The University of Iowa

27th

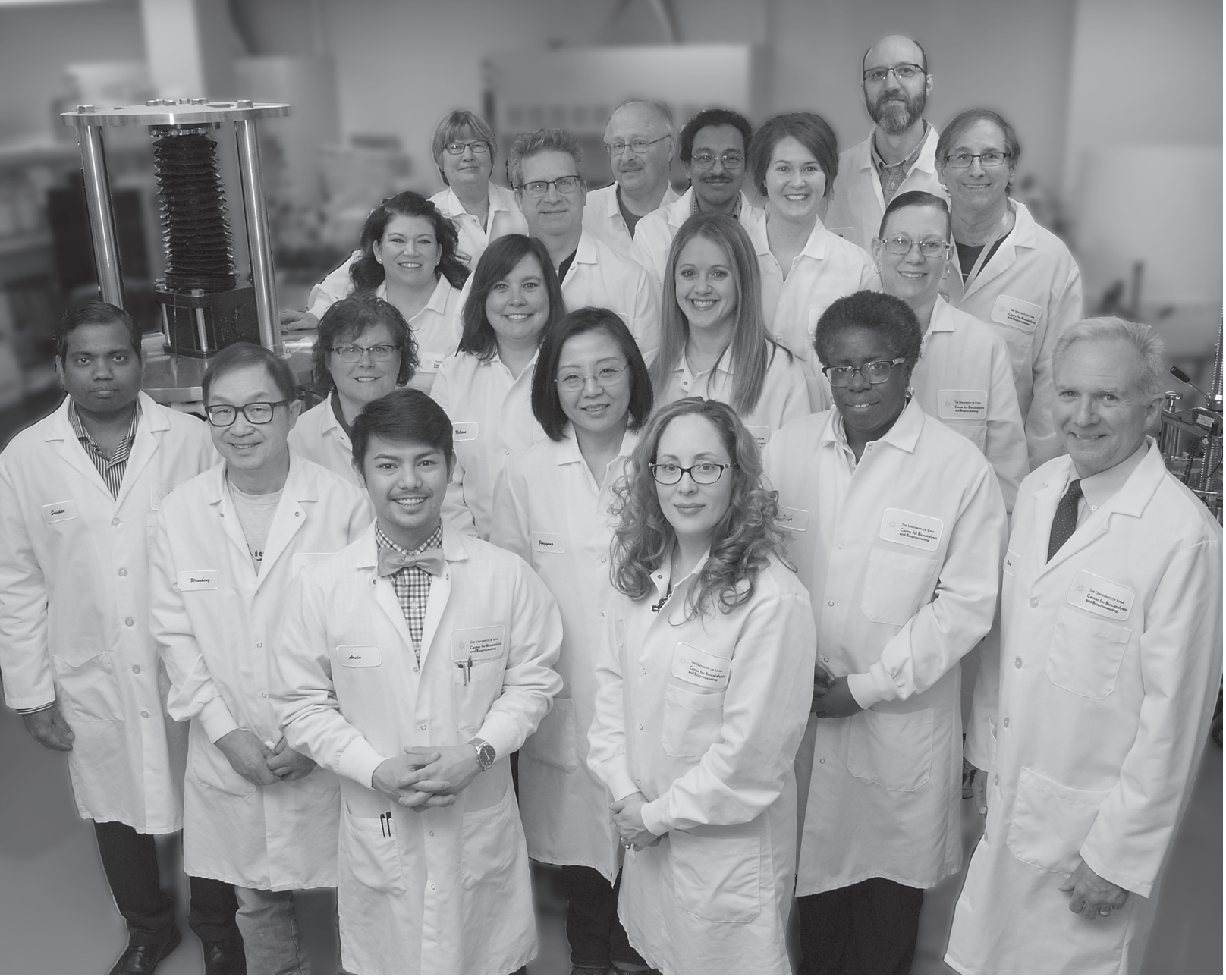
Center for Biocatalysis and Bioprocessing Conference

Frontiers in Biocatalytic Science

http://cbb.research.uiowa.edu

The University of Iowa

October 16, 2018
Iowa Memorial Union
Iowa City, Iowa



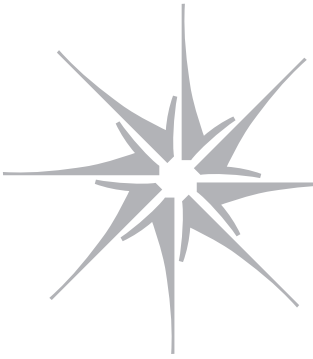
Welcome from the staff of the Center's Microbal Fermentation and Processing Facility

THE UNIVERSITY OF IOWA

27th Annual Biocatalysis and Bioprocessing Conference

"Frontiers in Biocatalytic Science"

Sponsored by:



THE UNIVERSITY OF IOWA

Center for Biocatalysis and Bioprocessing

October 16, 2018

http://cbb.research.uiowa.edu

27th Annual
Biocatalysis and Bioprocessing Conference

"FRONTIERS IN BIOCATALYTIC SCIENCE"

Sponsored by:

The University of Iowa

Center for Biocatalysis and Bioprocessing

October 16, 2018

Conference Organizing Committee:

Mark Arnold, Ph.D.
Sridhar Gopishetty, Ph.D.
Shuvendu Das, Ph.D.
Robert Kern, Ph.D.
Mitchell Rotman, MA, MS, MHA

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Message from the Director

Welcome to the 27th annual CBB Conference. The title for this year's conference is *Frontiers in Biocatalytic Science* and, as is our custom, the conference brings together both accomplished and up-and-coming researchers interested in solving long-standing problems through advances in Biocatalytic Science. The morning session features the following group of world-renowned speakers:

Professor Veena Prahlad, in the Department of Biology at the University of Iowa, will talk about her research to understand, at the molecular level, how organisms detect and repair protein damage caused by stressful environments, such as heat shock response.

Professor Koji Sode, in the Department of Biomedical Engineering at the University of North Carolina, will explain strategies developed by his research team for optimizing targeted properties of enzymes for specific applications, such as in the engineering of oxidoreductase enzymes to meet the demands of future biosensors.
Professor Chris Ahern, in the Department of Physiology at the University of Iowa, will describe his progress in understanding fundamental biochemical mechanisms for function and pharmacology of ion channels through novel labeling strategies.

Dr. Shane Climie and *Mr. Brett Cohen*, collaborators with LEV Therapeutics, will team up to present their challenges and successes in developing an enzyme-biotherapeutic for treating mitochondrial disorders. Their presentation will cover the science behind mitochondrial enzyme-replacement therapy as well as business factors that impact the road to clinical testing.
A poster session scheduled over the lunch period will highlight a wide array of biocatalytic science projects pursued by student researchers. Last year, the poster session seemed to fly by with enthusiastic discussion between the guests, students, faculty and representatives at the vendor booths.

I informally call the afternoon session "The Quinn Symposium," in honor of Professor Daniel Quinn who was an original member of the Biocats and who retired from the University at the end of the 2018 spring semester. The symposium recognizes Dan's long-time contributions to the Center, including his tenure as the Principal Investigator of the NIH-supported Predoctoral Training Grant in Biotechnology. Two of Dan's former students, *Nathan Baker* and *Joe Topczewski*, will give presentations. Nathan, Director for the Advanced Computing, Mathematics and Data Division at Pacific Northwest National Laboratory will talk about computation methods to understand interactions between biomolecules. Joe, an Assistant Professor in the Department of Chemistry at the University of Minnesota, will educate us on the Winstein Rearrangement. The Quinn Symposium will end with a presentation from Dan himself speaking about the mechanism of serine esterase.

It is my pleasure to welcome each of you to this wonderful day of science and engineering. Please take advantage of the opportunity to learn from others and establish new collaborations.

Thank you for your interest,

Mark Arnold, Ph.D.
Director, Center for Biocatalysis and Bioprocessing, Office of the Vice President for Research and Economic Development, University of Iowa Research Park, Coralville, IA
Professor and Edwin B. Green Chair in Laser Chemistry, College of Liberal Arts and Sciences, Department of Chemistry, The University of Iowa, Iowa City, IA

27th Annual Center for Biocatalysis and Bioprocessing Conference
"Advances in Biocatalytic Sciences: Attacking Societal Problems"
The University of Iowa, Iowa Memorial Union, Iowa City, IA

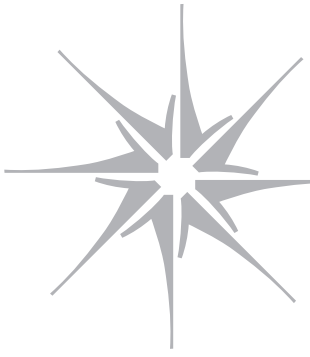
TUESDAY, OCTOBER 16, 2018

IOWA THEATER (1ST FLOOR)

7:30 – 8:15 AM	Registration – Hubbard Commons (outside Iowa Theater 1st floor, IMU)
7:30 – 8:15	Continental Breakfast – across from Iowa Theater Lower level, IMU
8:15– 8:30	Program – Iowa Theater Lower Level, IMU Introduction and Welcome **Richard Hichwa,** Senior Associate VP for Research, Office of the Vice President for Research and Economic Development, The University of Iowa, Iowa City, IA
8:30– 9:15	**Veena Prahlad, Ph.D.**, Associate Professor, Department of Biology, College of Liberal Arts and Sciences, The University of Iowa, Iowa City, IA *"Organismal Control of Cellular Defense Mechanisms"*
9:15– 10:00	**Koji Sode, Ph.D.**, W.R. Kenan Jr. Distinguished Professor, Joint Department of Biomedical Engineering, The University of North Carolina, Chapel Hill, NC and North Carolina State University, Raleigh, NC *"Science and Engineering of Oxidative Half-reactions of Flavin-oxidoreductase for Future Biosensing Enzymes~engineering of the electron acceptor preference~*"
10:00– 10:15	Break – Hubbard Commons (outside Iowa Theater Lower Level, IMU)
10:15– 11:00	**Christopher Ahern, Ph.D.**, Professor, Department of Molecular Physiology and Biophysics, Carver College of Medicine, The University of Iowa, Iowa City, IA *"Atomic Engineering in Ion Channels"*
11:00– 11:45	**Shane Climie, Ph.D.,** Principal, Popper and Company, Apsley, ON Canada and **Brett Cohen**, Founder, LEV Therapeutics, Skokie, IL *"A personal journey to develop an enzyme replacement therapy for DLD deficiency, a rare mitochondrial disease"*
11:45– 12:00	Relocation to 1st Floor Main Lounge, IMU
12:00– 12:45 PM	Lunch – Poster Session 1-Main Lounge 1st Floor, IMU S3 Product Show
12:45– 1:30	Lunch – Poster Session 2-Main Lounge 1st Floor, IMU S3 Product Show
1:30– 1:45	Relocation to Iowa Theater Lower Level, IMU

Afternoon Session – Iowa Theater Lower Level, IMU

1:45– 2:15 PM	**Nathan Baker, Ph.D.**, Director, Advanced Computing, Mathematics and Data Division, Pacific Northwest National Laboratories, Richland, WA; Visiting Professor, Division of Applied Mathematics, Brown University, Providence, RI *"Inspired by AChE: Computational Methods for Electrostatics and Diffusion"*
2:15:–2:45 PM	**Joseph J. Topczewski, Ph.D.,** Assistant Professor, Department of Chemistry, University of Minnesota, Twins Cities, MN *"Dynamic Kinetic Resolution with Azides"*
2:45:–3:30 PM	**Daniel Quinn, Ph.D.**, Emeritus Professor, Department of Chemistry, College of Liberal Arts and Sciences, The University of Iowa, Iowa City, IA *"Adventures in Serine Esterase Enzymology"*
3:30	Closing Remarks
3:45	Adjourn
	Tour of CBB Fermentation Facility (Immediately following end of conference)



List of Oral Presentations

ORAL PRESENTATIONS

1. **ORGANISMAL CONTROL OF CELLULAR DEFENSE MECHANISMS**
   Veena Prahlad, Ph.D.
   Associate Professor, Department of Biology, College of Liberal Arts and Sciences, The University of Iowa, Iowa City, IA

2. **SCIENCE AND ENGINEERING OF OXIDATIVE HALF-REACTIONS OF FLAVIN-OXIDOREDUCTASE FOR FUTURE BIOSENSING ENZYMES**
   Koji Sode, Ph.D.
   W.R. Kenan Jr. Distinguished Professor, Joint Department of Biomedical Engineering, The University of North Carolina, Chapel Hill, NC and North Carolina State University, Raleigh, NC

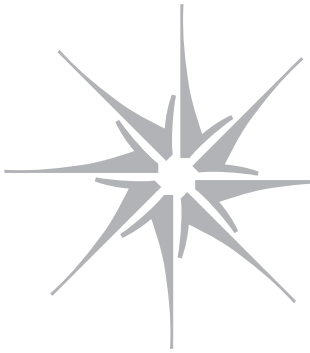
3. **ATOMIC ENGINEERING IN ION CHANNELS**
   Christopher Ahern, Ph.D.
   Professor, Department of Molecular Physiology and Biophysics, College of Medicine, The University of Iowa, Iowa City, IA

