scales of femtoseconds to milliseconds. These tools give us the ability to directly image electrons as they move through materials and spectroscopically study interfaces with exceptionally high structural specificity. Ultimately, we seek to understand fundamental questions about material functionality: How does charge separation occur in bulk heterojunction solar cells? Where are the active sites on nanostructured catalysts? How does electron mobility change at the interface of two domains or materials?

To tackle such far-reaching questions, our group draws from a wide range of disciplines including nonlinear optics, ultrafast spectroscopy, material synthesis, and quantum mechanical and semiclassical computer modeling. Research projects will reflect this multi-faceted approach and generate opportunities for highly motivated students to develop wide-ranging expertise and collaborate with a diverse group of researchers.

REPRESENTATIVE PUBLICATIONS

Hill, A. H.; Smyser, K. E.; Kennedy, C. L.; Massaro, E. S.; Grumstrup, E. M., Screened Charge Carrier Transport in Methylammonium Lead Iodide Perovskite Thin Films. J. Phys. Chem. Lett. 2017, Just Accepted. dx.doi.org/10.1021/acs.jpclett.7b00046

Massaro, E. S.; Hill, A. H.; Kennedy, C. L.; Grumstrup, E. M., Imaging theory of structured pump-probe microscopy. *Opt. Express* **2016**, 24, 20868.

Massaro, E. S.; Hill, A. H.; Grumstrup, E. M., Super-Resolution Structured Pump–Probe Microscopy. ACS Photonics **2016**, 3, 501-506.

Grumstrup, E. M.; Gabriel, M. M.; Cating, E. E. M.; Van Goethem, E. M.; Papanikolas, J. M., Pump–probe microscopy: Visualization and spectroscopy of ultrafast dynamics at the nanoscale. Chem. Phys. **2015**, 458, 30-40.

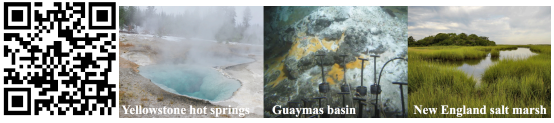
ROLAND HATZENPICHLER

Assistant Professor, Biochemistry

111 Chemistry and Biochemistry

roland.hatzenpichler@montana.edu

www.environmental-microbiology.com



Biochemistry

Environmental Microbiology

Bioorthogonal Chemistry

RESEARCH OVERVIEW

Our research activities focus on microbial ecophysiology: the study of the physiology of microorganisms with respect to their habitat. We are interested in how the activity of the "uncultured majority" – the large number of microbes that evades cultivation under laboratory conditions – impacts humans and the environment on a micron to global scale. We are convinced that only by gaining an understanding of microbes directly in their habitats researchers will be able to elucidate the mechanisms of microbial interactions with the biotic and abiotic world. To accomplish these goals, we apply an integrative approach that bridges the two extremes of the microbial scale bar: the individual cell and the whole community.

The research questions we address are: (i) who is doing what (linking phylogenetic identity and physiological function); (ii) what are the abiotic and biotic factors controlling microbial activity; (iii) how does this activity affect the environment and us humans; (iv) what are the limits to microbial metabolism in terms of energy, space, and time; and (v) how can we discover novel structures, functions, and biotechnological potential within uncharted branches of the tree of life? Our approach to these problems is inherently multi-disciplinary and multi-scaled. In order to address previously unrecognized physiologies and cellular interactions of uncultured microbes, we employ a unique combination of single cell and meta-genomics (as hypotheses generator), high-through-put bioorthogonal compound labeling-based metabolic screening (to identify geochemical and biotic parameters driving microbial ecology), and targeted stable isotope probing (to identify specific growth-sustaining substrates). We currently work with three main sample types: sediments from the Guaymas deep-sea basin, geothermal springs in Yellowstone National Park, and a New England salt marsh. We are particularly interested in revealing the physiology, biogeochemical impact, and ecology of only very recently discovered archaea.

Research projects in our group are suitable for students with interests in biochemistry, bioorthogonal chemistry, cell physiology, biogeochemistry, and/or environmental microbiology. Students can expect to learn techniques that may include: in field experimentation, genome sequencing, genome annotation, fluorescence *in situ* hybridization, bioorthogonal compound labeling, stable isotope labeling, single cell resolved Raman spectroscopy, and proteomics.

REPRESENTATIVE PUBLICATIONS

Hatzenpichler R, Connon SA, Goudeau D, et al. Visualizing in situ translational activity for identifying and sorting slow-growing archaeal-bacterial consortia. Proc Natl Acad Sci USA, 113: E4069-E4078 (2016)

Hatzenpichler R, Scheller S, Tavormina PL, et al. In situ visualization of newly synthesized proteins in environmental microbes using amino acid tagging and click chemistry. Environ Microbiol, 16: 2568-2590 (2014)

Ma L, Kim J, **Hatzenpichler R**, et al. Gene-targeted microfluidic cultivation validated by isolation of a gut bacterium listed in Human Microbiome Project's Most Wanted taxa. Proc Natl Acad Sci USA, 111: 9768–9773 (2014)

Lebedeva EV, **Hatzenpichler R**, et al. Enrichment and genome sequence of the group I.1a ammonia-oxidizing archaeon "Ca. Nitrosotenuis uzonensis" representing a clade globally distributed in thermal habitats. PLoS One, 8: e80835 (2013)

Hatzenpichler R. Diversity, physiology, and niche differentiation of ammonia-oxidizing archaea. Appl Environ Microbiol, 78: 7501-7510 (2012)

Shapiro OH, **Hatzenpichler R**, et al. Multicellular photo-magnetotactic bacteria. Environ Microbiol Rep, 3: 233-238 (2011)

MARTIN LAWRENCE

Professor, Biochemistry

159 Chemistry and Biochemistry Building

lawrence@chemistry.montana.edu

(406) 994-5625

Biochemistry

Structural Biology

CRISPR/Cas and Virology

Iron Transport

RESEARCH OVERVIEW

CRISPR/Cas: The CRISPR/Cas system is a recently discovered adaptive immune system present in Bacteria and Archaea. While CRISPR/Cas9 is currently the rage for genome editing purposes in eukaryotes, there is still much we do not understand about the workings of CRISPR/Cas in general. Our lab has made seminal contributions to our understanding of Type 1 CRISPR/Cas systems and in elucidating the regulatory roles of Cas proteins containing the CRISPR Associated Rossmann Fold, or CARF domain. However, much work remains to be done in this exciting area.

