The University of Iowa

28th

Center for Biocatalysis and Bioprocessing Conference

Expanding the Frontiers in Biocatalytic Science

http://cbb.research.uiowa.edu

The University of Iowa

October 22, 2019
Iowa Memorial Union
Iowa City, Iowa

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

THE UNIVERSITY OF IOWA

28th Annual Biocatalysis and Bioprocessing Conference

"Expanding the Frontiers in Biocatalytic Science"

Sponsored by:

THE UNIVERSITY OF IOWA

Center for Biocatalysis and Bioprocessing

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"EXPANDING THE FRONTIERS IN BIOCATALYTIC SCIENCE"

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October 22, 2019

Conference Organizing Committee:

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

Director
Mark Arnold, Ph.D.

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Message from the Director

Welcome to the 28th annual gathering of the students, faculty and guests of the Center for Biocatalysis and Bioprocessing at the University of Iowa. It is my pleasure to welcome you to an exciting combination of oral presentations and posters highlighting research that is *Expanding the Frontiers of Biocatalytic Sciences*.

I am also pleased to welcome Professor Marty Scholtz who is the newly appointed Vice President for Research at the University of Iowa. Vice President Scholtz recently visited the Center's facilities on the University of Iowa Research Park and learned how our expertise in fermentation, downstream processing, and system scale-up is being used to manufacture state-of-the-art protein-based products for a wide variety of clients. Vice President Scholtz has generously agreed to open the conference this year.

Our 2019 program was organized with an eye toward demonstrating how research programs that fit under the umbrella of Biocatalytic Sciences are advancing science and technology to better humankind. The morning session begins with a presentation from Professor **James Ankrum** (Biomedical Engineering at the University of Iowa). Professor Ankrum will discuss the potential of cell-based therapies and how the way these programmed cells are treated during scaleup and manufacturing can dramatically impact function and efficacy. Dr. **Laura Sawyer** will then present efforts at Synthorx to develop cancer therapies based on an expanded genetic alphabet strain of *E. coli*. Synthorx is using their proprietary genetic alphabet to direct chemical modifications at specific protein sites, thereby modifying function. Dr. Sawver is the Chief Executive Officer and Director at Synthorx and currently serves on the CBB's External Advisory Board. She is also an alumnus from the Departments of Pharmacology and Microbiology at the University of Iowa.

Professor **Jennifer Fiegel** (appointments in the Colleges of Engineering and Pharmacy at the University of Iowa) will lead off the second morning session by discussing her research to understand the properties and potential of protein coronas surrounding nano-particles. Interestingly, the identity of the protein used to form these coronas strongly impacts particle uptake within cells. The morning session ends with a presentation from Professor **Kevin Walker** from the Departments of Chemistry, Biochemistry, and Molecular Biology at Michigan State University. Professor Walker's expertise includes the creative use of enzymes to synthesize natural product targets in a search for the next generation of pharmaceutical agents.

The Conference poster session and luncheon will feature 37 posters presented by an array of researchers representing many departments across campus. In the spirit of collaboration, all participants are encouraged to ask questions and offer suggestions. The posters will be surrounded by vendors offering the latest product information.

The afternoon session begins with a forward-looking presentation from Professor **Brent Shanks**, who is Director of the Center for Biorenewable Chemicals at Iowa State University. Professor Shanks will describe his vision for driving the bioeconomy through strategic methods to create high-value biobased chemicals from the sources of biomass commonly generated in Iowa and other midwestern states. The Conference concludes with a series of student presentations that highlight exceptional research accomplishments from students supported by either NIH or CBB fellowships. This year's fellow-presenters are **Partik Rajesh Chheda** (Kern's group), **Danielle Webb** (LeFevre's group) and **Nathan Delyaux** (Rice's group).

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, establish new collaborations, and widen your professional network.