4. **A PERSONAL JOURNEY TO DEVELOP AN ENZYME REPLACEMENT THERAPY FOR DLD DEFICIENCY, A RARE MITOCHONDRIAL DISEASE**
   [1]Shane Climie, Ph.D. and [2]Brett Cohen
   [1]Principal, Popper and Company, Apsley, ON Canada
   [2]LEV Therapeutics, Skokie, IL

5. **INSPIRED BY AChE: COMPUTATIONAL METHODS FOR ELECTROSTATICS AND DIFFUSION**
   Nathan Baker, Ph.D.
   Director, Advanced Computing, Mathematics and Data Division, Pacific Northwest National Laboratory, Richland, WA; Visiting Professor, Division of Applied Mathematics, Brown University, Providence, RI

6. **DYNAMIC KINETIC RESOLUTION WITH AZIDES**
   Joseph J. Topczewski, Ph.D.
   Assistant Professor, Department of Chemistry, University of Minnesota, Twins Cities, MN

7. **ADVENTURES IN SERINE ESTERASE ENZYMOLOGY**
   Daniel Quinn, Ph.D.
   Emeritus Professor, Department of Chemistry, College of Liberal Arts and Sciences, The University of Iowa, Iowa City, IA



Speakers' Profiles

Veena Prahlad, Ph.D.
Associate Professor
Department of Biology
College of Liberal Arts and Sciences
The University of Iowa
Iowa City, IA

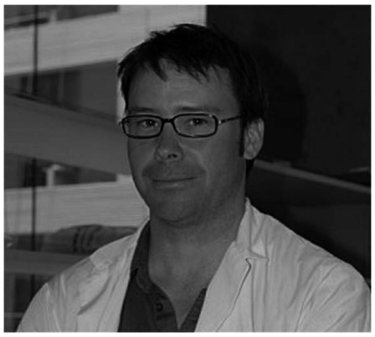
Veena Prahlad received her Ph.D. from Northwestern University and completed postdoctoral fellowships working on the gene-environment interactions. She is currently an Associate professor in Biology and a member of the Aging Mind and Brain Institute at the University of Iowa. Her lab's major contribution to Science is the discovery that the highly conserved transcriptional program that exists in all cells to counteract protein damage, the so-called heat-shock response, previously thought to be a cell-autonomous response, can instead be activated cell non-autonomously by the nervous system through sensory training. Her laboratory also recently discovered that activating the innate immune response in cells of the nematode model organism *C. elegans* protects from mitochondrial toxicity induced neurodegeneration. Her lab is currently working on a number of questions regarding how animals respond to stressful environments and hope to understand how to harness neurosensory stimuli to activate cytoprotective pathways to suppress toxicity in neurodegenerative disease.

Koji Sode, Ph.D.
W.R. Kenan Jr. Distinguished Professor
Joint Department of Biomedical Engineering
The University of North Carolina
Chapel Hill, NC and
North Carolina State University
Raleigh, NC

Dr. Koji Sode is a Professor of Biomedical Engineering, William R. Kenan Jr. Distinguished Professor in the Joint Department of Biomedical Engineering, The University of North Carolina at Chapel Hill and North Carolina State University. He has also served as the Adjunct Professor at Tokyo University of Agriculture and Technology, Japan.

He is the author of more than 300 peer reviewed papers and holds numerous international patents relating on biosensing technologies. His current research interests are 1) Biomolecular engineering toward the application for biodevice development and novel bioprocess design, 2) Biodevice development including biosensors, 3) Synthetic biology to creating novel biocatalyst/microorganisms to realize novel bioprocesses.

Christopher Ahern, Ph.D.
Professor
Department of Molecular Physiology and Biophysics
Carver College of Medicine
The University of Iowa
Iowa City, IA



Dr. Ahern received his B.S in Chemistry and Ph.D. in Physiology and Biophysics at the University of Wisconsin-Madison where he was supported by the American Heart Association through a Predoctoral Fellowship. He then undertook a post-doctoral training in Biophysics at the Thomas Jefferson University (Philadelphia, PA) as a Farber Institute of Neuroscience Fellow, and then received advanced training in Chemical Biology at the California Institute of Technology (Pasadena, CA) through an NRSA Fellowship. He began his independent research career as an Assistant Professor at the University of British Columbia in the Department of Anesthesiology and Therapeutics, where he was promoted to Associate Professor in in 2011. He relocated his research program in 2012 to the University of Iowa in the Department Molecular Physiology and Biophysics. Dr. Ahern is an American Heart Association Established Investigator, is a standing member of the BPNS NIH study section and was the Chair of the 2018 Ion Channels Gordon Research Conference. He currently oversees an NIH funded research portfolio to study ion channel proteins with chemical biology approaches.

Shane Climie, Ph.D.
Principal
Popper and Company
Apsley, ON
Canada

Shane Climie, Ph.D. is a Principal with Popper and Company, which is focused on building life science organizations by meeting the needs of entrepreneurial, life science startups and the investors that support those early stage organizations. Dr. Climie is also Vice President of Corporate Development at Cyclica Inc. where he supports company growth by managing corporate relationships and strategic planning. Dr. Climie has more than 25 years of R&D and business development experience in the life sciences and pharmaceutical industry. He has led research teams involved in all aspects of drug discovery and technology development, and has designed, negotiated and managed many R&D collaborations. He has extensive experience in technology evaluation, technology development and strategic planning. Dr. Climie has been a Principal at Popper and Company for 12 years where he has provided interim executive management services to early-stage biotechnology companies in the areas of diagnostics and drug discovery / drug development as well as support in the areas of business management, marketing strategy and technology or opportunity assessment. Also prior to joining Cyclica and Popper, Dr. Climie held several positions at Protana (formerly MDS Proteomics) including Senior Vice President of Science Strategy and Business Development, Senior Vice President of Research Collaborations, and Vice President of Proteomics and Business Development. Dr. Climie was also co-founder, Vice President and Chief Technology Officer of MDS Ocata and was a Visiting Research Scientist at the Samuel Lunenfeld Research Institute. Prior to that, Dr. Climie held several managerial positions at Allelix Biopharmaceuticals, Inc. including Principal Scientist. Dr. Climie completed postdoctoral work at the University of California at San Francisco and received a Ph.D. in Medical Biophysics from the University of Toronto.

Brett Cohen
Founder
Lev Therapeutics
Skokie, IL

Brett Cohen founded JGB Management, an investment firm based in Westport, CT, in 2005. He has over 20 years of investment management experience. Brett founded Lev Therapeutics in 2017. Lev is focused on finding solutions for rare pediatric diseases, and is in pre-clinical studies using enzyme replacement therapy for its first indication -- dihydrolipoamide dehydrogenase deficiency. He earned his J.D. from Yale Law School and B.A. from Columbia University, and is a CFA charter holder.

Nathan Baker, Ph.D.
Director, Advanced Computing, Mathematics and Data Division
Pacific Northwest National Laboratory
Richland, WA

Visiting Professor
Division of Applied Mathematics
Brown University
Providence, RI

Nathan Baker, Ph.D., is the Director for the Advanced Computing, Mathematics, and Data Division at Pacific Northwest National Laboratory and a Visiting Faculty member in the Brown University Division of Applied Mathematics. His research focuses on developing new algorithms and mathematical methods in biophysics, nanotechnology, and informatics. His research projects include computational methods for modeling solvation in biomolecular systems, mathematical methods for mesoscale materials modeling, and development of methods for signature discovery. His research has been funded by the National Institutes of Health, U.S. Department of Energy, and National Science Foundation.

Dr. Baker has served as co-principal investigator and project manager for the DOE Advanced Scientific Computing Research CM4: Collaboratory on Mathematics for Mesoscopic Modeling of Materials and as lead for the Signature Discovery Initiative at PNNL. He also managed the Applied Statistics and Computational Modeling Group at PNNL from 2013 to 2015, which comprised approximately 50 staff with expertise in statistics, mathematics, and operations research.

Dr. Baker has served on review panels for various agencies, including as a member of the NIH Macromolecular Structure and Function D study section. He currently is an editorial board member for Biophysical Journal and serves on the editorial board for NPG Scientific Data. Dr. Baker previously served as associate editor for Biophysical Journal, editor-in-chief for Computational Science and Discovery, and section editor for Annual Reports in Computational Chemistry. He has authored more than 100 peer-reviewed publications.

Dr. Baker is a Fellow of the American Association for the Advancement of Science and has been awarded the Hewlett-Packard Junior Faculty Excellence Award by the American Chemical Society, the National Cancer Institute caBIG Connecting Collaborators Award, and an Alfred P. Sloan Research Fellowship.

Joseph J. Topczewski, Ph.D.
Assistant Professor
Department of Chemistry
The University of Minnesota
Twins Cities, MN

Professor Topczewski (Joe) was born in southeastern Wisconsin and grew up in the city of Racine. He attended the University of Wisconsin at Parkside and graduated in 2007 after conducting research with Prof. Lori Allen. Joe moved to the University of Iowa for graduate school and graduated in 2011. Joe worked with Prof. David Wiemer and synthesized many schweinfurtin natural products and analogues as part of a collaboration with the National Cancer Institute. During this time, he explored the utility of a cascade cyclization terminated by an electrophilic aromatic substitution. Joe was awarded a predoctoral fellowship from the ACS Medicinal Chemistry Division for this work. After graduation, Joe stayed in Iowa City for two additional years. During this time, he worked with Prof. Hien Nguyen to develop an enantioselective iridium catalyzed (radio-)fluorination reaction. Then Joe worked with Prof. Dan Quinn to develop new antidotes for sarin agents by re-activating AChE as part of the COUNTERACT program. Joe moved to the University of Michigan and joined the lab of Prof. Melanie Sanford. While at Michigan, Joe collaborated with Prof. Peter Scott and Dr. Naoko Ichiishi on new methods of radio-fluorination. A second project was funded (NIH-F32) and Joe shifted his attention to the C-H activation of piperidine derivatives.

In the summer of 2015, Joe moved to the Twin–Cities and started his independent career at the University of Minnesota-Twin Cities. Joe's lab focuses on developing new and efficient methods of chemical synthesis. Joe is exceptionally passionate about developing highly selective reactions and on reactions that exploit dynamic systems. To this end, one major thrust of his lab's research involves the selective differentiation of allylic azides.

Daniel Quinn, Ph.D.
Emeritus Professor
Department of Chemistry
College of Liberal Arts and Sciences
The University of Iowa
Iowa City, IA

Dan Quinn received a B.S. degree in Chemistry in 1972 from Quincy College and a Ph.D. in Bioorganic Chemistry from Kansas University in 1977. From 1978 to 1980 he was a Postdoctoral Associate in the Department of Chemistry of Indiana University, where he studied the phase behavior and structural organization of cholesteryl esters in neat lipid samples and atherosclerotic lesions by ^{13}C NMR spectroscopy. From 1980 to 1982 he was a NIH Lipids, Atherosclerosis and Nutrition Postdoctoral Trainee at the University of Cincinnati College of Medicine, where he studied the mechanisms of enzymes that catalyze the hydrolysis of acylglycerols. He joined the faculty of the Department of Chemistry of the University of Iowa in 1982 as an Assistant Professor, and was promoted to Associate Professor in 1987 and to Professor in 1992. He was Director of the NIH-funded Predoctoral Training Program in Biotechnology at the University of Iowa from 1998 to 2013. His research group studied the mechanisms and inhibition of serine esterases that catalyze the hydrolysis of lipid esters or choline esters.

Oral Presentation Abstracts

Presenter 1

ORGANISMAL CONTROL OF CELLULAR DEFENSE MECHANISMS

Veena Prahlad, Ph.D.
Associate Professor, Department of Biology, College of Liberal Arts and Sciences,
The University of Iowa, Iowa City, IA

Although protein-based biological processes function efficiently only within a narrow range of optimal conditions, organisms survive a wide variety of environmental fluctuations. The mechanisms that allow for stable physiology, despite the temperature sensitivity of metabolic reactions, are poorly understood. Many animals possess neurosensory circuits dedicated to seeking out optimal conditions and can modify their behavior as a result of experience, enabling them to synthesize information from their surroundings to acquire resources and avoid danger. In addition, all cells possess conserved defense mechanisms to protect against macromolecular damage that can be caused by environmental fluctuations. One such mechanism is the activation of the transcription factor HSF1 by thermal stress. HSF1 upregulates the heat shock proteins (HSPs) that function as molecular chaperones to maintain protein stability. In the nematode *Caenorhabditis elegans*, circuits formed by thermosensory AFD neurons control behavioral responses to temperature change. We discovered that this neurosensory circuitry also controls the activation transcription factor HSF1 within all cells throughout the organism. Moreover previous experience of a threat prepares *C. elegans* to survive subsequent exposure to the threat by pre-emptively increasing the expression of genes encoding molecular chaperones. We believe our studies are uncovering novel mechanisms by which animals couple sensory stimuli to cellular stress responses to respond to environmental change. Understanding details of these mechanisms could impact our treatment of neurodegenerative diseases where these cytoprotective gene expression programs fail to be activated.