Hyperthermophilic Viruses from Yellowstone National Park: Viruses have been found in almost every known environment on earth, including extreme acidic, thermal environments. However, while more than 5,000 eukaryotic viruses and bacteriophage have been studied in detail, fewer than 50 archaeal viruses have been investigated at any level. Thus, our knowledge of viruses in the 3rd domain of life is minimal. What is clear, is that these viruses differ significantly in morphology and genetic content from their bacterial and eukaryotic counterparts. We are using structural and biochemical approaches to investigate these fascinating viruses.

Iron Transport and Homeostasis: Iron containing metallo-proteins are necessary for the synthesis of DNA, respiration and many key metabolic reactions. Thus, life as we know it is fully dependent on iron. However, excess iron is toxic, as Fe^{2+} combines with naturally occurring peroxide to produce the hydroxyl radical, one of several reactive oxygen species (ROS) that contribute to oxidative stress, reacting indiscriminately with DNA, proteins and lipids. Hence, iron levels must be carefully balanced to sustain key metabolic processes, while minimizing production of ROS. To this end, an elaborate system of transport, storage and regulatory proteins has evolved to effect iron homeostasis in humans and other organisms, including human pathogens. We are involved in structural and biochemical studies of the iron transport machinery in an effort to address the many, prevalent diseases exacerbated by errors in human iron metabolism (anemia, diabetes, cancer, heart attack, stroke, liver cirrhosis and arthritis).

REPRESENTATIVE PUBLICATIONS

Topuzlu E, Lawrence CM. Recognition of a pseudo-symmetric RNA tetranucleotide by Csx3, a new member of the CRISPR associated Rossmann fold superfamily. RNA Biol. 2016;13(2):254-7.

Sorek R, Lawrence CM, Wiedenheft B. CRISPR-mediated adaptive immune systems in bacteria and archaea. Annu Rev Biochem. 2013;82:237-66.

Veesler D, Ng TS, Sendamarai AK, Eilers BJ, Lawrence CM, Lok SM, Young MJ, Johnson JE, Fu CY. Atomic structure of the 75 MDa extremophile Sulfolobus turreted icosahedral virus determined by CryoEM and X-ray crystallography. Proc Natl Acad Sci U S A. 2013 Apr 2;110(14):5504-9.

Kleven MD, Dlakić M, Lawrence CM. Characterization of a single b-type heme, FAD, and metal binding sites in the transmembrane domain of six-transmembrane epithelial antigen of the prostate (STEAP) family proteins. J Biol Chem. 2015 Sep11;290(37):22558-69.

Sendamarai AK, Ohgami RS, Fleming MD, Lawrence CM. Structure of the membrane proximal oxidoreductase domain of human Steap3, the dominant ferrireductase of the erythroid transferrin cycle. Proc Natl Acad Sci U S A. 2008 May 27;105(21):7410-5.

THOMAS S. LIVINGHOUSE

Professor, Organic Chemistry

315 Chemistry and Biochemistry Building

thomas.livinghouse@montana.edu

Tel.: (406) 994-5408

Natural Product Synthesis

Organometallic Chemistry

Homogeneous Catalysis

Quorum Sensing Bacteria (Biofilms)

RESEARCH OVERVIEW

My research program specializes in the areas of organic synthesis, organometallic chemistry and quorum sensing bacteria (biofilm) regulation. Selected influential contributions and innovations include (in chronological order); the development of intramolecular imidate methylide cycloadditions, acylnitrilium and episulfonium ion initiated carbocyclizations, imidotitanium-alkyne [2+2] cycloadditions, the first examples of catalytic intramolecular Rh(1) [4+2] and Co(0) [2+2+1] cycloadditions, the synthesis of P-chiral phosphines by dynamic resolution, stereoselective cyclizations terminated by 2-propylidine-1,3-bis(silane)s, and hydroaminations, hydroborations and hydrosilylations catalyzed by nonmetallocene complexes of the early transition metals. Most recently, we have developed a novel and unusually efficient method for complex heterocycle synthesis that relies on a diethylzinc mediated metalloamination/cyclization-electrophilic functionalization sequence.

The scientific objectives of a collaborative research with the Center for Biofilm Engineering are to design and synthesize a conceptually new set of first-in-class antimicrobial molecules and to subsequently evaluate these for efficacy against an array of biofilm forming microorganisms. Our strategy is based on the concept of "selective uptake" of a less toxic derivative of the corresponding antimicrobial that would subsequently undergo rapid chemical conversion to the unmasked antimicrobial that is *trapped within the cell*. Interestingly, the chemical basis that underlies the foregoing hypothesis has been known for years and is routinely used for the selective concentration of fluorescent dyes within living cells. Accordingly, we develop new antimicrobial agents that partition readily into the biofilm phase, both improving their activity in that phase and reducing their loss in the milieu outside the biofilm. The pro-drugs of interest, molecules with limited reactivity or antimicrobial activity themselves, are designed to be sufficiently non-polar that they can passively move across the microbial cell membrane. Once inside the cell, multiple ester linkages in the pro-drug will be cleaved by ubiquitous esterases, releasing the charged, active antimicrobial agent. This chemical transformation provide a mechanism for concentrating the antimicrobial agent in the biofilm as well as preventing its destruction by neutralizing reactions in the fluid medium external to the biofilm.