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

28th Annual Center for Biocatalysis and Bioprocessing Conference
"Expanding the Frontiers in Biocatalytic Sciences"
The University of Iowa, Iowa Memorial Union, Iowa City, IA

MONDAY, OCTOBER 21, 2019

BALLROOM (2ND FLOOR, IMU)

3:00-4:00 PM **Mark A. Arnold, Ph.D.,** Director, Center for Biocatalysis and Bioprocessing, Office of the Vice President for Research, University of Iowa Research Park, University of Iowa, Coralville, IA; Edwin B. Green Chair Professor in Laser Chemistry, Department of Chemistry, College of Liberal Arts and Sciences, University of Iowa, Iowa City, IA

"Career Planning for the Bio Economy-Presentation and Discussion"
(Undergraduate and graduate students are welcomed)

3:00-5:00 PM Poster set up (see hand-out for your #)

TUESDAY, OCTOBER 22, 2019

IOWA THEATER (LOWER LEVEL, IMU)

7:30 – 8:15 AM Registration – Hubbard Commons (outside Iowa Theater, Lower Level, IMU)

7:30 – 8:15 Continental Breakfast – Hubbard Commons across from Iowa Theater, Lower level, IMU

8:15– 8:30 **Program** – Iowa Theater, Lower Level, IMU
Introduction and Welcome

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

Marty Scholtz, Ph.D. Vice President for Research, Office for the Vice President for Research, University of Iowa, Iowa City, IA

8:30– 9:15 **James A. Ankrum, Ph.D.**, Assistant Professor, Department of Biomedical Engineering, College of Engineering, University of Iowa, Iowa City, IA
"*The role of biomanufacturing decisions on the therapeutic function of Mesenchymal Stromal Cells (MSC)"*

9:15– 10:00 **Laura Shawver, Ph.D.**, President and CEO, Synthorx, Inc., La Jolla, CA
"THOR-707 – An Engineered "Not Alpha" Interleukin 2 using an Expanded Genetic Alphabet"

10:00– 10:15 Break – Hubbard Commons (outside Iowa Theater, Lower Level, IMU)

10:15– 11:00	**Jennifer Fiegel, Ph.D.**, Associate Professor, Department of Chemical and Biochemical Engineering, College of Engineering, University of Iowa. Iowa City, IA ***"Protein Coronas Formed in BALF and Serum Differentially Impact Nanoparticle Stability and Cell Uptake"***
11:00– 11:45	**Kevin D. Walker, Ph.D.,** Associate Professor, Department of Chemistry and Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI ***"Biocatalysis of Paclitaxel Analogs and Hydroxy Amino Acids"***
11:45– 12:00	Relocation to 2ND Floor, Ballroom, IMU
12:00– 12:45 PM	Lunch – Poster Session 1-2ND Floor, Ballroom, IMU S3 Product Show
12:45– 1:30	Lunch – Poster Session 2-2ND Floor, Ballroom, IMU S3 Product Show
1:30– 1:45	Relocation to Iowa Theater, Lower Level, IMU
Afternoon Session	Iowa Theater, Lower Level, IMU
1:45– 2:30 PM	**Brent H. Shanks, Ph.D.,** Mike and Jean Steffenson Chair, Anson Marston Distinguished Professor, Department of Chemical and Biological Engineering, Iowa State University, Ames, IA ***"Developing Novel Chemicals through Biopriviled Molecules"***
2:30:3:30 PM	Student Presentations
	Pratik Rajesh Chheda, Ph.D. candidate, Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, University of Iowa, Iowa City, IA ***"Allosteric inhibitors of apicoplast DNA polymerase: New antimalarials that bind a novel allosteric pocket"***
	Danielle T. Webb, Ph.D. candidate, Department of Civil and Environmental Engineering, Environmental Engineering and Sciences, College of Engineering, University of Iowa, Iowa City, IA ***"Sorption of Neonicotinoid Insecticides and their Metabolites to Granular Activated Carbon during Drinking Water Treatment: Implications for Human Exposure, Treatment, and Biofilm Transformations"***
	Nathan Delvaux, Ph.D. candidate, Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, University of Iowa, Iowa City, IA ***"Overcoming the Cell Membrane Barrier in Non-Viral Gene Delivery with Modular Pore-Forming Peptide Conjugates"***
3:30	Closing Remarks
3:45	**Adjourn**
Approx. 3:45	Tour of CBB Fermentation Facility (Immediately following end of conference)