Presenter 2

SCIENCE AND ENGINEERING OF OXIDATIVE HALF-REACTIONS OF FLAVIN OXIDOREDUCTASE FOR FUTURE BIOSENSING ENZYMES ~ *ENGINEERING OF THE ELECTRON ACCEPTOR PREFERENCE~*

Koji Sode Ph.D.
W.R. Kenan Jr. Distinguish Professor, Joint Department of Biomedical Engineering, The University of North Carolina, Chapel Hill, NC and North Carolina State University, Raleigh, NC

The history of biosensors has started since the invention of glucose sensor by Professor Clark in 1956, which was constructed by the combination of Clark type oxygen electrode and the legendary enzyme, glucose oxidase (GOx). Since then, the development of biosensors, especially those employing redox enzymes as *Bio-recognition Elements*, has been strongly depend on the discovery and engineering of redox enzymes. The reaction of redox enzymes can be divided into two catalytic reactions; reductive half reaction, where the substrate is oxidized and the cofactor of enzyme is reduced, and oxidative half reaction, where the reduced cofactor is oxidized by the electron acceptor. Vigorous studies in the engineering of reductive half reactions have been reported to improve various catalytic properties of enzymatic reactions, such as substrate specificity which is the essential to specify the molecule for biosensor applications. Besides, the studies on oxidative half reactions are the studies on the principles of the detections, thereby the decision was made which transducers would be available to construct biosensing devices in the practical uses. In spite of such a significant impact of the studies on oxidative half reactions, the biomolecular engineering of the oxidative half reaction has not been paid much attention. We have been engaged in the biomolecule engineering of redox enzymes, not only by focusing their reductive half reactions, but recently more focusing on their oxidative half reaction. In this presentation, I report our success and the recent challenges in the engineering approaches to alter electron acceptor preference of redox enzymes.

Presenter 3

ATOMIC ENGINEERING IN ION CHANNELS

Christopher Ahern, Ph.D.
Professor, Department of Physiology and Biophysics, Carver College of Medicine
The University of Iowa, Iowa City, IA

The Ahern laboratory has a long-standing interest in the pharmacology and function of the voltage-gated ion channels that support electrical signaling in muscle and nerve cells. My laboratory uses chemical biology, protein engineering and biophysics to quantify membrane protein function at high resolution. Our use of genetic code expansion and the design, synthesis and encoding of unnatural amino acids to rescue ion channel genes harboring nonsense (stop) codons, has yielded several interesting recent discoveries: atomic and subatomic details of the function of ion-channel voltage sensors; new protein-chemical interactions relevant for potassium channel gating; H-bond networks that act as molecular timers in potassium channels; and novel mechanisms of drug interactions with ion channels. Data will be discussed related to the role of cation-pi interactions between sodium channel aromatic residues and toxins or therapeutics, and in context of protein structure. Further, data are provided for a novel mechanistic basis for a therapeutic potassium channel opener.

Presenter 4

A PERSONAL JOURNEY TO DEVELOP AN ENZYME REPLACEMENT THERAPY FOR DLD DEFICIENCY, A RARE MITOCHONDRIAL DISEASE

[1]Shane Climie, Ph.D. and [2]Brett Cohen
[1]Principal, Popper and Company, Apsley, ON Canada
[2] Founder, Lev Therapeutics, Skokie, IL

DLD deficiency is a rare autosomal recessive disorder that affects the function of the E3 components of the mitochondria, including the pyruvate dehydrogenase complex (PDHC) and alpha ketoglutarate. The incidence of DLD deficiency is very low—there may be fewer than 30 to 40 cases worldwide, and treatments do not exist. DLD deficiency leads to malfunctioning of the mitochondria, lack of adequate ATP production, an excess of reactive oxygen species, and lactic acidosis, causing progressive organ-level dysfunction from the highest demanders of energy (such as the brain). DLD deficiency has a variable clinical course depending on the type of mutation and homozygosity, but often includes infantile neurogenerative disease and liver failure.

Because of the low incidence of the disease, there is little commercial incentive to develop therapies. We will discuss a personal journey led by Mr. Cohen (whose son is affected by the disease) to develop an enzyme replacement therapy to treat DLD deficiency. We will describe the underlying rationale for the approach, assembly of a team to oversee production and development, the creation of Lev Therapeutics, and various challenges that we have faced along the way.

Because the incidence of DLD deficiency is so low, the enzyme replacement product is being developed for a very small clinical trial (potentially N=1). We will describe our strategy to investigate the use of recombinant TAT-LAD as an enzyme replacement therapy in order to replace the missing LAD enzyme within the mitochondria, and thereby restore mitochondrial function. If successful, this approach may also prove to be suitable for the treatment of other rare mitochondrial and metabolic disorders.

Presenter 5

INSPIRED BY AChE: COMPUTATIONAL METHODS FOR ELECTROSTATICS AND DIFFUSION

Nathan Baker, Ph.D.
Director, Advanced Computing, Mathematics and Data Division, Pacific Northwest National Laboratory, Richland, WA; Visiting Professor, Division of Applied Mathematics, Brown University, Providence, RI

"Nature's perfect (diffusion-limited) enzymes" have undisputable biological importance. However, as Quinn lab research has repeatedly demonstrated, these systems also tremendous value for understanding basic physical (organic) chemistry processes. Acetylcholinesterase (AChE) is a particularly interesting system for developing and testing computational and theoretical models for diffusion and electrostatics. The complicated geometry of the AChE system—a buried active site accessible only by a narrow "gorge"—can confound simple diffusional encounter models for the system. At the same time, the charge distribution of AChE—which helps overcome these geometric barriers—has motivated numerous computational models of biomolecular electrostatics. This talk has two goals. The first goal is to introduce and explain some computational approaches for understanding diffusion and electrostatics in biomolecular systems. The second goal is to describe how the research questions I encountered in ~3 years of undergraduate study in the Quinn lab have inspired my research for the last ~25 years.

Presenter 6

DYNAMIC KINETIC RESOLUTION WITH AZIDES

Joseph J. Topczewski, Ph.D.
Assistant Professor, Department of Chemistry, University of Minnesota, Twins Cities, MN

This presentation will discuss dynamic kinetic resolution as a means to accomplish enantioselective synthesis. Examples from the literature will be used to highlight the power and limitations of this process. Recent work from our lab will be described in the context of gaining selectivity and developing systems capable of dynamic kinetic resolution that use organic azides. Organic azides are exciting to us because they are classically recognized as chiral amine surrogates. The presentation will include a description of the allylic azide rearrangement, mechanistic aspects of this process, and applications in the context of synthesis.

Presenter 7

ADVENTURES IN SERINE ESTERASE ENZYMOLOGY

Daniel Quinn, Ph.D.
Emeritus Professor, Department of Chemistry, College of Liberal Arts and Sciences, The University of Iowa, Iowa City, IA

A focus of the Quinn research group has been study of the catalytic mechanisms and inhibition of serine esterases of the α,β-hydrolase fold supergene family. This family is populated by enzymes that hydrolyze choline esters and lipid esters, among other reactions. The structure, function and inhibition of two serine esterases will be discussed: 1) acetylcholinesterase, an enzyme of the central and peripheral nervous systems that is the target of chemical warfare agents; 2) cholesterol esterase, an enzyme that plays a role in the absorption of fatty acids and cholesterol derived from dietary cholesteryl esters

List of Posters and Authors

Posters

1. **SIMULATED BODY FLUID (SBF) MINERALIZED MATRICES EMBEDDED WITH NON-VIRAL GENE-BASED GROWTH FACTORS FOR BONE TISSUE ENGINEERING**
   Timothy M. Acri, Kyungsup Shin and Aliasger K. Salem*
   Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Pharmaceutics and Translational Therapeutics, College of Pharmacy, The University of Iowa, Iowa City, IA

2. **THERMAL SHOCK EFFECTS OF BIOFILM ELIMINATION ON BIOMEDICAL SURFACES**
   Haydar Al Jaafari and Eric Nuxoll*
   Department of Chemical and Biochemical Engineering, College of Engineering, The University of Iowa, Iowa City, IA

3. **GAMBIT: COMBINING SINGLE-MOLECULE MICROSCOPY AND NEXTGEN SEQUENCING**
   Fletcher Bain and Maria Spies*
   Department of Biochemistry, College of Medicine, The University of Iowa, Iowa City, IA

4. **EFFICIENT AND ACCURATE SAMPLING OF THE THERMODYNAMIC PATH BETWEEN MOLECULAR STATES USING A GPU ACCELERATED HYBRID MOLECULAR DYNAMICS ALGORITHM**
   Hernan V Bernabe[1], Jacob M. Litman[2] and Michael J. Schnieders[1,2]*
   [1]Department of Biomedical Engineering, College of Engineering, The University of Iowa, Iowa City, IA
   [2]Department of Biochemistry, College of Medicine, The University of Iowa, Iowa City, IA

5. **PCB-52 AND METABOLITES: TOXICITY TO DOPAMINERGIC CELLS**
   Brianna S. Cagle, Hans Lehmler and Jonathan A. Doorn*
   Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA

6. **BIOMARKERS OF ALTERED DOPAMINE METABOLISM AND PRODUCTION OF REACTIVE METABOLITES**
   Rachel Crawford and Jonathan Doorn*
   Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA

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Benjamin J. Foust[1], Andrew Wiemer[2] and David F. Wiemer[1]*
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Noah Z. Laird, Jaidev Chakka, Satheesh Elangovan*, and Aliasger Salem*
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[1]Department of Chemistry, College of Liberal Arts and Sciences, The University of Iowa, Iowa City, IA
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30. **SORPTION OF NEONICOTINOID INSECTICIDES AND THEIR METABOLITES TO GRANULAR ACTIVATED CARBON DURING DRINKING WATER TREATMENT: IMPLICATIONS FOR TREATMENT, BIOFILM TRANSFORMATION, AND HUMAN EXPOSURE**
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Shuvendu Das[1,2], Samuel Denhartog[1], Daning Lu[1], Anna Bauer[1], Sridhar Gopishetty[1], Elizabeth R. Gibson[1], Ronen Tchelet[3], Jenő Szilagyi[3], and Mark Arnold[1,2*]
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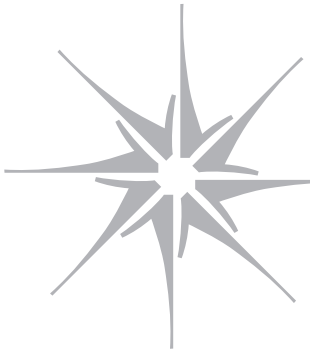

Poster Abstracts

Poster 1

SIMULATED BODY FLUID (SBF) MINERALIZED MATRICES EMBEDDED WITH NON-VIRAL GENE-BASED GROWTH FACTORS FOR BONE TISSUE ENGINEERING

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Development of a synthetic material for bone tissue engineering will alleviate the issue of rapidly increasing demand for bone grafts. Alternatives to autografts have been limited as both allografts and xenografts introduce a multitude of problems during the wound healing process. Our priority is to develop scaffolds capable of non-viral-mediated gene delivery as well as supporting the migration of cells and providing an optimal environment for osteogenesis. The goal was to evaluate the effect of calcium phosphate coated gene activated matrices (CAp-GAM) on the osteogenesis of stem cells *in vitro* and to determine the effect of these scaffolds on bone tissue regeneration *in vivo*. Calcium phosphate coatings have been shown to provide a cell compatible surface that is osteoinductive, and non-viral gene delivery has been a promising method to induce osteogenesis in vivo. Our hypothesis is that combining calcium phosphate coatings and non-viral gene delivery in a single scaffold will further enhance bone regeneration as compared to either treatment alone.

The mineralized collagen scaffolds were prepared using SBF immersion. Scanning electron microscopy showed plate-like calcium phosphate crystal growths on the collagen, and energy dispersive spectroscopy analysis revealed a calcium phosphate ratio of 1.5 which is similar to calcium deficient hydroxyapatite. Also, the formation of two distinct growth factor layers suggests a biphasic release of growth factors may be achieved based upon the confocal images. In the cell culture, bone marrow stromal cells demonstrated high cell viability and increased osteogenic gene expression when cultured on the CAp-GAM as compared to collagen scaffolds alone. Rat calvarial defects treated with the CAp-GAM contained significantly more bone compared to collagen scaffolds based on the microCT analysis. Additionally, histology revealed new bone formation was present throughout the core of the mineralized GAM.

The work presented suggests mineralization and incorporation of gene therapeutic agents in a collagen scaffold enhanced new bone formation over the collagen scaffold alone. This work provides the basis for future investigations of CAp-GAM in bone tissue engineering.