REPRESENTATIVE PUBLICATIONS

"1,2-Disubstituted Alkenes as Migratory Insertion Participants in Zn(II) Promoted Metalloamination/ Cyclizations of *N,N*-Dimethylhydrazinoalkenes." Sunsdahl, B.; Mickelsen, K.; Zabawa, S.; Anderson, B. K.; Livinghouse, T. *J. Org. Chem.* **2016**, *81*, 10.1021/acs.joc.6b01328.

"A Divergent Stereocontrolled Synthesis of the Enantiopure Tetracyclic Cores of Asparagamine A and Stemofoline via an Intramolecular 2-Propylidine-1,3-(bis)silane Bicyclization" Anderson, B. K.; Livinghouse, T. *J. Org. Chem.* **2015**, *80*, 9847-9855.

"Intramolecular Metalloaminations of N,N-Dimethylhydrazinoalkenes. A Versatile Method for the Synthesis of Functionalized Piperidines and Pyrrolidines." Sunsdahl, B.; Smith, A. R.; Livinghouse, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 14352- 14356.

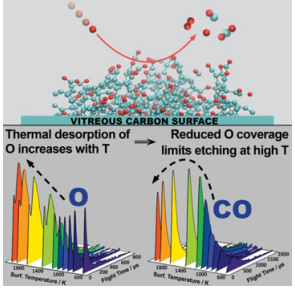
"*N,N*'-Dibenzosuberyl-1,1'-Binaphthyl-2,2'-diamine. A Highly Effective Supporting Ligand for the Enantioselective Cyclization of Aminoalkenes Catalyzed by Chelating Diamide Complexes of La(III) and Y(III)." Huynh, K.; Tom Livinghouse. T.; Lovick, H. M. *Synlett*, **2014**, 1721-1724.

TIMOTHY K. MINTON

Professor, Physical Chemistry
Molecular Beam Facility
tminton@montana.edu
(406) 994-5394

Reaction dynamics in the gas phase and at the gas-surface interface; Materials reactivity and degradation

RESEARCH OVERVIEW



Research in the Minton Lab comprises gas-phase and gas-surface reaction dynamics and kinetics. Specifically, crossed-beams and beam-surface scattering methods are used to study energy transfer and reaction dynamics, typically at hyperthermal energies, with applications to the analysis of liquid surface chemical structure and spacecraft-environment interactions. Current research projects include studies of structure, reactivity, and transport at the gas/ionic liquid interface, oxidation of carbon and silicon carbide at high temperatures, decomposition of ablative heat shield materials on spacecraft and hypersonic vehicles, a concentrator for detection of trace gases in tenuous planetary atmospheres, and the development of new and more durable materials for use on spacecraft in low Earth orbit. Experimental techniques commonly used in the Minton Lab include the creation of atomic and molecular beams (including hyperthermal beams), crossed-beams scattering, beam-surface scattering, mass spectrometry, laser-induced fluorescence (LIF), resonance-enhanced multiphoton ionization (REMPI), ion velocity-map imaging, surface topographical analysis (AFM, SEM), surface chemical analysis (XPS) and surface structural and chemical analysis by MD and QM/MM simulations.

REPRESENTATIVE PUBLICATIONS

"Inelastic and Reactive Scattering Dynamics of Hyperthermal O and O_2 on Hot Vitreous Carbon Surfaces," V. J. Murray, B. C. Marshall, P. J. Woodburn, and T. K. Minton, *J. Phys. Chem. C* **119**, 14780-14796 (2015).

"Atomic and Molecular Collisions at Liquid Surfaces," M. A. Tesa-Serrate, E. J. Smoll, Jr., T. K. Minton, K. G. McKendrick, *Annu. Rev. Phys. Chem.* **67**, 515-540 (2016).

"Scattering Dynamics of Oxygen Atoms on Imidazolium Tetrafluoroborate Ionic Liquid Surfaces: Dependence on Alkyl Chain Length," B. C. Marshall, E. J. Smoll, Jr., S. M. Purcell, M. L. Costen, K. G. McKendrick, and T. K. Minton," *J. Phys. Chem. C* **120**, 12472-12483 (2016).

"Dynamics of the O-Atom Exchange Reaction $^{16}O(^3P) + {}^{18}O^{18}O(^3\Sigma_g^-) \rightarrow {}^{16}O^{18}O(^3\Sigma_g^-) + {}^{18}O(^3P)$ at Hyperthermal Energies," S. A. Lahankar, J. Zhang, T. K. Minton, H. Guo, and G. Lendvay, *J. Phys. Chem A* **120**, 5348-5359 (2016).

"Resistance of POSS Polyimide Blends to Hyperthermal Atomic Oxygen Attack," M. Qian, V. J. Murray, W. Wei, B. C. Marshall, and T. K. Minton, *ACS Appl. Mater. Interfaces* **8**, 33982–33992 (2016).

"Finite-Rate Oxidation Model for Carbon Surfaces from Molecular Beam Experiments," S. Poovathingal, T. E. Schwartzentruber, V. J. Murray, T. K. Minton, and G. V. Candler, *AIAA J.*, published on line; DOI: 10.2514/1.J055371.