List of Oral Presentations

ORAL PRESENTATIONS

1. **THE ROLE OF BIOMANUFACTURING DECISIONS ON THE THERAPEUTIC FUNCTION OF MESENCHYMAL STROMAL CELLS (MSC)**
   James A. Ankum, Ph.D.
   Assistant Professor, Department of Biomedical Engineering, College of Engineering, University of Iowa, Iowa City, IA

2. **THOR-707 – AN ENGINEERED "NOT ALPHA" INTERLEUKIN 2 USING AN EXPANDED GENETIC ALPHABET**
   Laura Shawver Ph.D.
   President and CEO, Synthorx, Inc., La Jolla, CA

3. **PROTEIN CORONAS FORMED IN BALF AND SERUM DIFFERENTIALLY IMPACT NANOPARTICLE STABILITY AND CELL UPTAKE**
   Jennifer Fiegel, Ph.D.
   Associate Professor, Department of Chemical and Biochemical Engineering, College of Engineering, University of Iowa, Iowa City, IA

4. **BIOCATALYSIS OF PACLITAXEL ANALOGS AND HYDROXY AMINO ACIDS**
   Kevin D. Walker, Ph.D.
   Associate Professor, Department of Chemistry, Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI

5. **DEVELOPING NOVEL CHEMICALS THROUGH BIOPRIVILEGED MOLECULES**
   Brent H. Shanks, Ph.D.
   Mike and Jean Steffenson Chair, Anson Marston Distinguished Professor, Department of Chemical and Biological Engineering, Iowa State University, Ames, IA

6. **ALLOSTERIC INHIBITORS OF APICOPLAST DNA POLYMERASE: NEW ANTIMALARIALS THAT BIND A NOVEL ALLOSTERIC POCKET**
   Pratik Rajesh Chheda, Ph.D. candidate
   Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, University of Iowa, Iowa City, IA

7. **SORPTION OF NEONICOTINOID INSECTICIDES AND THEIR METABOLITES TO GRANULAR ACTIVATED CARBON DURING DRINKING WATER TREATMENT: IMPLICATIONS FOR HUMAN EXPOSRURE, TREATMENT, AND BIOFILM TRANSFORMATIONS**
   Danielle T. Webb, Ph.D. candidate
   Department of Civil and Environmental Engineering, Environmental Engineering and Sciences, College of Engineering, University of Iowa, Iowa City, IA

8. **OVERCOMING THE CELL MEMBRANE BARRIER IN NON-VIRAL GENE DELIVERY WITH MODULAR PORE-FORMING PEPTIDE CONJUGATES**
   Nathan A. Delvaux, Ph.D. candidate
   Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, University of Iowa, Iowa City, IA

Speakers' Profiles

James A. Ankrum, Ph.D.
Assistant Professor
Department of Biomedical Engineering
College of Engineering
University of Iowa
Iowa City, IA

Dr. James Ankrum is an Assistant Professor of Biomedical Engineering at the University of Iowa. An Iowa native and first generation college student, Dr. Ankrum studied biomedical engineering as an undergraduate at the University of Iowa. He then went on to earn his Masters at Cambridge University as the first University of Iowa alum to receive a Winston Churchill Scholarship. He earned his PhD in Medical Engineering and Medical Physics through Harvard-MIT's Health Science and Technology Program where he studied under the guidance of Prof. Jeff Karp. After his PhD., Dr. Ankrum spent a year at the University of Minnesota as a Senior Innovation Fellow in the Medical Device Center where he developed tissue engineered strategies for preventing heart failure in collaboration with Boston Scientific. In 2014, he was recruited to the University of Iowa to join the Pappajohn Biomedical Institute and Fraternal Order of Eagles Diabetes Research Center. Dr. Ankrum's curiosity and collaborative nature has enabled him to work on a diverse set of projects ranging from cell therapy, to human organoid models, to medical devices. His lab is primarily interested in engineering mesenchymal stromal cell-based therapies and developing bioengineering strategies to overcome challenges in delivery and control of cell phenotype after transplantation. Using a combination of biologics, chemistry, and biomaterials his lab seeks to create tools that enable cell phenotype to be controlled even after transplantation into harsh disease environments.