This material is based upon work supported by the Martin "Bud" Schulman Postdoctoral Fellowship Award from the American Association of Orthodontists Foundation

Poster 2

THERMAL SHOCK EFFECTS OF BIOFILM ELIMINATION ON BIOMEDICAL SURFACES

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When bacteria colonize a medical implant surface, they form a biofilm which cannot be eradicated chemically. The current standard of care is surgical explantation of the device and surrounding tissue, with eventual reimplantation of a replacement device with twice the probability of infection. These infections are a $5 billion problem in the U.S. alone, impacting over 100,000 patients annually. One approach to mitigating these biofilms is *in situ* thermal eradication by generating a thermal shock directly at the device/biofilm interface. We have developed magnetic nanoparticle / polymer composite coatings which heat rapidly when exposed to an externally applied alternating magnetic field, and have quantified immediate bacterial population reductions of up to 6 orders of magnitude (i.e., "6 log" reductions).

Moreover, under certain circumstances the biofilm bacterial population continues to decrease for hours after the thermal shock is removed and physiological temperature is restored, resulting in complete eradication of the biofilm. Re-incubation studies at a variety of shock temperatures (50 – 80 °C) and exposure times (1 – 30 min) showed that thermal shocks producing immediate population reductions greater than four log resulted in complete elimination of the biofilm approximately 4 hours later, regardless of the temperature/exposure time combination used to achieve the immediate reduction. Biofilms subjected to thermal shocks with more modest immediate population reductions (less than four log) grew back to their initial population density within 24 hours. These investigations were extended to biofilms with different culture conditions producing pre-shock population densities 100 times greater than the earlier biofilms (nearly 10^9 CFU/cm2). Despite the substantially larger initial population density, the immediate population reduction (four orders of magnitude) was required to prompt eventual die-off of the biofilm, even though the population density immediately after the thermal shock was 100 times greater than in the previous studies. This suggests that the degree of thermal shock required to eradicate a biofilm is independent of the biofilm's initial population density.

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Furthermore, this approach may be integrated with other modifications to the biofilm/device interface to prevent or eliminate biofilms with even milder thermal shocks. Investigations of combined thermal shock and antibiotic exposure yielded orders of magnitude population reductions greater than the sum of the orders of magnitude reduction for either treatment alone, enabling significantly milder thermal shocks to provide the same efficacy and providing an impetus for localized delivery at the device interface of antibiotics which are by themselves insufficient for biofilm elimination.

Poster 3

GAMBIT: COMBINING SINGLE-MOLECULE MICROSCOPY AND NEXTGEN SEQUENCING

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Single-molecule microscopy has developed into a robust physical tool set for examining biomolecular interaction, and in particular protein:nucleic acid interactions. From examining kinetics, to molecular motion, via FRET, and even macromolecular complex assembly, these tools have led to many insights into the mechanisms of DNA repair, replication and recombination. One limiting factor in these studies is the limited ability to surface tether molecules. A single species of DNA molecule or protein must be tethered to the slide surface for experimentation. This limitation is in general not a problem, however, to examine sequence specific protein:nucleic acid interactions this is severely limiting. Recent work examining g-quadruplex DNA has brought this limitation to the forefront of our experimental approach. G-quadruplexes are secondary single-strand DNA structures that form in guanine rich regions of single-strand DNA. Runs of guanine can hoogstein base pair, forming a square planar structure, these square planar structures can then undergo base stacking, creating the g-quadruplex. These quadruplexes can form in multiple conformations and are greatly enriched in the human telomere sequence TTAGGG. Of greater interest, are recent studies using Nextgen sequencing, that have identified of 10,000 unique G-quadruplex structures play in genome maintenance, we are developing a toll which will combine Nextgen sequencing with single-molecule total internal reflection fluorescence methodologies to perform massively parallel, high-throughput examination of these structures.

Poster 4

EFFICIENT AND ACCURATE SAMPLING OF THE THERMODYNAMIC PATH BETWEEN MOLECULAR STATES USING A GPU ACCELERATED HYBRID MOLECULAR DYNAMICS ALGORITHM

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Efficient and accurate calculation of free energy differences between two atomic resolution molecular states by sampling the thermodynamic path between them is of central importance to predicting the effect of missense mutations and to designing new therapeutics. In the former case, the change in folding stability of a protein due to an amino acid change can explain disease phenotypes, while in the latter case the relative binding affinity of ligands to a protein can inform a lead optimization campaign. A prominent hurdle in the exploration of the thermodynamic path between states of interest has been the large computational expense to converge ensemble averages (especially for large systems). Here we introduce a novel algorithm that takes advantage of the processing power of GPU coprocessors to dramatically accelerate the energy and force evaluations associated with molecular dynamics simulations, while the synchronization between processes and thermodynamic integration are executed on CPU cores. This hybrid approach combines the molecular dynamics packages Force Field X (FFX) and OpenMM to offer a sharp increase in computational speed and faster convergence of the free energy landscape (i.e. the ensemble average thermodynamic force along the path between states). For example, for a 5000 atom system, it takes the CPU only FFX algorithm approximately 15 seconds to generate a 100 femtosecond molecular dynamics trajectory while the new hybrid algorithm generates this same trajectory in approximately .45 seconds. The dramatic decrease in time necessary to generate similar trajectories represents roughly a 35 times speed up in simulation power with the hybrid approach. To validate this new approach, here we compare the efficiency and accuracy of the novel method to the established free energy calculation methods available through the software package FFX (without OpenMM) and TINKER (with OpenMM). The property of interest is a standard calculation of the contribution of electrostatic potential of a side chain of an amino acid dipeptide to the energy of the dipeptide immersed in a water box. Validating the novel approach will offer a concrete step towards using this method for quantifying the effects of missense mutations on regular protein function and thus their role in disease. The approach would provide a robust framework to analyzing the role of missense mutations in diseases by adding a complimentary quantitative aspect to the qualitative methods used by bioinformaticians when analyzing missense mutations screened in patients with disease.
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Poster 5

PCB-52 AND METABOLITES: TOXICITY TO DOPAMINERGIC CELLS

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Polychlorinated biphenyls (PCBs) are man-made toxicants found in the environment. Although they are no longer in use, they are still found in the environment – especially the lower chlorinated biphenyls. Exposure to these compounds may occur through inhalation or the consumption of food and water. PCBs have been shown to contribute to neurotoxicity and learning abilities in both the developing and adult brain. These compounds accumulate in brain tissue and have been shown to alter the dopaminergic system important for movement. For example, PCBs lower extra-cellular dopamine concentrations, inhibit tyrosine hydroxylase, and are associated with free radical production. Furthermore, they impair dopamine packaging and re-uptake into synaptosomes. PCB 52 is a lower-chlorinated biphenyl which shows toxicity in neuronal cell lines. PCBs are often hydroxylated via P450 metabolism in the body which can be more toxic than the parent compounds. Preliminary results show that 4-OH PCB 52 is more toxic than PCB 52 to N27 cells – a dopaminergic cell line. Our work intends to understand how PCB 52 and its metabolites modulate the dopaminergic system. This includes analyzing dopamine metabolism in cell culture and rat brain tissue. We have also performed preliminary studies on detecting reactive oxygen species. PCB 52 and its hydroxylated metabolite have shown little increase in ROS. However, it is likely these compounds alter dopamine metabolism or dopamine cell trafficking. PCB 52 and 4-OH PCB 52 have previously shown toxicity in neuronal cell lines. However, not much is known about how these compounds alter and modulate the dopaminergic system. Future studies will include determining changes in gene expression due to PCB 52 and 4-OH PCB 52 as well as employing neuroprotective strategies.

Poster 6

BIOMARKERS OF ALTERED DOPAMINE METABOLISM AND PRODUCTION OF REACTIVE METABOLITES

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Parkinson's Disease (PD) is a degenerative disease of the central nervous system characterized by bradykinesia and tremors with a loss of dopaminergic cells in the brain, particularly in the substantia nigra. Dopamine, an important neurotransmitter, is metabolized to the aldehyde 3,4-dihydroxyphenylacetaldehyde (DOPAL) by monoamine oxidase and further biotransformed to an acid or alcohol product. DOPAL is a highly reactive metabolite that is toxic to dopaminergic cells, where it is produced. Under normal conditions, DOPAL is further metabolized to the nontoxic acid or alcohol products, however, under pathological conditions or following insult, DOPAL can increase to harmful levels. DOPAL and other biogenic aldehydes are hypothesized as chemical triggers of disease (catecholaldehyde hypothesis) that cause cell death, protein aggregation and oxidative stress. Identifying targets of and quantifying dopamine metabolite protein adducts is valuable because of their implication in PD and may yield elucidation of biomarkers for earlier diagnosis or mechanistic targets for drug discovery. Such findings may yield novel biotechnology to diagnose disease earlier and development of therapeutics which address the pathogenic process. This project focuses on the identification of viable biomarkers for determination and quantification of DOPAL conjugates in neuronal cells using various technology, including: near-infrared fluorescence (protein adducts), HPLC-ECD (conjugates) and mass spectrometry (protein and peptide adducts).

Poster 7

DESIGN, SYNTHESIS AND EVALUATION OF NOVEL ANTIMALARIALS TARGETING APICOPLAST DNA POLYMERASE (APPOL) FROM *P. falciparum*

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Plasmodium spp. are the causative agents of malaria, killing nearly 600,000 people each year. Resistance of *Plasmodium* to current therapies accentuates the need for new drugs that target novel aspects of the parasite's biology. Parasites in the phylum *Apicocomplexa* have an unusual organelle; apicoplast, which participates in the biosynthesis of fatty acids, heme, iron-sulfur clusters, and isoprenoids. Any defect in apicoplast metabolism or its failure to replicate leads to the death of the parasite. Additionally, lack of a human counterpart makes apicoplast a promising drug target. The apicoplast genome is replicated by select DNA replication enzymes, of which apicoplast DNA polymerase (apPOL) is unique to the parasite. The apPOLs from *P. falciparum* and *P. vivax* have 84% homology, while the most similar human DNA polymerases are the lesion bypass polymerases theta and nu (23 and 22% identity, respectively). Towards identifying inhibitors of apPOL, a high throughput screen of 400 compounds from the Open Malaria Box provided by (Medicines for Malaria Venture (MMV) identified a sub-micromolar inhibitor of apPOL. Preliminary studies indicate that MMV666123 is specific for apPOL, with no inhibition of human DNA Pol or *E. coli* DNA Pol I. Additionally, being a malaria-box compound substantiates the anti-malarial activity of MMV666123. Presented here are initial design, synthesis and *in-vitro* evaluation efforts toward understanding the structural requirements of MMV666123 for inhibition of apPOL and identifying more potent and drug-like apPOL inhibitors.

Poster 8

MIMICKING VIRUSES: MODULAR CONJUGATION OF PROTEINS TO THE SURFACE OF DNA NANOPARTICLES FOR NON-VIRAL GENE DELIVERY TO THE LIVER

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Non-viral gene delivery to the liver faces many challenges including maintaining DNA stability in circulation, avoiding macrophage uptake, and selectively inducing hepatocyte gene expression. Previously we developed a plasmid DNA carrier system utilizing a PEGylated polylysine/acridine peptide capable of condensing DNA into nanoparticles. These nanoparticles exhibit circulatory stability and hepatocyte gene expression in mice under hydrodynamic dosing, but lack intrinsic liver targeting. This study reports on the use of tetrazine click-chemistry to append NeutrAvidin to the surface of nanoparticles as a modular system for attachment of biotinylated proteins. To furnish the reactive handle, a heterobifunctional 5-kDa PEG was synthesized containing the tetrazine moiety on one end and a maleimide on the other for attachment to the DNA-condensing peptide. The counterpart, *trans*-cyclooctene (TCO) labeled NeutrAvidin, was constructed using NHS ester coupling. Gel filtration chromatography and dynamic light scattering verified the covalent linkage of NeutrAvidin-TCO to the DNA nanoparticles. The sizes of NeutrAvidin-labeled nanoparticles were found to be dependent on the mole percentage of tetrazine in the nanoparticles. Furthermore, NeutrAvidin nanoparticles were functionalized with the biotinylated targeting proteins apolipoprotein E (LDL receptor-specific), *Sambucus nigra* lectin (sialic acid specific), and *Erythrina cristagalli* lectin (galactose specific). A HepG2-based binding assay with fluorescently labeled DNA revealed that the targeting proteins promoted cellular uptake over controls, with the sialic acid-binding lectin displaying the best internalization. Further work involves co-labeling the nanoparticles with biotinylated endosomal escape agents and elucidating the *in vitro* luciferase gene expression of these targeted systems. This novel strategy thus provides a modular platform for rapidly testing biotinylated ligands and optimizing virus-like non-viral gene delivery systems.