SHARON R. NEUFELDT

Assistant Professor, Chemistry

319 Chemistry and Biochemistry Building

sharon.neufeldt@gmail.com

(406) 994-5692

neufeldt-chemistry.com

Catalysis

Organic Chemistry

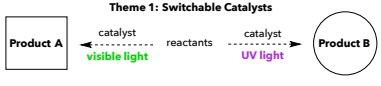
Organometallic Chemistry

Computational Chemistry

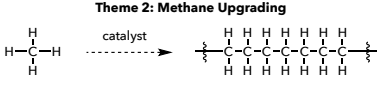
RESEARCH OVERVIEW

Our research group works to develop transition metal catalyzed chemical reactions. We focus on reactions that transform small organic molecules into structures that are more valuable and complex. We use "homogeneous" catalysts that are discrete organometallic complexes containing a set of small molecule fragments ("ligands") clustered around a single metal atom. One major advantage of using these structurally well-defined catalysts is that their behavior can be understood and predicted through computational and experimental studies. Furthermore, the catalysts' properties can be tuned through ligand modification or by changing the identity of the metal center. We use initial computational studies to help streamline the design of catalytic systems in our laboratory.

The first research theme is "switchable catalysts", which are defined as one that is able to switch between two or more tasks (types of reactions) in response to an external stimulus. Such catalysts would have numerous applications that are not feasible with traditional catalysts, such as effecting sequences of transformations in a particular order to synthesize a complex molecule or sequence-controlled multiblock copolymers.



The second research theme is "methane upgrading". Despite being one of the most abundant energy sources in the United States, natural gas is underutilized. Worse, large quantities of natural gas are squandered by flaring or venting at oil fields, a practice that is both wasteful and detrimental to the environment. These misuses are largely due to the difficulty and cost of transporting natural gas (methane) over long distances to bring it to the market. To encourage more efficient and responsible use of natural gas, we are working on techniques to upgrade methane using transition metals to transform methane into chemicals that are more easily transported and/or that are more valuable to counterbalance the cost of transport.



REPRESENTATIVE PUBLICATIONS

Neufeldt, S. R.; Jiménez-Osés, G.; Huckins, J. R.; Thiel, O. R.; Houk, K. N. Pyridine *N*-Oxide vs. Pyridine Substrates for Rh(III)-Catalyzed Oxidative C–H Bond Functionalization. *J. Am. Chem. Soc.* **2015**, *137*, 9843.

Neufeldt, S. R.; Jiménez-Osés, G.; Comins, D. L.; Houk, K. N. A Twist on Facial Selectivity of Hydride Reductions of Cyclic Ketones: Twist-Boat Conformers in Cyclohexanone, Piperidone, and Tropinone Reactions. *J. Org. Chem*. **2014**, *79*, 11609.

Neufeldt, S. R.; Seigerman, C. K.; Sanford, M. S. Mild Palladium-Catalyzed C–H Alkylation Using Potassium Alkyltrifluoroborates in Combination with MnF_3. *Org. Lett*. **2013**, *15*, 2302.

Neufeldt, S. R.; Sanford, M. S. Asymmetric Chiral Ligand-Directed Alkene Dioxygenation. *Org. Lett*. **2013**, *15*, 46.

Neufeldt, S. R.; Sanford, M. S. Combining Transition Metal Catalysis with Radical Chemistry: Dramatic Acceleration of Palladium-Catalyzed C–H Arylation with Diaryliodonium Salts. *Adv. Synth. Catal*. **2012**, *354*, 3517.

RENEE REIJO PERA

Vice President of Research at Montana State University, Professor Biochemistry and Cell Biology and Neuroscience

Montana Hall room 207 (office)
244 Chemistry and Biochemistry (lab)
renee.reijopera@montana.edu
(406)-994-5062

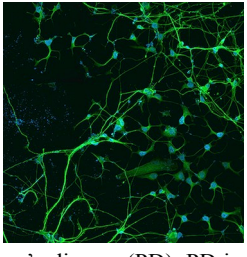
Stem Cells

Biochemistry

Parkinson's Disease

Neurodegeneration

RESEARCH OVERVIEW



The Reijo Pera Lab focuses on understanding the molecular mechanisms underpinning human development and disease through the use of human pluripotent stem cell based systems. Pluripotent stem cells are unique in their ability to give rise to all the cells of the human body—neurons, skins, epithelia, and germ line. As such, they have become a valuable resource for in vitro studies that seek to understand human development and disease.

The Reijo Pera Lab is actively harnessing the power of stem cells to study neurodegenerative diseases such as Parkinson's disease (PD). PD is a neurodegenerative disease that arises after the dopaminergic neurons of the midbrain begin to die off, leading to severe motor control issues, among other symptoms. Even though approximately 60,000 Americans are diagnosed with the disease every year, the cause of death of the midbrain dopaminergic neurons is not well understood—and furthermore, efficient long-term treatments are unavailable.

Using stem cell derived dopaminergic neurons, the Reijo Pera Lab is actively studying PD via combined approaches that include proteomics, metabolomics, and genetics, the Reijo Pera lab hopes to not only understand the etiology of the disease but also to develop potential treatments for PD via small molecule screening and identification of factors that modulate neuronal demise.

REPRESENTATIVE PUBLICATIONS

Durruthy-Durruthy J, Sebastiano V, Wossidlo M, Cepeda D, Cui J, Grow EJ, Davila J, Mall M, Wong WH, Wysocka J, Au KF, Reijo Pera RA. The primate-specific noncoding RNA HPAT5 regulates pluripotency during human preimplantation development and nuclear reprogramming. Nature Genet. 2016 Jan;48:44-52.

Cui J, Rothstein M, Bennett T, Zhang P, Xia N, Reijo Pera RA. Quantification of dopaminergic neuron differentiation and neurotoxicity via a genetic reporter. Scientific Rep. 2016 Apr 28; 6:25181.