Laura Shawver, Ph.D.
President and CEO
Synthorx, Inc.
La Jolla, CA

Laura Shawver, Ph.D., is president, chief executive officer, and director of Synthorx. Prior to joining Synthorx, Dr. Shawver held the following positions: CEO and director of Cleave Biosciences, entrepreneur-in-residence for 5AM Ventures, CEO and director of Phenomix Corporation, and president of SUGEN Inc. (acquired by Pharmacia). Dr. Shawver has been involved with a number of clinical development programs including two FDA-approved therapies. Dr. Shawver is currently a director of Relay Therapeutics as well as an advisor to the industry. She is an active member of the American Association for Cancer Research serving on the Scientific Advisory Committee for Stand Up to Cancer. Dr. Shawver knows firsthand what it is like to be a cancer patient. Having survived ovarian cancer, she turned that experience into the founding of The Clearity Foundation, a nonprofit organization providing access to molecular profiling for ovarian cancer patients to improve their treatment options. Dr. Shawver received her Ph.D. in pharmacology and a B.S. degree in microbiology both from the University of Iowa

Jennifer Fiegel, Ph.D.
Associate Professor
Department of Chemical and Biochemical Engineering
College of Engineering
University of Iowa
Iowa City, IA

Dr. Fiegel received her B.S. in Chemical Engineering at the University of Massachusetts Amherst and her Ph.D. in Chemical and Biomolecular Engineering at Johns Hopkins University in 2004, where she was supported by an NSF Fellowship for Graduate Research. Prior to joining the faculty she completed a two-year postdoctoral fellowship at Harvard University in the area of Medical Aerosols. Dr. Fiegel is currently an Associate Professor of Chemical and Biochemical Engineering in the College of Engineering, with a secondary appointment in the College of Pharmacy. At the University of Iowa, Dr. Fiegel has developed a multidisciplinary research program focused on designing therapeutic drug delivery systems for the treatment and prevention of infections of the lungs and skin, and the development of tools to evaluate particle interactions in biological environments. Her work in aerosol biointeractions is applied to both environmental aerosols and inhalable drug delivery systems.

Kevin D. Walker, Ph.D.
Associate Professor
Department of Chemistry
Department of Biochemistry and Molecular Biology
Michigan State University
East Lansing, MI

Kevin D. Walker was born and raised in Seattle, Washington. After receiving a B.S. major in Chemistry in 1987 at the University of Washington, he worked for two years in a joint appointment at the Food & Drug Administration's Seafood Products Research Center in Bothell, WA and at the National Marine Fisheries Service in Seattle, WA. After his government service, he continued his academic studies in a doctoral with support from Graduate Student Fellowships from the NIH and NSF at the University of Washington. His doctoral work was with Heinz G. Floss on natural products biosynthesis and mechanistic analysis of enzymes from bacteria and plants.

After receiving his Ph.D. degree, Kevin worked with Rodney Croteau as a postdoctoral fellow and as an Assistant Scientist at the Institute of Biological Chemistry (IBC) at Washington State University (Pullman, WA) from 1997 to 2003. At the IBC, he discovered several genes on the biosynthetic pathway of the anticancer drug paclitaxel in *Taxus* plant cell cultures.
In July 2004, Kevin joined the Department of Chemistry at Michigan State University (MSU), East Lansing, MI, where he works as an Associate Professor of Chemistry and Biochemistry & Molecular Biology.