Poster 9

SPATIALLY VARIABLE PCB DECHLORIATION ACTIVITY AND REDUCTIVE DEHALOGENASE GENES IN A CONTAMINATED WASTE WATER LAGOON

Jessica M. Ewald, Andres Martinez, Keri C. Hornbuckle, Jerald L. Schnoor, and Timothy E. Mattes*
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Aquatic sediments represent a terminal sink for accidentally released and improperly disposed PCB mixtures, and because these recalcitrant compounds bioaccumulate and biomagnify in the food chain, PCB contaminated sediments threaten human and environmental health. Anaerobic biodegradation of PCBs offers a pathway for the transformation of these persistent organic pollutants to less toxic compounds, but the organisms and enzymes involved remain poorly understood. To enhance understanding of the microbial community structure within PCB contaminated aquatic sediments and identify enzymes with the potential to catalyze PCB transformation we studied sediments from a PCB contaminated lagoon.

Sediment samples collected from the PCB contaminated lagoon were analyzed for PCBs to determine the congener profile and concentration. Sediment DNA was sequenced with Illumina 16S rRNA high-throughput methods, and reductive dehalogenase genes were isolated and extracted after amplification with degenerate primers designed to target all known reductive dehalogenase genes. Additionally, anaerobic microcosms were established with sediments from the lagoon locations with the most dechlorination potential. To assess the dechlorination activity in the microcosms pore water PCBs and abundances of potential anaerobic degraders were measured over time.

Total PCB congener analysis from 27 sample locations within the lagoon revealed profiles very similar to that of Aroclor 1248 with a range of concentrations from 6.3 mg/kg to 12,700 mg/kg. Among the 27 samples, several perceived hotspots of dechlorination became evident. Illumina sequencing of extracted DNA revealed variation in microbial community structure, but was consistently dominated by Proteobacteria and Firmicutes. Chloroflexi, the phylum containing known anaerobic PCB dechlorinators, ranged from 1.43 - 10.70% in the samples. The reductive dehalogenase gene survey resulted in 11 sequences most closely related to those found in *Dehalococcoides mccartyi* strain CG5 and strain CBDB1. These results represent the first time reductive dehalogenase genes were isolated from unenriched sediments After 170 days, microcosm studies reveal PCB dechlorination resulting in an accumulation of PCBS 4, 8, and 17. The native microbial community appears able to dechlorinate a range of pentachlorinated PCB congeners in the pore water including PCBs 110, 101, 95.

Poster 10

INVESTIGATING BIOSENSORS FOR THE INDUSTRIAL PRODUCTION OF 3-HYDROXYPROPIONIC ACID

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Many industrial manufacturing processes revolve around the molecule 3-hydroxypropionic acid (3HP). This organic molecule can be used in a variety of industrial products, from biofuels to bioplastic production. While much research is focusing on maximizing the production of this important molecule, our team belongs to a smaller subset focused on finding ways to sense and measure its production. In a recent study, genes from the bacteria *Pseudomonas putida* were incorporated into *Escherichia coli* and demonstrated that re-purposed regulatory proteins from *P. putida* could be used as a biosensor for 3HP (Hanko et al. 2017). A separate study identified similar 3HP responsive genes in *Pseudomonas denitrificans* (Zhou et al. 2015). Our research team has transformed a promoter-regulator system that recognizes 3HP into *Bacillus subtilis*. *B.subtilis* is a hardy bacterium that has great potential as a 3HP producer for industrial processes and metabolic engineering experiments.

Poster 11

SYNTHESIS AND BIOACTIVITY OF PRODRUG CONTAINING PHOSPHONATE LIGANDS OF A BUTRYOPHILIN PROTEIN

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The development of drugs that can modify immune function via stimulation of T-cell activity is of great and increasing interest. The γδ-T-cells show promise in the treatment of diseases such as lymphoma, leukemia, melanoma, and hepatitis C. Certain phosphorus-containing molecules can be recognized as ligands through binding to the intracellular domain of a protein (BTN3A1) within a subset of immune cells, the Vγ9Vδ2 T-cells. This process stimulates the proliferation of these cells and promotes an adaptive immune response. The molecules that display this activity often are referred to as phosphoantigens. One of the most potent phosphoantigens known, (*E*)-4-hydroxy-3-methyl-but-2enyl diphosphate (HMBPP), is naturally occurring in the non-mevalonate isoprenoid biosynthetic pathway of bacteria. While HMBPP does display potent activity for stimulation of Vγ9Vδ2 T-cell proliferation, it also has several undesirable A.D.M.E.T. (Absorption, Distribution, Metabolism, Excretion, and Toxicity) characteristics. Most notably, the cellular absorption is negatively impacted by the high charge to mass ratio of the diphosphate functionality, which diminishes the permeability of HMBPP with respect to the lipid bilayer of cell membranes. The exceptionally rapid metabolism of the diphosphate group in blood plasma also detracts from HMBPP's clinical potential.

With the potent activity of HMBPP and the potential clinical utility of phosphoantigens in mind, much of my research has been aimed at the design and synthesis of structurally similar compounds with enhanced A.D.M.E.T. properties. One of the contributions I have made to this field is the development of an efficient synthesis of prodrug masked mixed aryloxy phosphonate esters. These compounds contain a prodrug functionality that effectively disguises the charge of the free phosphonic acid while in plasma, but can be liberated to the active form intracellularly by certain enzymes. The series of compounds I have synthesized also demonstrates greater stability by virtue of the –C-P- bond replacing the more biochemically labile anhydride –O-P-O-P- arrangement. The effect measured by our collaborator at the University of Connecticut indicates a great payoff in the metabolic stability of these compounds relative to HMBPP with minimal loss in potency showing a successful step toward the desired set of characteristics.

Poster 12

INTERACTIONS BETWEEN THE BPTF BROMODOMAIN AND HISTONE H4 TAIL IN THE CONTEXT OF THE NUCLEOSOME

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Chromatin structure is a key regulator of gene expression. The basic subunit of chromatin, the nucleosome, consists of an octamer of histones wrapped by ~147 base-pairs of DNA. Protruding from each nucleosome are unstructured histone tails that can be post-translationally modified in a bevy of ways, playing a key role in directing the association and function of chromatin regulators. These regulatory complexes recognize histone tails through effector domains, which are often referred to as reader domains. The interactions between histone tails and effector domains have been widely investigated. However, these studies have largely been conducted using peptide fragments representative of the histone tails, leaving a large gap in our knowledge of how effector domains recognize their substrate in the proper context of the nucleosome. Recently, our lab has shown that the conformation of the histone H3 tail with respect to the nucleosome core inhibits binding of the BPTF PHD finger to H3K4me3.[1] Thus, confirming the importance of investigating effector domain binding in the context of the entire nucleosome. Here, we present results on the conformation of the H4 tail in the context of the nucleosome and our investigation into the effect of this conformation on the interaction between the BPTF bromodomain and the acetylated H4 tail. Utilizing NMR spectroscopy, we find that lysine acetylation alters histone tail conformational dynamics in a site-specific manner. Additionally, we find that H4K16ac may alter bromodomain specificity for the H4 tail in the context of the nucleosome.

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Poster 13

RELATIVE INHIBITION POTENCY OF 5-FLUORO DEOXYURIDYLATE TOWARD WT AND Y33H MUTANT HUMAN THYMIDYLATE SYNTHASE

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All organisms must maintain a pool of the four kinds of deoxynucleoside triphosphates in order to use them for DNA synthesis by polymerase enzymes.[1] In order to keep an adequate supply of deoxythymidine triphosphate, the wide majority of organisms rely on the enzyme thymidylate synthase (TSase), which converts deoxyuridine monophosphate (dUMP) and methylene tetrahydrofolate (MTHF) into deoxythymidine monophosphate (dTMP) and dihydrofolate (DHF), respectively.[2] In this process, a proton is replaced with a net methyl group. This enzyme is the target of cancer chemotherapeutic drugs, because cancerous cells grow faster and require even more deoxynucleoside triphosphates.

In humans, a clinically isolated cancerous cell population with a mutation in one amino acid has been reported and found, via whole-cell assays, to be less susceptible to 5-fluoro dUMP, an inhibitor of TSase used medically. This is known as drug resistance; we sought to confirm that the decreased vulnerability was at the TSase level rather than, for instance, as a result of overexpressed drug efflux pumps or altered enzyme expression levels. The mutation is away from the active site, with Tyr33 replaced with His.[3-4] Because 5-fluoro dUMP can be a non-covalent and a covalent inhibitor[2] that competes with dUMP for binding to TSase, monitoring the degree of rate slowdown as a function of time was reported to be informative to best characterize this inhibition.[5]

Therefore, we monitored the A_{340} change that accompanies the conversion of MTHF to DHF at various concentrations of 5-fluoro dUMP for both WT and Y33H human TSase over the course of 90 minutes. By comparing slopes of these progress curves in different time regions, we were able to obtain a pattern of variation of K_i with time for both enzymes. Our results indicated that indeed Y33H was less susceptible to inhibition by 5-fluoro dUMP. This suggests that the origin of the drug resistance of clinical cell populations bearing this mutation in TSase is indeed likely direct, occurring at the level of drug-enzyme interaction. Other studies performed by our team and others implicate protein motions and structural traits to explain the inhibition findings.

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Poster 14

UNWEAVING THE ROLE OF STAPHYLOCOCCAL SUPERANTIGENS IN THE PATHOGENESIS OF INFECTIVE ENDOCARDITIS

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Staphylococcus aureus is the leading cause of infective endocarditis (IE). *S. aureus* IE is an aggressive infection of the heart, characterized by the formation of vegetative lesions on the inner leaflet of the valves. Infections can become life threatening within a few days, leading to around 20,000 deaths annually. Recent studies have shown the importance of superantigens (SAgs) in the establishment of staphylococcal IE. All SAgs share multiple binding sites such as the TCR binding site, MHCII binding site, and the dodecapeptide region. Classically, SAgs cause massive immune activation and dysfunction through TCR/MHCII interactions. The less characterized dodecapeptide region was shown to interact with and modulate immune responses in epithelial cells; little is known about its contribution to disease. Currently, the understanding of the SAg biological functions that promote the pathogenesis of IE is not understood. Here we addressed the mechanism by which SAgs contribute to IE pathogenesis. We tested TCR binding site mutants of the SAgs SEC and TSST1 complemented in the IE deficient strain MW2ΔSEC to determine the role of superantigenicity in the rabbit model of native valve, left-sided IE. The TCR binding site mutant, SECN23A, resulted in vegetation formation and systemic pathology, indicating the superantigen is required for vegetation formation and disease, but not the function of superantigenicity. To further elucidate the biological function of SAgs during IE, we tested the effects of SEC and TSST1 directly on endothelial cells. We found that these SAgs lead to modulations of immune responses in cytokine production and wound healing assays that are not dependent on TCR/MHCII binding sites. Using a LPS-suppression assay, we showed that specific residues of the dodecapeptide influence SAg interaction with the endothelium. These findings provide insights into the underlying molecular mechanisms of SAg involvement in *S. aureus* IE. Importantly, it provides further evidence of the bifunctionality of SAgs.

Poster 15

TITANIUM SURFACES COATED WITH A 1% SUCROSE SOLUTION CONTAINING POLYETHYELENIMINE (PEI)-GENE POLYPLEXES SUCCESSFULLY TRANSFECT CELLS *IN VITRO*: A STEP TOWARDS REDUCING DENTAL IMPLANT COMPLICATIONS

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Dental implants are now one of the highly successful medical devices with a survival rate in the ninety percent range, but implant failures do occur and implants are not immune to biological complications such as peri-implant mucositis and peri-implantitis. Currently there is a lack of evidence suggesting that surgical reconstructive approaches are effective in predictably resolving the disease process, suggesting that the best management practice is prevention. The integrity of the soft tissue seal encircling dental implants is a crucial barrier to prevent the down growth of bacterial biofilm that leads to peri-implantitis or to prevent gingival recession around dental implants. In this study the potential to coat titanium surfaces with transfection reagents to transfect local cells *in vitro* was investigated. The ability to transfect cells reliably was established with the HEK 293 cell line and plasmid eGFP. The system was then used to transfect primary gingival cells with PDGF-B with the aim of enhancing expression of genes associated with proliferation and adhesion.

Poster 16

MOLECULAR RECOGNITION ATOMIC FORCE SPECTROSCOPY TOWARDS QUANTIFYING SINGLE MOLECULE LEVEL ENZYME-LIGAND INTERACTIONS

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Single molecule level studies can lay the foundation towards understanding the microscopic nature of interaction forces between ligands and enzymes that in turn strongly influence majority of biological processes. Experiments utilizing a large ensemble of molecules does not truly represent the interaction between individual molecules. Such information is important since the averaged ensemble properties may not accurately represent the single molecular responses. This study utilizes high spatial and force resolution provided by the Atomic Force Microscopy (AFM) under physiological conditions to quantify the force-distance information of enzyme-ligand interaction. Different immobilization techniques were utilized to covalently bind the enzyme to the surface and ligand molecules to the AFM tip and then results were quantitatively compared to improve the accuracy and reproducibility of the measurements. Measurements of forces required to rupture enzyme-ligand complex were carried out on directly immobilized enzymatic monolayer and compared with enzymes bound to surface through a rigid double stranded (ds) DNA spacers. Ligand molecules were attached to the tip via either flexible polyethylene glycol or rigid dsDNA linkers. This 123-base pair containing 41 nm long rigid dsDNA linker was proved to withstand repetitive force measurements of enzyme-ligand rupturing. The findings of this study indicate that new single molecule approach for measuring enzyme-ligand interactions based on rigid dsDNA linker on both tip and surface afford highly specific and accurate force measurements.