Xia N, Zhang P, Fang F, Wang Z, Rothstein M, Angulo B, Chiang R, Taylor J, Reijo Pera RA. Transcriptional comparison of human induced and primary midbrain dopaminergic neurons. Scientific Rep. 2016 Feb 4;6:20270.

Grow EJ, Flynn RA, Chavez SL, Bayless NL, Wossidlo M, Wesche DJ, Martin L, Ware CB, Blish CA, Chang HY, Reijo Pera RA, Wysocka J. Intrinsic retroviral reactivation in human preimplantation embryos and pluripotent cells. Nature 2015 Jun 11;522:221-5.

Byers B, Cord B, Nguyen HN, Schüle B, Fenno L, Lee PC, Deisseroth K, Langston JW, Reijo Pera RR, Palmer TD. SNCA triplication Parkinson's patient's iPSC-derived DA neurons accumulate α-synuclein and are susceptible to oxidative stress. PLoS One 2011;6(11):e26159.

Nguyen HN, Byers B, Cord B, Shcheglovitov A, Byrne J, Gujar P, Kee K, Schüle B, Dolmetsch RE, Langston W, Palmer TD, Reijo Pera RA. LRRK2 mutant iPSC-derived DA neurons demonstrate increased susceptibility to oxidative stress. Cell Stem Cell 2011 Mar 4;8:267-80.

ERIC M. SHEPARD

Assistant Research Professor, Biochemistry

256 Chemistry and Biochemistry

eshepard@montana.edu

(406) 994-4071

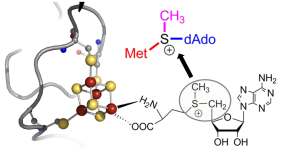
Metalloenzymology

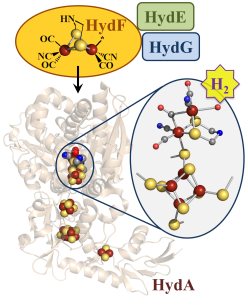
Biomimetic Protein Maquettes

Fe-S Cofactor Biosynthesis

RESEARCH OVERVIEW

Biomimetic Design of Radical S-Adenosylmethionine (SAM) Maquettes. This project focuses on the radical SAM superfamily of enzymes; these metalloenzymes harbor an essential redox active [4Fe-4S] cluster that contains a site differentiated Fe site that promotes the bidentate coordination of SAM and the subsequent reductive cleavage at its sulfonium center (*see image above*). Using a retrosynthetic approach, we employ parallel synthetic, spectroscopic, and computational investigations to develop and characterize small CX_3CX_2C containing oligopeptides that coordinate [4Fe-4S] clusters which are functional in SAM chemistry. We address chemical, structural, and mechanistic issues through structure-function relationships and the insights gained from these maquette studies will contribute to our understanding of how and why nature uses this platform as its preferred method for generating and propagating radical reactions.





[FeFe]-Hydrogenase Maturation: Biosynthesis of the H-cluster. Metal cluster assembly in [FeFe]-hydrogenase is examined via physical biochemical approaches. Three gene products, denoted HydE, HydF, and HydG, function in the assembly and maturation of [FeFe]-hydrogenase through their specific role in the biosynthesis of the uniquely decorated 2Fe subcluster that is the catalytic center for hydrogen production (known as the H-cluster). Two of these enzymes (HydE and HydG) belong to the radical SAM superfamily, and are proposed to synthesize the unusual carbon monoxide, cyanide, and dithiomethylamine ligands of the H-cluster. HydE and HydG interact with HydF, which is a GTPase that functions as a scaffold/carrier during H-cluster assembly. Our goals are to develop a molecular-level understanding of the reactions catalyzed by HydE, HydF, and HydG and to elucidate how these three enzymes come together to synthesize one of nature's most extraordinary metallocofactors.

REPRESENTATIVE PUBLICATIONS

Shepard E.M., Byer A.S., Aggarwal P., Betz J.N., Scott A.G., Shisler K., Usselman R.J., Eaton G.R., Eaton S.S., Broderick J.B. (2017) Electron spin relaxation and biochemical characterization of HydF: Insights into [2Fe-2S] and [4Fe-4S] cluster communication and hydrogenase activation, *Biochemistry*, In Press.

Shepard E.M., Byer A.S., Betz J.N., Peters J.W., Broderick J.B. (2016) A redox active [2Fe-2S] cluster on the hydrogenase maturase HydF, *Biochemistry*, 55, 3514-3527.

Shepard E.M., Dooley D.M. (2015) Inhibition and oxygen activation in copper amine oxidases, *Acc. Chem. Res.* 48, 1218-1226.

Broderick J.B., Duffus B.R., Duschene K.S., Shepard E.M. (2014) Radical S-adenosylmethionine enzymes, *Chem. Rev.* 114, 4229-4317.

Shepard E.M., Duffus B.R., George S.J., McGlynn S.E., Challand M.R., Swanson K.D., Roach P.L., Cramer S.P., Peters J.W., Broderick J.B. (2010) [FeFe]-hydrogenase maturation: HydG-catalyzed synthesis of carbon monoxide, *J. Amer. Chem. Soc.* 132, 9247-9249.

Shepard E.M., McGlynn S.E., Bueling A.L., Grady-Smith C.S., George S.J., Winslow M.A., Cramer S.P., Peters J.W., Broderick J.B. (2010) Synthesis of the 2Fe subcluster of the [FeFe]-hydrogenase H-cluster on HydF scaffold, *Proc. Natl. Acad. Sci. USA*, 107, 10448-10453.