At MSU Kevin has received recognition for his research and outreach: the Neish Young Investigator Award (2006), a National Science Foundation CAREER Award (2007–2013), and the MSU Diversity Research Network Launch Award (2018). His service includes Organizer/Chair of session for the Ron Breslow Award: Biomimetic Chemistry (Eric Kool Awardee) ACS National Meeting, Denver, CO (2015); Organizer/Chair/Fundraiser of Midwest Enzyme Chemistry Conference, Loyola University, Chicago, IL (2017); and Co-Chair at the 2014 ASBMB National Conference, San Diego, CA. Prof. Walker was an elected Member-at-Large of the American Chemical Society (ACS) Division of Organic Chemistry (DOC) (2017 – 2019), and currently He currently serves on the Editorial Board for the Journal of Biological Chemistry.

Kevin's research interests span a wide area of biochemistry, organic chemistry, and analytical chemistry (https://www2.chemistry.msu.edu/faculty/walker/index.html). A primary research focus studies the biocatalytic assembly of new generation anticancer paclitaxel compounds that are effective against drug resistant cancer cells. Another research interest centers on repurposing an aminomutase enzyme to make value-added hydroxy amino acids using a variety of analytical techniques to define the stereochemistry. A current project includes expanding the application of a CoA ligase to make various nonnatural isoserinyl CoA thioesters for use in enzyme cascade reactions to new generation paclitaxels. Kevin has published numerous papers, a book chapter, and patents highlighting his research, and has presented these works at several invited lectures. Kevin enjoys free time with his partner (a theoretical nuclear physicist) and her daughter; they all enjoy swimming, biking, pickleball, traveling, while Kevin enjoys chess, woodworking in his shop, home improvement projects, and automotive interests.

Brent H. Shanks, Ph.D.
Mike and Jean Steffenson Chair
Anson Marston Distinguished Professor in Engineering
Department of Chemical and Biological Engineering
Iowa State University
Ames, IA

Brent Shanks is an Anson Marston Distinguished Professor in Engineering and the Mike and Jean Steffenson Faculty Chair in Chemical and Biological Engineering at Iowa State University. He established and serves as Director of the Center for Biorenewable Chemicals (CBiRC), formerly a NSF Engineering Research Center. After receiving his B.S. degree from Iowa State University in 1983, he completed his Ph.D. degree at the California Institute of Technology in 1988. From 1988 to 1999 he worked as a Research Engineer and Department Manager in the Catalyst Department at the Shell Chemical Company technology center in Houston, Texas. He joined the faculty at Iowa State University in 1999 where his group's research has primarily involved novel heterogeneous catalyst systems for efficiently converting biological-based feedstocks to chemicals.

Pratik Rajesh Chheda
Ph.D. Candidate
Robert J. Kerns Research Group
Department of Pharmaceutical Sciences and Experimental Therapeutics
Division of Medicinal and Natural Products Chemistry
College of Pharmacy
University of Iowa
Iowa City, IA

Pharmacy in 2013 and then completed his Masters in Medicinal Chemistry from National Institute for Pharmaceutical Education and Research, India in 2015. After graduation, he came to The University of Iowa to obtain his Ph.D. in Medicinal and Natural Products Chemistry from the College of Pharmacy. Pratik joined the laboratory of Robert Kerns and has focused on identification of bioactive compounds using virtual screening along with the design and synthesis of novel organic compounds that exhibit high affinity for target enzymes. He has been working on different classes of compounds that are being developed as potential therapeutics for the management of Helicobacter pylori and Plasmodium falciparum infections as well as probes/leads to better modulate the biological processes leading mitochondrial dysfunction, type-2 Diabetes and obesity.

Danielle Webb
Ph.D. Candidate
Gregory H. LeFevre Research Group
Department of Civil and Environmental Engineering
Environmental Engineering and Sciences
College of Engineering
The University of Iowa
Iowa City, IA

Originally from Minnesota, Danielle obtained her Bachelor of Science in Biochemistry in 2016 from the University of St. Thomas (St. Paul, MN). As an undergraduate student, she conducted research in the St. Thomas Department of Chemistry working in an environmental chemistry lab. She came to the University of Iowa to work with Dr. Gregory LeFevre in the Department of Civil and Environmental Engineering where she explores the fate of neonicotinoid insecticides in drinking water. Her current work delves into understanding how neonicotinoid insecticides can be removed from drinking water by black carbon and how they can be degraded on the carbon by microorganisms. Following graduate school, she plans on a career as an environmental analytical chemist (focusing on chromatography and mass spectrometry).