Poster 17

ESTABLISHING THE ROLE OF ADYNAMIC NETWORK OF PROTEIN MOTIONS COUPLED TO CHEMICAL STEP IN HUMAN DIHYDROFOLATE REDUCTASE

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Understanding various protein motions and their roles in the complex enzymatic reactions is an attractive yet challenging topic for researchers. Allosteric motions that are correlated to the chemical step of catalysis are particularly intriguing but difficult to isolate. A "global dynamic network" of coupled residues in *Escherichia coli* dihydrofolate reductase (ecDHFR) that assist in catalyzing the chemical step has been demonstrated through quantum mechanical/molecular mechanical studies, molecular dynamic simulations and bioinformatic analysis. A few specific residues (*i.e.* M42, G121, and I14) have been demonstrated to function synergistically through measurements of single turnover rates and the temperature dependence of intrinsic kinetic isotope effects (KIEs) of site directed mutants of the enzyme. Despite the fact that a similar network has been found in other enzymes, the general features of this network are still unclear. Current studies focused on exploring the homologous residues of the proposed global network in human DHFR (hsDHFR) by both measurements of the temperature dependence of intrinsic KIEs and computer simulations. The results found that both mutants of M53W and S145V show significant decrease in catalytic efficiency although they are distal. Non-additive characteristic of the isotope effect on activation energy were observed between the two residues of M53 and S145 justifying the synergistic effect for hydride transfer hsDHFR catalyzed. These demonstrated that a similar network exists in hsDHFR as in the *E. coli* enzyme for the first time. This confirms that this type of network is preserved from the bacterial system to the more evolved human enzyme. The results suggest that the network could be a general phenomenon in the same superfamily.

Poster 18

SHARED-COORDINATE DUAL FORCE FIELD: APPLICATION OF A LARGE-SCALE INDIRECT FREE ENERGY METHOD TO DIVALENT METAL CATION BINDING

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While many biological systems can be adequately represented in simulations at a fixed partial charge level of electrostatic detail, complicated electrostatic environments such as buried ion-binding pockets, solvent-membrane interfaces, and nucleic acid binding sites require more detailed electrostatic representations. Indirect free energy methods produce rigorous thermodynamic transformations between efficient fixed-charge models and more accurate (but also more expensive) polarizable models such as the AMOEBA polarizable atomic multipole force field. While this family of methods has previously been limited to systems of ~50 atoms, here we demonstrate a new Shared Coordinate Dual Force Field (SC-DFF) approach on the relative ion binding thermodynamics of divalent metal cation-binding proteins, with systems of up to ~3000 atoms. Fixed charge estimates of over 50 kcal/mol error are brought close to experimental accuracy, indistinguishable from direct AMOEBA simulations, demonstrating the validity of SC-DFF as the first large-scale indirect free energy method.

Poster 19

EXPLAINING ENZYME EVOLUTION BY EVALUATING PHYLOGENETICALLY COHERENT EVENTS IN DIHYDROFOLATE REDUCTASE

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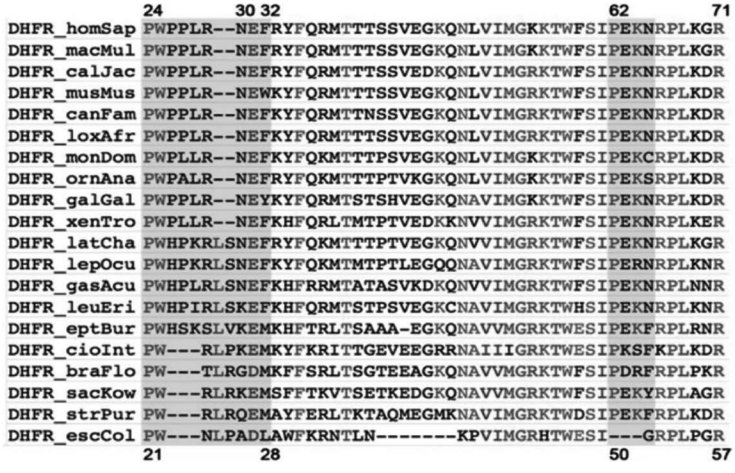
Phylogenetically coherent events (PCEs), or evolution-derived genetic variations of one enzyme across multiple organisms, have been identified for the enzyme dihydrofolate reductase (DHFR) (Figure A) and are suggested to play a role in how this enzyme catalyzes hydride transfer. The PCEs relevant to DHFR are N23PP, L28F, and G51PEKN (numbering for *E. coli*). Previous studies on this enzyme have made N23PP and N23PP/G51PEKN *ec*DHFR to determine if these PCEs interact with one another or optimize hydride transfer of *ec*DHFR on their own. The performance of hydride transfer in DHFR and its sensitivity to temperature have been evaluated with intrinsic kinetic isotope effects (KIE_{int}). If a single PCE insertion is made and it requires another PCE for optimal activity, a temperature dependent KIE_{int} will be observed; otherwise, a single PCE may be temperature independent. Individually, N23PP was found to have a temperature dependent KIE_{int} while N23PP/G51PEKN had a temperature independent KIE_{int} (Figure B). This suggests the PCEs may be evolutionarily significant and cooperate in a network of residues. L28F *ec*DHFR may display a temperature-dependent KIE_{int} and is the subject of the current investigation.



Phylogenetically aligned sequences of DHFR and corresponding relevant Arrhenius plot of intrinsic KIEs. (A) bottom sequence is *E. coli* DHFR and ascends to the top sequence corresponds to the highest organism, *H. sapiens* DHFR. Highlighted in magenta are the two PCEs examined by previous work. (B) Plotted as log of primary intrinsic KIE versus inverse temperature are the KIEs of WT, N23PP, and N23PP/G51PEKN *ec*DHFR. Horizontal trends indicate temperature independent KIEs (WT and double mutant) while N23PP has a non-zero slope which indicates a temperature dependent KIE. Figure from Francis et al. *Biochemistry* **2016,** *55* (7), 1100-6.

Poster 20

TRANSFORMATION OF DICHLOROACETAMIDE SAFENERS IN BIOTIC AND ABIOTIC SYSTEMS FOR ENDOTHELIUM INTERACTION AND DYSFUNCTION

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Dichloroacetamide safeners are used extensively in herbicide formulations to selectively protect crops from the detrimental effects of herbicide active ingredients. Despite their demonstrated bioactivity, dichloroacetamides are regulated as “inert”, and, consequently, information pertaining to their fate and transformation in the environment is largely absent from the peer-reviewed literature. Recent studies suggest dichloroacetamide safeners can transform over environmentally-relevant timescales via dechlorination into products with increased bioactivity. This work aims to elucidate the fate of dichloroacetamides by examining biotic and abiotic transformations and sorptive behavior. Current studies focus on one dichloroacetamide species, benoxacor. Photolysis experiments demonstrated that benoxacor readily undergoes direct photolysis to a closed-ring intermediate, then further reacts to a stable end product. Based on preliminary LC-MS/MS characterization, we expect this coupling product to possess bioaccumulative potential and structural features evocative of other bioactive pollutant classes. Hydrolysis of benoxacor proceeds rapidly at high pH, such as that used in water softening processes. Sorption experiments demonstrated that benoxacor exhibits partitioning behavior similar to its active herbicide co-formulant, metolachlor. These findings suggest that benoxacor and its potentially bioactive transformation products are likely present in surface waters and may impact aquatic ecosystems and drinking water supplies.

Poster 21

GROWING NUTRITIOUS MICROALGAE FROM WASTE NUTRIENTS, CARBON DIOXIDE AND NITRATE

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High-protein microalgae are a promising alternative to soy for more rapidly and sustainably produced protein-rich animal feed. However, there are still significant barriers to growing nutritious salable microalgae, recovering nutrients from wastewater, and fixing CO_2 from flue gas in full-scale sustainable operations. Currently, it is generally assumed that nutritious microalgae, including *Scenedesmus obliquus*, are inhibited by CO_2 levels relevant to industrial flue gases. Experiments in a 2-L photobioreactor with ability to control CO_2 concentrations demonstrated that inhibition of *S. obliquus* was not important until 10% CO_2 and growth rates were not prohibitively reduced even at 25%. The rate of growth exceeded all values in the literature, and the amino acid content of the microalgae was equal or superior to that of soy. A substrate inhibition model indicated that CO_2 levels comparable to flue gases do not substantially inhibit *S. obliquus* growth, with careful pH control. The model indicated maximum biomass productivity of 890 mg L^{-1} d^{-1} at 1.8% CO_2 (K_m of 0.9 ± 0.4% CO_2, K_i of 25 ± 8% CO_2, and v_{max} of 890 ± 130 mg L^{-1} d^{-1}), which exceeds previously measured biomass productivity values at inhibitory CO_2 concentrations. Protein contents of *S. obliquus* and soy were comparable.

Poster 22

BIOCHEMICAL AND STRUCTURAL INSIGHT INTO THE ALLOSTERIC MECHANISM OF PYRUVATE KINASE M2 BY POST-TRANSLATIONAL MODIFICATIONS

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Pyruvate kinase muscle isoform 2 (PKM2) is a predominantly tetrameric enzyme, which is primarily expressed in tumor cells. In rapidly proliferating cells, PKM2 undergoes a switch from a tetrameric to a predominantly dimeric form and translocates itself to the nucleus. There it functions as a transcriptional coactivator upregulating the expression of oncogenes, like *c-myc*, which aids in cancer cell growth. Previous cell-based studies indicate that the tetramer-to-dimer switch is brought upon by phosphorylation of PKM2 at serine37 and acetylation at lysine433, the molecular mechanism of which is yet unknown. Moreover, the studies do not answer the question as to whether phosphorylation or acetylation alone is sufficient to induce dimerization or there is an involvement of other factors inside the cell. Our crystal structure of the PKM2 variants, which mimic phosphorylated and acetylated PKM2 indicate that the post-translational modifications result in structural changes in the fructose 1, 6-bisphosphate (FBP) binding pocket of PKM2, which prevents binding of the allosteric activator to the enzyme. The observation is supported by fluorescence quenching studies, where we observe a reduced binding affinity of FBP to the acetyl and phosphomimics compared to wtPKM2. Size exclusion studies indicate that the post-translational modifications cause significant tetramer-to-dimer conversion of the enzyme. Activity studies of the phosphomimetic PKM2 show a reduced activity compared to wtPKM2 as dimeric PKM2 exhibits reduced activity than its tetrameric form. Based on these structural and *in vitro* biochemical assays, we hypothesize that acetylation and phosphorylation by itself is sufficient to cause a tetramer-to-dimer conversion of PKM2 due to structural changes in the FBP binding pocket of the enzyme.

Poster 23

THE MECHANISTIC ROLE OF METAL IONS, CA^{2+} AND MG^{2+}, IN RGS: G-PROTEIN INTERACTIONS

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Regulator of G protein signaling (RGS) proteins are negative regulators of G protein-coupled receptor (GPCR) signaling through their ability to act as GTPase activating proteins (GAPs) for some Gα subunits. The RZ subfamily, of which RGS17 is a member, binds to activated $G\alpha_o$, $G\alpha_z$, and $G\alpha_{il\text{-}3}$ proteins to modulate downstream pathways, including those involved in formation of cyclic AMP. In contrast to other RGS proteins, less is known about the regulation of RZ family members. Both Crystallization and $^{1}H\text{-}^{15}N$ 2D HSQC NMR experiments revealed an interaction of the metal ion Ca^{2+} with RGS17 at a defined binding site. Subsequent protein-protein interaction experiments, using AlphaScreen were used to assess the impact of the ions Ca^{2+} and Mg^{2+} on the RGS17 interaction with activated $G\alpha_o$. The results indicate that both Ca^{2+} and Mg^{2+} have an effect of promoting the RGS17-Gα interaction. These studies will extend to examining the selectivity and affinity of RGS17 for other physiologically relevant divalent metal cations, such as Zn^{2+}, Cu^{2+}, and Mn^{2+}. In addition, the residues of RGS17 that bind Ca^{2+} are conserved in multiple RGS proteins. The functional impact of metal ion binding is likely not limited to RGS17 and a more in-depth evaluation of these proteins for metal binding deserves further attention.

Poster 24

FORMULATING AN ASPIRIN-ELUTING DEGRADABLE POLYMER COATING FOR INTRACRANIAL FLOW DIVERTERS

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The international subarachnoid hemorrhage aneurysm trial (ISAT) transformed the treatment of intracranial aneurysms (IAs). It showed a superior outcome treating IAs using endovascular means versus microsurgical clipping. One of the advances in the field is the use of stent assisted coiling or flow diverters. These two techniques require the use of dual anti-platelet therapy (DAPT). The role of DAPT is to minimize the risk of thromboembolic events in patients, however, DAPT use is associated with increased risk of brain hemorrhage. Here we propose a novel strategy using a drug eluting biodegradable coating that can be deposited directly onto the intracranial flow diverter surface. We expect that the negative effects associated with DAPT can be decreased when delivering the drugs locally as opposed to systemically.