NICHOLAS P. STADIE

Assistant Professor, Chemistry

049 Chemistry and Biochemistry Building

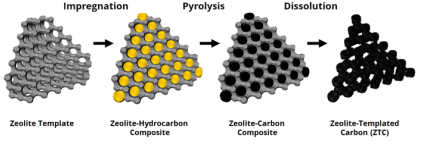
(406) 994-4801

Materials Synthesis

Thermodynamics

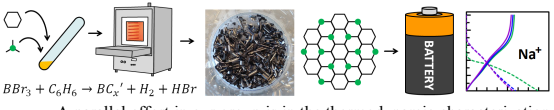
Energy Storage

RESEARCH OVERVIEW



Porous materials abound in useful applications and are also fundamentally interesting; after all, at what length scale do large macromolecules end and solid-state frameworks begin? Our group is focused on the design, synthesis, and characterization of porous adsorbent materials based on carbon using a templating approach. We have practical interests in the gas-solid interface (for storing chemical fuels) as well as the ion-solid interface (for electrochemical energy storage) in these materials, and control of this interface via structure (e.g., pore size) and chemistry (B-, N-, S-, P-doping, etc.) are goals of this work.

En route to exploring synthetic routes to high surface area carbon-based materials of differing chemical nature, we also explore analogous pathways to bulk, nonporous materials (i.e., graphites). We use solid-state synthesis techniques to substitute carbon for heteroatom dopants within the graphitic structure; a challenge in this work is in the accurate characterization of the resulting changes in composition and/or structure, which often have coupled effects. This challenge necessitates the use of multiple techniques, from microscopy and diffraction methods to Raman spectroscopy and sometimes unusual (light-element specific) techniques like elastic recoil detection analysis.



A parallel effort in our group is in the thermodynamic characterization and modeling of physical adsorption systems at the gas-solid interface, especially in understanding the unusual phenomena that exist under "high pressures" (for us, defined as the region of the phase diagram wherein the gas phase is *significantly non-ideal*). We not only seek the practical information of "how much" gas is stored on a particular solid under these conditions, but we also seek to know "how strong" the interaction is. Neither property is particularly easy to measure at high pressures, but the results have important implications for questions in wide-ranging applications such as on-board automotive fuel storage (e.g., hydrogen storage) and geological energy resources (think deep underground!).

REPRESENTATIVE PUBLICATIONS

N. P. Stadie, E. Billeter, L. Piveteau, K. Kravchyk, M. Döbeli, M. V. Kovalenko, "Direct Synthesis of Bulk Boron-Doped Graphitic Carbon" **Chem. Mater.**, 29 (7), 3211 (2017).

N. P. Stadie, S. Wang, K. V. Kravchyk, M. V. Kovalenko, "Zeolite-Templated Carbon as an Ordered Microporous Electrode for Aluminum Batteries" **ACS Nano**, 11 (2), 1911 (2017).

N. P. Stadie, E. Callini, B. Richter, T. R. Jensen, A. Borgschulte, A. Züttel, "Supercritical N_2 Processing as a Route to the Clean Dehydrogenation of Porous $Mg(BH_4)_2$" **J. Am. Chem. Soc.**, 136, 8181 (2014).

N. P. Stadie, M. Murialdo, C. C. Ahn, B. Fultz, "Anomalous Isosteric Enthalpy of Adsorption of Methane on Zeolite-Templated Carbon" **J. Am. Chem. Soc.**, 135, 990 (2013).

ROBERT K. SZILAGYI

Associate Professor, Physical Inorganic Chemistry

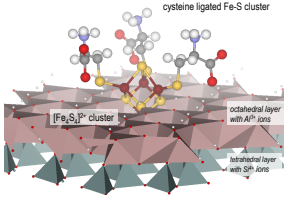
253 Chemistry and Biochemistry Building
szilagyi@montana.edu
computational.chemistry.montana.edu
(406) 994-5263

Electronic Structure Theory
Coordination Chemistry
Organometallic Chemistry
Synchrotron Radiation
Materials Science

RESEARCH OVERVIEW

Despite their simple chemical composition, clay minerals have rather remarkable structures, and practically unexplored chemical reactivity. Nowadays, clays are being widely considered as industrial raw materials; however, their application greatly depends on their surface properties. Separation of clay layers (delamination) and elimination of the crystallographic order (exfoliation) alter their morphology and in parallel enhances their industrial value. The exfoliated clay layers are of great interest due to their high surface area and feasibility for functionalization. The current approach for delamination and exfoliation processes is shockingly 'trial-and-error' based. Contrary, computer-aided rationalized design allows for economic preparation of nanoscale clay particles and hybrid materials containing organic and/or inorganic reagents with tailored properties.

Using $Fe^{(III)}$-containing clays from natural sources and hydrothermal syntheses, we explore the molecular mechanism of delamination and exfoliation for chips- and tube-like nanoscale materials, and functionalize the $Fe^{(III)}$-sites to form biology inspired Fe-S clusters. We synthesize transition metal doped kaolinites that open up new chemical reactivity patterns. We develop computational models to understand and design experiments. The combined application of chemical synthesis, analytical measurements, and computer modelling enable us to construct functional models of metalloenzymes, heterogenized homogeneous catalysts, and manufacture surfaces that are tailored to a given chemical transformation.