Nathan Delvaux
Ph.D. Candidate
Kevin G. Rice Research Group
Department of Pharmaceutical Sciences and Experimental Therapeutics
Division of Medicinal and Natural Products Chemistry
College of Pharmacy
University of Iowa
Iowa City, IA

Nathan was born in Hilbert, Wisconsin, a small town south of Green Bay, and earned a Bachelor of Science degree in Biochemistry with Honors in Research from the University of Wisconsin – Madison in 2016. After graduation, he joined the University of Iowa to obtain his Ph.D. in Medicinal and Natural Products Chemistry from the College of Pharmacy. Nathan became a member of the Rice research group, studying peptide-based bioconjugate synthesis and in vitro transfection assays. He primarily has focused on synthesizing and testing melittin-based non-viral gene delivery systems in cell culture. Nathan plans to pursue a career in industry as an analytical chemistry or molecular biology research scientist.

Oral Presentation Abstracts

Presenter 1

THE ROLE OF BIOMANUFACTURING DECISIONS ON THE THERAPEUTIC FUNCTION OF MESENCHYMAL STROMAL CELLS (MSC)

James A. Ankum, Ph.D.
Assistant Professor, Department of Biomedical Engineering, College of Engineering, University Iowa, Iowa City, IA

Mesenchymal stromal cells (MSCs) are being explored as a cell based therapy for the treatment of devastating immune conditions that are refractory to standard of care anti-inflammatory therapies. With both academic health centers and commercial entities launching clinical studies of the utility of MSCs to treat graft versus host disease, Crohn's disease, and other chronic inflammatory conditions, the diversity of MSC products has grown substantially. However, while MSCs share common base characteristics, as a living therapeutic, they are responsive to stresses and cues within their local environment. Thus, while MSCs from different companies or labs may at first look similar, at the functional level, their phenotypes could be highly divergent. Decisions in the biomanufacturing process from selection of donors, outgrowth strategy, and cryopreservation technique all contribute the ultimate therapeutic utility of MSC therapies and need to be actively chosen to tailor the product to the clinical indication. In this talk we will examine the influence of individual bioprocessing decisions have on the immunomodulatory potential and resiliency of the resultant MSC product.

Presenter 2

THOR-707 – AN ENGINEERED "NOT ALPHA" INTERLEUKIN 2 USING AN EXPANDED GENETIC ALPHABET

Laura Sawver, Ph.D.
President and CEO, Synthorx, Inc., La Jolla, CA

Aldesleukin is a recombinant form of IL-2 approved for metastatic melanoma and renal cell carcinoma that induced complete, durable remissions in certain patients. Yet, its use is infrequent because of vascular leak syndrome, a severe dose-limiting adverse event stemming from the engagement of the high affinity IL-2 receptor (IL-2R) alpha chain in type 2 innate lymphoid cells, eosinophils and vascular endothelial cells. THOR-707 is a site-directed, singly pegylated form of IL-2 completely lacking IL-2R alpha chain engagement yet retaining normal binding to the intermediate affinity IL-2R beta-gamma signaling complex expressed by natural killer (NK) and CD8+ T tumor-killing cells. Site-directed pegylation is enabled by utilizing the Synthorx Expanded Genetic Alphabet. A new DNA base pair (X-Y) creates new distinct codons that code for novel amino acids. The X-Y pair is fully functional for replication, transcription and translation in E. coli. The new amino acid placed in the THOR-707 polypeptide chain allows for covalent attachment of a PEG via click chemistry. THOR-707 is now in a Phase 1/2 dose escalation and expansion clinical trial.