Intracranial flow diverters [Pipeline™, Medtronic] were coated using a solution of 1% w/v poly(lactic-co-glycolic) acid (PLGA) in acetone incorporated with 1% w/v acetylsalicylic acid (aspirin) [Sigma]. The dip coating process involved leaving the flow diverter in the coating solution on a shaker for 30 minutes, removing it from the solution and allowing it to dry completely, then returning the flow diverter to the solution for the next coat. This process was repeated several times and the success of the coating procedure determined using scanning electron microscopy (SEM) imaging [Hitachi S-4800]. Before a release study could be performed on the coated flow diverters, it was necessary to develop a method to accurately determine the concentration of aspirin. UV-Vis spectroscopy was used to verify appropriate wavelengths to use as well as the linear range for each wavelength using known standard solutions. High performance liquid chromatography (HPLC) was used to determine the amount of aspirin loaded onto the stent and the concentration of aspirin in each sample of the release study.

The amount of aspirin loaded onto the stent was determined by dissolving the aspirin/PLGA coating in acetone, using a rotary evaporator to remove the acetone, then reconstituting the solid in the HPLC mobile phase. The release study design involved having the coated flow diverters placed in a sealed 6 well plate filled with sufficient 1X PBS solution to cover it completely. The plate was left in a 37°C incubator for 7 days and each day, 200µL samples were taken from the well and replaced with fresh release media. The samples were stored in a 4°C fridge until the last day of the experiment, at which point the concentrations for each sample was determined and a release profile compiled. All HPLC samples were measured using a UV-Vis detector measuring dual wavelengths of 230 and 270nm.

The intracranial flow diverters were successfully coated with PLGA/aspirin and the coating was confirmed using SEM imaging. Aspirin loading and release profile from the coated flow diverters results will be shown. In the field of neurosurgery, there is a medical need to find an alternative to systemic use of DAPT. Here we demonstrate the ability to coat intracranial flow diverters with PLGA incorporated with aspirin which we believe will be able to deliver a controlled and sustained release of the anti-platelet drug at the implantation site and reduce the risks associated with administration of a systemic antiplatelet therapy.

Poster 25

EFFECTS OF PROTEIN VIBRATIONAL AND STRUCTURAL PERTURBATIONS ON HYDRIDE TRANSFER REACTION CATALYZED BY FORMATE DEHYDROGENASE

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Enzymes and proteins are effective biological catalysts that are essential for life. Protein motions have been identified as being important for efficient catalysis. Unraveling the role of protein dynamics is of contemporary interest as such understanding would allow inhibitor and biomimetic catalyst design. Formate dehydrogenase (FDH) is a model system that catalyzes a hydride transfer from formate anion (donor) to NAD^+ cofactor (acceptor). We perturb protein motions on a range of timescales by isotopically labeling the protein with ^{15}N (singly labeled), ^{13}C and ^{15}N (doubly labeled), and ^{13}C, ^{15}N, and ^{2}H (triply labeled). Increasing temperature dependence of the kinetic isotope effect (KIE) in direct correlation with protein mass suggests broadening of the donor-acceptor distance (DAD) distributions in the hydride transfer step. Further investigations are done using two-dimensional infrared (2D IR) spectroscopy to directly probe the active site dynamics on the timescale of femtoseconds to picoseconds. Interestingly, comparison of the 2D IR results between the labeled and unlabeled (native) FDHs leads to the conclusion that isotopic labeling results in electrostatic perturbations that affect the protein beyond just the mass effects.

Poster 26

A qPCR-BASED MODEL FOR AEROBIC VINYL CHLORIDE BIODEGREDATION UNDER SIMULATED FIELD CONDITIONS

Patrick M. Richards and Timothy E. Mattes*
Department of Civil and Environmental Engineering, College of Engineering, The University of Iowa, Iowa City, IA

Chlorinated solvents, such as tetrachloroethene (PCE) and trichloroethene (TCE) are toxic chemicals and common groundwater contaminants. PCE and TCE contamination is commonly treated via anaerobic bioremediation, in which they are reductively dechlorinated to non-toxic ethene. However this process is often incomplete, resulting in an accumulation of vinyl chloride (VC), a known carcinogen. Certain aerobic bacteria are known to degrade VC, and may offer a promising complementary remediation strategy. Regulatory acceptance of such a strategy would require a sound method for predicting degradation kinetics in the field.

Aerobic VC degradation kinetics have been successfully modeled under laboratory conditions. However, these experiments relied on pure cultures and non-specific measures of active biomass, such as protein concentrations. VC degrading bacteria may only comprise a small portion of total microbial biomass in the field, and may include members of several unrelated genera, making their quantification challenging.

Quantitative polymerase chain reaction (qPCR) targeting the VC-oxidation functional genes *etnC* and *etnE*, have been shown to be specific and sensitive measures of aerobic VC degrading bacteria in mixed cultures and groundwater. A recent field study has also demonstrated a semi-quantitative relationship between observed bulk VC attenuation rates and the abundance these genes. The objective of this study is to develop a qPCR-based kinetic model using the functional genes *etnC* and *etnE* as specific measurements of aerobic VC degrader biomass in mixed cultures. This model will be based on Monod kinetics, and will incorporate important field parameters such the VC and oxygen concentrations, pH, and temperature. Modeling, including parameter fitting and sensitivity analysis, will be conducted using AQUASIM 2.0 software.

Poster 27

MANIPULATION OF AZINE ANHYDROBASES TO ACCESS A DIVERSE RANGE OF PHARMACOPHORES

Grant N. Shivers and F. Christopher Pigge*
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Heterocycles are the most common structural moiety among FDA approved pharmaceuticals. The most common of these heterocycles are piperidine and pyridine, present in 35% of all small molecule drugs.[1] Novel synthetic manipulation of these heterocycles are in high demand in drug discovery programs, particularly methods capable of introducing enantioenriched carbon centers or $sp^{2 \text{ or } 3}$-sp^3 coupled products.[2] An underexplored route to achieve these transformations was envisioned to proceed through dearomatized pyridine rings, generating the so-called azine anhydrobases.

Efforts to achieve these desirable transformations through azine anhydrobase intermediates are underway in the Pigge lab with promising initial results. The dearomatization process converts the unreactive pyridine aromatic system into highly malleable olefins. Azine anhydrobases are versatile intermediates, allowing facile functionalization and subsequent conversion to the relevant pyridine or piperidine

Several intermediates of interest in drug discovery programs including 4-pyridylenamides and 4-pyridylindolinones have been produced with improved simplicity and yields compared to the original methods.[3] The synthesis of azafluorenes endowed with antidiabetic activity is also being explored through this method, but current attempts to produce this unique pharmacophore have failed.[4] Preliminary data also indicates a net sp^3-sp^3 allylative coupling reaction.

References:

1. *J. Med. Chem.* **2014**, *57*, 10257-10274.
2. *Nat Chem.* **2018**, *10*, 383-394.
3. *Org. Process Res. Dev.* **2014**, *18*, 904-911.
4. *J. Am. Chem. Soc.* **2016**, *138*, 15473–15481.

Poster 28

BIOAUGMENTATION AND PHYTOREMEDIATION OF 1,4-DIOXANE IN SIMULATED GROUNDWATER

Reid A. Simmer, Jacques Mathieu, Pedro J. J. Alvarez, and Jerald L. Schnoor*
Department of Civil and Environmental Engineering, College of Engineering, The University of Iowa, Iowa City, IA

1,4-dioxane (dioxane), a probable human carcinogen, is a persistent and highly mobile groundwater pollutant. Because of this, dioxane plumes are often large and diffuse, which pose a challenge for remediation. To make matters worse, dioxane is commonly found comingled with various chlorinated solvents. Many states have issued heath-based cleanup guidelines for dioxane, ranging from 1 μg/L in California, to 0.35 μg/L in Colorado, and to 0.25 μg/L in New Hampshire. Reaching these low cleanup guidelines through remediation has proven to be particularly difficult and costly. Utilizing aggressive pump-and-treat and *ex situ* technologies such as advanced oxidation on dilute dioxane plumes is prohibitively expensive. Alternatively, phytoremediation using poplar trees has been proposed as a cost-effective clean-up strategy. However, questions remain if this technology can alone remediate dioxane, especially from deep groundwater plumes. Bioaugmentation of deeper plumes with dioxane-degrading microbes is one possibility. Another promising solution is to pump the contaminated water onto plantations of trees and to bioaugment the poplar rhizosphere with dioxane degrading bacteria to speed degradation. In prior laboratory studies, *Pseudonocardia dioxanivorans* CB1190 has been utilized as a pure culture bacterium to speed the biodegradation rate of 1,4-dioxane by hybrid poplar (*Populus deltoides x nigra*, DN34) via bioaugmentation. However, CB1190 has been shown to be ineffective at low dioxane concentrations (<500 $\mu g\ L^{-1}$) commonly encountered in the field, which also violate health advisory guidelines. In addition, chlorinated solvents have been shown to inhibit dioxane degradation by CB1190. Due to these shortcomings, there is a need to isolate novel bacteria better suited for bioaugmentation of hybrid poplar.

In this research, we report the degradation rates of dioxane in simulated groundwater by CB1190 as well as novel bioaugmentation candidates. Furthermore, unplanted systems and those planted with hybrid poplar are investigated to determine the relative potential for bioaugmentation and/or phytoremediation to be effectively applied at various sites contaminated with dioxane.

Poster 29

ENHANCING THE ANTITUMOR ACTIVITY OF ADENOVIRUS VACCINES BY COMBINING WITH INTRATUMORAL DELIVERY OF CpG-LOADED NANOPARTICLES

Rasheid Smith, Sean Geary and Aliasger K. Salem*
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Homologous recombination is a vital process for maintaining genome stability. This process is essential when the cell encounters double-strand breaks during replication. During homologous recombination RAD51 recombinase binds single-strand DNA, forming a nucleoprotein filament. Strand invasion is initiated, displacing the nascent complimentary strand of nearby double-strand DNA and the RAD51 coated ssDNA is brought into proximity of the newly single-stranded DNA. A homology search, for complimentary DNA, is carried out and recombination proceeds when the D-loop is formed. Without RAD51, persistent double-strand breaks are formed, and the cell is marked for death, apoptosis. We use single molecule total internal reflection microscopy techniques to examine the ability of RAD51 to form nucleoprotein filaments on the many DNA structures that are found in the cell, such as collapsed replication forks, resected double-strand DNA, and D-loops, with the goal of determining if RAD51 has preference for certain DNA structures, that point to a mechanism of controlling homologous recombination.

Poster 30

SORPTION OF NEONICOTINOID INSECTICIDES AND THEIR METABOLITES TO GRANULAR ACTIVATED CARBON DURING DRINKING WATER TREATMENT: IMPLICATIONS FOR TREATMENT, BIOFILM TRANSFORMATION, AND HUMAN EXPOSURE

Danielle T. Webb, Kathryn L. Klarich, David M. Cwiertny, and Gregory H. LeFevre*
Environmental Engineering and Science, Department of Civil and Environmental Engineering, College of Engineering, The University of Iowa, Iowa City, IA

The widespread application of neonicotinoid insecticides has led to their detection in waters across the U.S., including those used as drinking water sources. Formation of vertebrate-toxic metabolites from microbial processes in watersheds creates a human exposure concern. Our prior work has demonstrated promise of granular activated carbon (GAC) as a possible method for removing imidacloprid, clothianidin, and thiamethoxam (common neonicotinoids) from drinking water and may also prove effective at removing neonic metabolites (desnitro imidacloprid and imidacloprid urea). Sorption isotherms were conducted with the neonics and metabolites to assess their affinity towards GAC and the likelihood of residual neonicotinoid desorption. Water samples were also analyzed pre- and post- GAC filtration at the Iowa City drinking water treatment plant (IC DWTP) to assess neonic and metabolite removal in a full scale GAC filter. Results indicate neonics and neonic metabolites (despite high polarity / solubility) readily adsorb to GAC (50 – 120 mg g^{-1}) and minimally desorb in buffered solutions at environmental pH. Neonicotinoid desorption from IC DWTP GAC occurred in solvents of medial polarity (acetonitrile, acetone, and dichloromethane) with concentrations of up to 600 ng neonic/ g GAC for parents but no desorption of metabolites. When analyzing drinking water samples from the IC DWTP, we observed that neonics were removed <95% by the GAC filter for all neonics and metabolites. Nevertheless, desnitro imidacloprid had the lowest removal efficiency, 2 ng L^{-1} to 0.08 ng L^{-1} from pre- to post- GAC filter compared to parent neonics, which were removed by 20 ng L^{-1} to 0.4 ng L^{-1} for the most concentrated neonic, clothianidin. These results suggest that although the parent and metabolite neonics are largely adsorbed, IC DWTP GAC has a lower capacity to adsorb the metabolite desnitro imidacloprid leading to its prevalence in the drinking water systems. Although desnitro imidacloprid is ubiquitous in drinking water, exposure to redox-active black carbon with biofilms may be capable of transforming toxic metabolites and parent neonics in the aqueous and adsorbed phase through abiotic and/or biotic reactions. In ongoing work, we are combining black carbon with biofilms to elucidate coupled abiotic and biotic transformations of neonics and their metabolites to develop new treatments methods.