REPRESENTATIVE PUBLICATIONS

ZSIRKA B, TÁBOROSI A, SZABÓ P, SZILÁGYI RK, HORVÁTH E, JUZSAKOVA T, FERTIG D, KRISTÓF J: **Surface Characterization of Mechanochemically Modified Exfoliated Halloysite Nanoscrolls** *Langmuir*, 2017, 33(14), 3534–3547

ZSIRKA B, HORVÁTH E, SZABÓ P, JUZSAKOVA T, SZILÁGYI RK, FERTIG D, MAKÓ É, VARGA T, KÓNYA Z, KUKOVECZ Á, KRISTÓF J: **Thin-walled nanoscrolls from multi-step intercalation of tubular halloysite-10Å and its rearrangement upon peroxide treatment** *Applied Surface Science*, 2016, 399, 245-254

HARRIS TV, SZILAGYI RK: **Protein environmental effects on iron-sulfur clusters: A set of rules for constructing computational models for inner and outer coordination spheres** *Journal of Computational Chemistry*, 2016, 37(18), 1681-1696

BARTON RL, GARDENGHI DJ, STOLTE WC, SZILAGYI RK: **Multiedge X-ray Absorption Spectroscopy Part II: XANES Analysis of Bridging and Terminal Chlorides in Hexachlorodipalladate(II) Complex** *Journal of Physical Chemistry A*, 2015, 119(22), 5579–5586

QUEEN MS, TOWEY BD, MURRAY KA, VELDKAMP BS, BYKER HJ, SZILAGYI RK: **Electronic structure of $[Ni^{(II)}S_4]$ complexes from S K-edge X-ray absorption spectroscopy** *Coordination Chemistry Reviews*, 2013, 257(2), 564-578

ROBERT USSELMAN

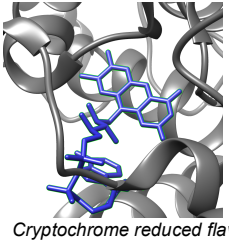
Assistant Research Professor, Biophysical Chemistry
252 Chemistry and Biochemistry Building
robert.ussleman@montana.edu
(406) 994-1781

Biophysical Chemistry

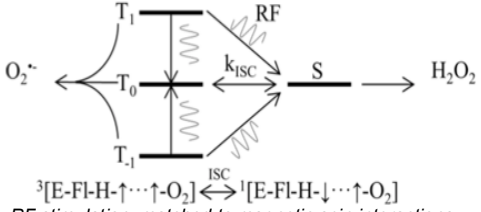
Quantum Biology

RESEARCH OVERVIEW

The overarching theme of the Usselman research program is to use advanced magnetic resonance and optical techniques to address biophysical chemistry problems in the areas of chemical biology, biomaterials, and redox biochemistry. We aim to develop novel methodologies and instrumentation that address the fundamental gap in knowledge between physical measurements and theoretical models for bio-engineered systems operating at the quantum/classical interface. We seek to understand how quantum properties play governing roles in biological function and apply theory-driven predictions of quantum biology for multi-scale integration of cellular function.



Cryptochrome reduced flavin activates molecular oxygen to create $FADH^{\bullet}:O_2^{\bullet-}$ radical pairs.



RF stimulation, matched to magnetic spin interactions, drives quantum biology by altering the branching among singlet and triplet quantum states respectively H_2O_2 and $O_2^{\bullet-}$.

REPRESENTATIVE PUBLICATIONS

Spin Biochemistry Modulates Reactive Oxygen Species (ROS) Production by Radio Frequency Magnetic Fields, Robert J. Usselman, Iain Hill, David Singel, and Carlos Martino, PLoS ONE 9(3), e93065 (2014).

Gadolinium-Loaded Viral Capsids as Magnetic Resonance Imaging Contrast Agents, Robert J. Usselman, Shefah Qazi, Priyanka Aggarwal, Sandra Eaton, Gareth Eaton, Trevor Douglas, and Stephen Russek, Applied Magnetic Resonance 46 (3), 349-355 (2015).

Temperature Dependence of Electron Magnetic Resonance Spectra of Iron Oxide Nanoparticles Mineralized in Listeria Innocua Protein Cages, Robert J. Usselman, Stephen E. Russek, Michael Klem, Mark Allen, Trevor Douglas, Mark Young, Yves Idzerda, and David Singel, Journal of Applied Physics 112, 084701 (2012).

Monitoring Structural Transitions in Icosahedral Virus Protein Cages by Site-Directed Spin Labeling, Robert J. Usselman, Eric D. Walter, Debbie Willits, Trevor Douglas, Mark Young, and David J. Singel, Journal of American Chemical Society, 133 (12), 4156-4159 (2011).

Impact of Mutations on Redox Potentials, g-Values, and Spin-Lattice Relaxation Rates of the $[4Fe\text{-}4S]^{2+,1+}$ Cluster in ETF-QO, Robert J. Usselman, Alistair Fielding, Frank E. Frerman, Nick Watmough, Gareth R. Eaton, and Sandra S. Eaton, Biochemistry. 47 (1), 92-100 (2008)

MARTIN TEINTZE

Associate Professor, Biochemistry
Director, WWAMI Medical Program
217 Chemistry and Biochemistry Building
mteintze@montana.edu
(406) 994-4411 (WWAMI office)

Protein Structure/Function
Antibacterial Drug Design
Antibacterial Mechanisms and Resistance

RESEARCH OVERVIEW

Development of guanide and biguanide antibiotics: Compounds containing multiple biguanide functional groups have long been used as topical antimicrobial agents in soaps, mouthwash, and contact lens solutions, but they have been too toxic to use internally. We have made new compounds containing 3-8 guanide or biguanide groups that have antibacterial activity and lower cytotoxicity, and are investigating their specificity and mechanism of action. One of these is particularly effective against methicillin-resistant *Staphylococcus aureus* (MRSA).

Mechanism of GRA and other membrane-binding antibacterials: 18-β-glycyrrhentinic acid (GRA) is a natural product that inhibits production of virulence factors in methicillin-resistant *Staphylococcus aureus* (MRSA). We are investigating its mechanism of action in both planktonic and biofilm cultures using a variety of techniques, including metabolomics, as well as potential synergies with the action of other antibiotics.