Presenter 3

PROTEIN CORONAS FORMED IN BALF AND SERUM DIFFERENTIALLY IMPACT NANOPARTICLE STABILITY AND CELL UPTAKE

Jennifer Fiegel, Ph.D.
Associate Professor, Department of Chemical and Biochemical Engineering, College of Engineering, University of Iowa, Iowa City, IA

Foreign material entering the human body first interacts with the bodily fluids, where proteins and other biomolecules can readily adsorb to the materials' surface. This thin biomolecular shell, often called the protein corona, directly interacts with cells and tissues in the body and helps determine the materials' fate. Nonspecific protein adsorption to particles can cause particle aggregation, impair the ability of particles to cross biological barriers, and induce clearance as part of the foreign body response. The majority of protein corona studies have focused on interactions with blood proteins, which have good clinical relevance for injected therapeutics, but is not compositionally representative of all bodily fluids. Therefore, we have compared the impact of protein coronas formed in human serum and concentrated bronchoalveolar lavage fluid (BALF) on particle stability and cellular responses. Overall, studies conducted in serum are not strong predictors of particle interactions in BALF, as the responses in each fluid are distinct. We have further been developing zwitterionic polymer coatings as nonfouling coatings to inhibit protein adsorption. We have observed that polymer coatings help maintain nanoparticle stability in BALF or serum, likely due to strong hydration of the polymers and reduced protein adsorption. However, while pMPC-coated particles exposed to serum experienced 3-to-10 fold increase in particle uptake compared to bare particles, no differences were observed with particles exposed to BALF. This suggests that differences in protein composition or protein abundance between the two fluids results in a distinct protein corona that influences cell interactions.

Presenter 4

BIOCATALYSIS OF PACLITAXEL ANALOGS AND HYDROXY AMINO ACIDS

Kevin D. Walker, Ph.D.
Associate Professor, Department of Chemistry, Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI

This presentation will summarize the biocatalysis of paclitaxel analogs and the repurposed application of an aminomutase to make hydroxy amino acids from epoxides. Paclitaxel (Taxol®) is a widely used chemotherapeutic drug with additional medical applications in drug-eluting stents as an anti-restenosis treatment. Paclitaxel is a structurally complex natural product with an excellent scaffold for designing analogs with improved pharmacological properties. Plant cell fermentation methods produce paclitaxel and larger quantities of its precursors 10-deacetylbaccatin III (10-DAB) and baccatin III (Bac). The complexity of the purported ~19-step paclitaxel biosynthetic pathway limits bioengineering the complete pathway in a chassis organism. However, the abundance of 10-DAB and Bacc and access to enzymes working on the latter parts of the pathway make a semi-biocatalytic approach to paclitaxel analogs possible. We have designed a short biocatalytic cascade capable that highlight its potential broader application toward making paclitaxel or value-added analogs of pharmacological interest. The success of this biocatalytic cascade centers on various enzymes co-opted from *Taxus* cell cultures, a baccatin III 3-amino-13-*O*-phenylpropanoyl CoA transferase (BAPT) and *N*-debenzoyltaxol-*N*-benzoyltransferase (NDTNBT); and CoA ligases from *Bacillus*, a (2*R*,3*S*)-phenylisoserinyl CoA ligase (PheAT) and from *Rhodopseudomonas*, a benzoate CoA ligase (BadA) to produce paclitaxel analogs. Here we show by proof-of-principle the biocatalysis of a paclitaxel analog, *N*-2-furanyl-*N*-debenzoylpaclitaxel, via a shortened assembly pathway.

Over several decades, many accounts on methylidene imidazolone (MIO)-dependent biocatalysts described how these enzymes add ammonia (at high concentrations from ammonium salts) across arylacrylate double bonds to make α- and, more recently, β-arylalanines. β-Amino acids are excellent building blocks of valuable bioactive compounds. These biocatalysis efforts have even drawn contributions from Nobel Laureate (Ben Feringa) to help dissect the dynamics of the catalysis among this family of enzymes. We diverge from this fixed program of aminating cinnamic acids and describe a first account of employing an MIO-aminomutase (*Tc*PAM) from *Taxus* plants to convert previously untested epoxy acid substrates to bifunctional hydroxy amino acids. Arylserines were made more abundantly over the arylisoserines when styrylalanine was used instead of ammonium salts, to selectively transaminate the MIO group of *Tc*PAM. This mild amine group delivery to the oxirane avoided nonenzymatic ring-opening of the epoxides.