Poster 31

LONG-TERM NONINVASIVE GLUCOSE MEASUREMENT BY MEANS OF NEAR-INRARED SPECTROSCOPY AND PRINCIPAL COMPONENT ANALYSIS COUPLED WITH NET ANALYTE SIGNAL

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According to a report published by the Centers for Disease Control and Prevention in 2017, more than 30 million people in the United States have diabetes. Glucose monitoring is critical element for proper management of glycemia in these patients. Currently, test-strip blood measurements are used for daily home monitoring, where such measurements require painful finger-sticks to collect a sample of blood for analysis. Noninvasive glucose measurements offer a pain-free method of measuring blood glucose levels without the need for the physical collection of a sample of blood.

Noninvasive spectroscopic measurements coupled with multivariate calibration analysis represent a viable approach to real-time glucose measurements in people with diabetes. State-of-the-art noninvasive sensing technology, however, lacks the ability to provide accurate glucose concentration predictions over periods of days to weeks. The immediate objective of our research program is to develop a combination of spectroscopy and chemometric methods capable to prospective concentration measurements.

In this work, near-infrared skin spectra were collected on the backside of the hand for a series of volunteers with Type 1 diabetes. The instrumentation comprises a customized light source, a Fourier-transform near-infrared spectrometer, a vacuum-controlled skin manifold and a thermoelectrically-cooled detector. For each trial, the protocol involves collecting 1.5 hours of fasting spectra, and then 3.5 hours of additional spectra after ingestion of a meal. Reference glucose measurements were performed every 15 minutes with commercial finger-stick monitors. This protocol was performed in triplicate for each subject.

High signal-to-noise values for these skin spectra gives promise for extracting glucose specific information from the complex skin matrix. Multivariate calibration models were constructed using the fasting spectral data by combining principal component analysis and net analyte signal methods (PCA-NAS). The resulting NAS calibration vector predicted glucose concentrations for after-meal periods both within-day and between-days. The resulting measurements were characterized as the standard error of prediction (SEP). Similar between-day and within-day SEP values demonstrates the existence of glucose specific information within these noninvasive skin spectra, thereby supporting the potential for successful long-term glucose measurements with this approach of combining near-infrared spectroscopy with PCA-NAS processing.

Poster 32

HIGH YIELD FUNGAL PROTEIN EXPRESSION SYSTEM FOR BIOLOGICS

Shuvendu Das[1,2], Samuel Denhartog[1], Daning Lu[1], Anna Bauer[1], Sridhar Gopishetty[1], Elizabeth R. Gibson[1], Ronen Tchelet[3], Jenő Szilagyi[3], and Mark Arnold[1,2*]
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High yield of protein production (> 25 g/L) is a major challenge in the pharmaceutical industry, specifically to enhance the production of biologics or enzymes required for the chiral synthesis of small molecule drugs. A novel protein expression platform capable of such high production yields is under investigation. This expression system uses a proprietary strain of *Myceliopthora thermophila* fungal cells (C1), developed by Dyadic International, for the production of enzymes. Expressed recombinant protein is secreted by this C1 cellular factory, thereby producing a relatively clean supernatant product with yields of 80 g/L for a single enzyme within a matrix yield of 100 g/L of total protein. We are interested in translating this C1 protein expression platform for pharmaceutical applications, including for the manufacturing of biologics, enzyme reagents and vaccines.

This presentation highlights findings from the initial C1 fermentations designed to express the enzyme cellulase. C1 fermentation process conducting with low cellulase containing strain produces 45.85 g/L of total protein in the supernatant. Analysis reveals 614.5 Units/mL cellulase activity produced in the supernatant fraction. Future efforts will focus on increasing protein yields, expanding this process to manufacture enzymatic systems of relevance to pharmaceutical applications, and assessing the utility of real-time process monitoring of both cell expansion and protein expression during fermentation.

Poster 33

SEROTONIN ACTIVATES HEAT SHOCK RESPONSE IN MAMMALIAN CELLS THROUGH cAMP/PROTEIN KINASE A SIGNALING

Srijit Das and Veena Prahlad*
Aging Mind and Brain Initiative, Department of Biology, College of Liberal Arts and Sciences, The University of Iowa, Iowa City, IA

When exposed to unfavorable conditions, cells maintain their proteome by robust and transient synthesis of heat shock proteins (HSPs). HSPs are expressed through the stress-induced activation of the transcription factor heat shock factor 1 (HSF1) which is an evolutionary conserved adaptive process broadly known as heat shock response (HSR). In eukaryotic cells, HSR is regulated cell autonomously, however; in metazoans, HSR is also subjected to cell non-autonomous control. In *Caenorhabditis elegans*, HSR is regulated by thermosensory neurons which can activate HSF1 in another cell even in absence of stress. Pioneering work from our lab demonstrated that neuronal regulation of HSR is mediated by enhanced release of the neurotransmitter serotonin (5-HT) and the metabotropic receptor SER-1 is responsible for this activation. Here we show that exogenous 5-HT can induce expression of heat shock proteins in cultured neuronal cells and mouse primary cortical neurons in a dose-dependent manner. This effect of exogenous 5-HT is HSF1-dependent and mediated through 5-HT4 receptor. The upregulation of heat shock proteins in presence of exogenous 5-HT is caused, at least, in part, by phosphorylation of serine 320 (S320) residue of HSF1 – a known substrate of protein kinase A (PKA) whose activity is regulated by intracellular concentration of cyclic AMP (cAMP). Our study demonstrates that the activation of heat shock response pathway by serotonergic signaling is conserved in mammalian system and occurs through cAMP/PKA signaling.

Poster 34

CRISPRi-TARGETED GENE INHIBITION IN *CLOSTRIDIUM DIFFICILE*: A NEW TOOL FOR DECIPHERING GENE FUNCTION

Ute Müh, Anthony G. Pannullo, David S. Weiss, and Craig D. Ellermeier*
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Clostridioides (Clostridium) difficile is the most common cause of hospital-acquired diarrhea and is considered an "Urgent" threat by the CDC. The lack of genetic tools adapted for use in *C. difficile* is a stumbling block for both basic and applied research. We established a *C. difficile* CRISPR interference (CRISPRi) system modeled on a similar one used in *Bacillus subtilis*. CRISPRi consists of a catalytically inactivate nuclease (dCas9) that is targeted to gene(s) of choice by a single guide RNA (sgRNA), where it binds tightly thereby blocking transcription. Adaption of this gene-silencing tool to *C. difficile* required the construction of a shuttle plasmid with constitutively expressed sgRNA and inducible *dCas9*. To achieve robust induction of *dCas9*, we used a xylose-inducible promoter together with the gene for the xylose repressor, *xylR*, from *C. difficile*. Control experiments using an *rfp* reporter verified that P_{xyl} is tight and tunable in *C. difficile*. Next, we built a *C. difficile* strain that expresses *rfp* from the chromosome in single copy. This enabled an easy quantitative readout to evaluate our initial, exploratory CRISPRi plasmids. Finally, we constructed CRISPRi plasmids that expressed *dCas9* under control of P_{xyl} and sgRNA under control of two constitutive promoters (P_{veg} and P_{gdh}). The sgRNA was designed to target *rfp*, and gene silencing was quantitated by measuring red fluorescence with and without induction of *dCas9*. We achieved about 90-95% repression of red fluorescence. CRISPRi allows us to deplete cells of a protein in question and study the effects on the cell (e.g., cell division, cell wall synthesis, DNA replication). Thus, CRISPRi can be used to tackle a variety of important problems such as the role of essential genes or to study synthetic phenotypes.

Poster 35

BIOCHEMICAL STUDIES OF A CELL WALL BINDING DOMAIN INVOLVED IN BACTERIAL CELL DIVISION

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[1]Department of Microbiology and Immunology, College of Medicine, The University of Iowa, Iowa City, IA
[2]NMR Core Facility, College of Medicine, The University of Iowa, Iowa City, IA

Bacterial SPOR domains are thought to target proteins to the cell division site by binding to "denuded" glycan strands that lack stem peptides. Here we show that fusions of the green fluorescent protein (GFP) to SPOR domains from the *Escherichia coli* cell division proteins DamX, DedD, FtsN and RlpA all localize to septal regions of purified PG sacculi obtained from E. coli and Bacillus subtilis. Treatment of sacculi with an amidase that removes stem peptides enhanced SPOR domain binding, while treatment with a lytic transglycosylase that removes denuded glycans reduced SPOR domain binding. HSQC NMR of ^{15}N-labeled DamX SPOR domain in the presence and absence of soluble PG oligosaccharides suggests the PG binding site is a groove on one face of the domain. Collectively, these findings demonstrate unequivocally that SPOR domains bind denuded glycans in septal PG and reveal we are on our way towards solving a structure that will reveal molecular details of the SPOR:PG interaction.

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1991-92	12	8
1992-93	12	6
1993-94	12	6
1994-95	13	10
1995-96	13	6
1996-97	12	6
1997-98	12	6
1998-99	12	6
1999-00	13	7
2000-01	14	7
2001-02	12	7
2002-03	11	8
2003-04	14	8
2004-05	12	7
2005-06	11	7
2006-07	10	7
2007-08	10	7
2008-09	10	8
2009-10	6	8
2010-11	7	8
2011-12	6	8
2012-13	5	6
2013-14	4	5
2014-15	4	6
2015-16	5	6
2016-17	6	0
2017-18	3	6
2018-19	6	6
TOTAL	277	190 *Partially Sponsored by CBB

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Winter Term Course Offering

CBB Offers a Course in Upstream Biotechnology Processing

The biotechnology industry is rapidly growing in the U.S. and beyond and represents a major manufacturing arm for the production of novel products, including industrial enzymes, food supplements, biotherapeutics, and renewal fuels. Bioprocessing describes the production of materials through fermentation with subsequent purification. Fermentation processes are generally referred to as upstream processing (USP) while purification is considered as downstream processing (DSP).

This new course entitled Upstream Biotechnology Processes is designed to provide students with hands-on experience in basic upstream fermentation processes applicable to the biotechnology industry. Basic concepts and general designs of upstream fermentations will be covered through a series of lectures. The bulk of the course, however, will be spent in the laboratory where students will have an opportunity to perform a fermentation on a 5-liter scale. All the fundamental steps used within the fermentation industry will be experienced, including selection of clones, growth of microorganism, monitoring purity of the culture, and bioassay to document product yield.

The course will be organized as 20% lectures and 80% laboratory experience. This format is designed to broaden student knowledge and understanding of upstream biotechnology processes while emphasizing practical laboratory experience.

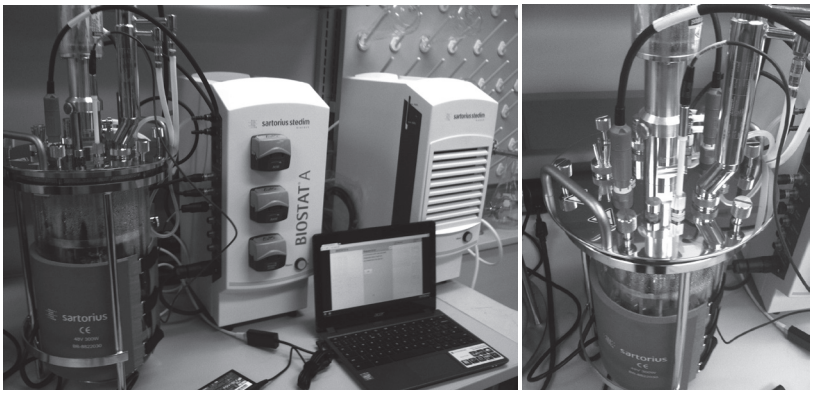

Figure: Sartorius Biostat A MO UniVessel 5-L Fermenters. These fermenters are dedicated for Upstream Biotechnology Processes course.

Course Details

Course Title: Upstream Biotechnology Processes

Course number: CHEM:4850:0001

Semester hours: 2

Instructors: Shuvendu Das (Primary Instructor), Sridhar Gopishetty, and Mark Arnold

Dates: 12/26/2018 – 1/11/2019

Meeting: WThF, 9:00-11:50 AM

Location: A164A, MTF (Lecture) and B145 MTF (Lab), Oakdale Campus

Course prerequisites: None

Target student: Students majoring in chemistry, biochemistry, chemical and biochemical engineering, biology, microbiology, and pharmaceutical science with interests in biotechnology

Topics covered: Hands-on experience with basic cloning, shake-flask growth, and microbial fermentation emphasizing reactor preparation, inoculation methods, reactor operation and control, product collection, and bioassay

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