REPRESENTATIVE PUBLICATIONS

Wilkinson, R.A., Pincus, S.H., Shepard, J.B., Walton, S.K., Bergin, E.P., Labib, M.E. and Teintze, M. (2011) Novel compounds containing multiple guanide groups which bind the HIV co-receptor CXCR4. Antimicrob. Agents Chemother. 55:255-263.

Wilkinson, R.A., Pincus, S.H., Song, K., Shepard, J.B., Weaver, A., Labib, M.E., and Teintze, M. (2013) Improved guanide compounds which bind the CXCR4 co-receptor and inhibit HIV infection. Bioorg. Med. Chem. Lett. 23:2197–2201.

Shepard, J.B., Wilkinson, R.A., Starkey, J.R. and Teintze, M. (2014) Novel Guanide Substituted Compounds bind to CXCR4 and Inhibit Breast Cancer Metastasis. Anti Cancer Drugs 25(1):8-16.

Weaver, A.J., Shepard, J.B., Wilkinson, R.A., Watkins, R.L., Walton, S.K., Radke, A.R., Wright, T.J., Awel, M.B., Cooper, C., Erikson, E., Labib, M., Voyich, J.M. and Teintze, M. (2014) Antibacterial activity of THAM trisphenylguanide against Methicillin-resistant Staphylococcus aureus. PLoS One 9(5): e97742.

Pomwised, R., Intamaso, U., Teintze, M., Young, M.J. and Pincus, S.H. (2016) Coupling Peptide Antigens to Virus-Like Particles or to Protein Carriers Influences the Th1/Th2 Polarity of the Resulting Immune Response. Vaccines 4(2):15.

ROBERT A. WALKER

Professor, Surface Chemistry & Spectroscopy
Director, Materials Science Graduate Program
057 Chemistry and Biochemistry Building
rawalker@montana.edu
(406) 994-7928

Solvation at liquid surfaces
Non-linear spectroscopy
Solid oxide fuel cells, Raman scattering,
Membrane Partitioning

RESEARCH OVERVIEW

Look around. Virtually everything you see is a surface. Surfaces are boundaries between materials where chemical species are subject to different interactions than they would experience were they buried inside the material's bulk. The effects of surfaces on every day processes are easy to see. Soap solubilizes dirt and oil because soap is surface active consisting of a hydrophilic end that remains solvated in water and a hydrophobic segment that solubilizes less polar (or "oily") deposits. Aluminum surfaces readily oxidize in air to form the aluminum oxide films that stabilize and protect objects ranging from aluminum cans to bicycle frames to automobiles.

Research in my group uses experimental methods – most notably linear and nonlinear optical spectroscopy – to understand chemical structure, organization and reactivity at interfaces. While the systems studied are diverse and far ranging, our goal is always the same: we work hard to understand how asymmetric forces found at surfaces alter interfacial chemistry from bulk material limits. Several research areas where we have made substantive contributions include 1) solvation at liquid interfaces, and 2) high temperature surface chemistry in electrochemical devices. Our studies of liquid interfaces focus on understanding how molecular structure and organization at interfaces change molecular structure, organization and reactivity from bulk solution limits. Recent work has examined the idea of 'cooperative adsorption' where an adsorbed film can draw solutes that would otherwise not be surface active from bulk solution to the interface.

In the second project, we have developed methods to acquire vibrational spectra from species reacting on surfaces as hot as 800˚C(!). Such capability affords us unprecedented opportunities to study the chemistry and materials in operating solid oxide fuel cells *in operando* and in real time. Of particular interest are mechanisms responsible for carbon accumulation (or 'coking') solid oxide fuel cells operating with heterogeneous fuel feeds. Recent work in this area has begun to focus on the role played by 2˚ phases on electrochemical redox efficiency and material degradation in high temperature environments.

Collectively, our work represents a broad based, discipline-spanning effort to understand better the relationships between structure and reactivity in a wide array of interfacial systems. While the projects themselves can be pursued independently, they also are intended to promote strong collaborative relationships with colleagues at Montana State, around the country and around the world.

REPRESENTATIVE PUBLICATIONS

K. W. Reeping, *et al.* "Chlorine-induced Degradation in SOFCs Identified by Operando Optical Methods" *J. Phys. Chem. C* **121** (5) 2588-2596 (2017).

C. A. Gobrogge, *et al.* "Temperature Dependent Partitioning of Coumarin 152 in Phosphatidylcholine Lipid Bilayers" *J. Phys. Chem. B*, **121** (16) 4061-4070 (2017).

D. R. Driscoll, *et al.* "Enhancement of High Temperature Metallic Catalysts: Aluminum Titanate in the Nickel-Zirconia System" *Applied Catalysis A* **527** 36 (2016).

M. L. Traulsen, *et al.* "Reversible Decomposition of Secondary Phases in BaO Infiltrated LSM Electrodes – Polarization Effects" *Advanced Materials-Interfaces* **3** (24) 1600750 (2016).

B. J. Berne, *et al.* "Nitriles at Silica Interfaces Resemble Supported Lipid Bilayers" *Accounts of Chemical Research* **49** (9) 1605-1613 (2016).

S. M. Burrows, *et al.* "OCEANFILMS-2: Representing co-adsorption of saccharides in marine films improves agreement of modelled and observed marine aerosol chemistry" *Geophys. Res. Lett.* **143** (15) 8306-8313 (2016).

MONTANA STATE UNIVERSITY

Mountains & Minds

Scan to connect!

For information please contact;
Doreen E. Brown Ed.D.
Graduate Program Director
Department of Chemistry and Biochemistry
1-877-472-3776
dbrown@montana.edu

Applying to the Program
http://www.montana.edu/gradschool/admissions/apply.html