Presenter 5

DEVELOPING NOVEL CHEMICALS THROUGH BIOPRIVILEGED MOLECULES

Brent H. Shanks, Ph.D.
Mike and Jean Steffenson Chair, Anson Marston Distinguished Professor, Department of Chemical and Biological Engineering, Iowa State University, Ames, IA

Much of the effort in converting biomass to biobased chemicals has been driven by the opportunistic synthesis/isolation of a specific molecule or the retrosynthesis of target molecules. While these are reasonable approaches for a technology area in its infancy, the realization of viable biobased chemical development will require more systematic strategies that are robust in the face of realistic constraints. Importantly, these postulated strategies will dictate the research questions that will need to be addressed. Presented will be a new strategy of synthesizing "bioprivileged molecules," which are biology-derived chemical species that can be readily converted to a diversity of chemical products including drop-in replacements and novel species while be discussed. The dual potential for bioprivileged molecule can help create value from biomass since innovative bioproducts represents a powerful driver for the development of biobased chemicals beyond just replacing fossil carbon with renewable carbon. Ongoing efforts involving combining synthetic routes with a computational framework will be discussed and several examples presented.

Presenter 6

ALLOSTERIC INHIBITORS OF APICOPLAST DNA POLYMERASE: NEW ANTIMALARIALS THAT BIND A NOVEL ALLOSTERIC POCKET

Pratik Rajesh Chheda and Robert J. Kerns*
Department of Pharmaceutical Sciences and Experimental Therapeutics, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, University of Iowa, Iowa City, IA

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. Our 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 our current design, synthesis, crystallographic, and *in vitro* evaluation efforts toward understanding the structural requirements of MMV666123 for inhibition of apPOL, identifying the binding site and designing more potent and drug-like apPOL inhibitor derivatives.

Presenter 7

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

Danielle T. Webb and Gregory H. LeFevre*
Department of Civil and Environmental Engineering, Environmental Engineering and Science, College of Engineering, University of Iowa, Iowa City, IA

Neonicotinoid pesticides are the most widely used insecticides in the world. The widespread application of neonicotinoids has led to their proliferation in waters across the U.S., including those used as drinking water sources. Although neonicotinoids exhibit relatively low toxicity towards mammals, formation of toxic metabolites is an exposure concern. Our prior studies identified granular activated carbon (GAC) as a method for neonicotinoid removal from drinking water. The objective of the present study is to determine if imidacloprid and its mammalian toxic metabolite, desnitro-imidacloprid, adsorbed to black carbon can be mineralized into less toxic products by coupling the sorptive and redox capabilities of black carbon with biofilm metabolism. Desorption tests conducted using five-year-old used GAC from the Iowa City DWTP to determine the likelihood of residual neonicotinoid desorption and provide further evidence that neonicotioids are removed from drinking water by the GAC filter. Imidacloprid adsorbs to GAC and desorbs in solvents of intermediate polarity (despite high polarity / solubility), but desnitro imidacloprid was not desorbed in any condition, indicating that this metabolite is not adsorbed to GAC or may be degraded following initial sorption. To probe possible imidacloprid and desnitro imidacloprid degradation on black carbon associated with biofilms, we are conducting experiments with biofilm coated corn biochar. Soil microorganisms were extracted grown on corn biochar until a biofilm was formed. Batch experiments show that imidacloprid is rapidly adsorbed to the spent IC DWTP GAC. Microorganisms desorbed from the spent GAC surface can degrade imidacloprid, forming the mammalian toxic desnitro imidacloprid metabolite, indicating the adsorbed neonicotinoid may be degraded on the black carbon surface. Similarly, imidacloprid is removed from solution in the presence of the bioaugmented corn biochar, though to a lesser extent than the GAC. Nevertheless, the bioaugmented biochar showed more rapid imidacloprid degradation and toxic metabolite formation than the GAC system. These results show that environmentally relevant microorganisms associated with black carbon are capable of degrading neonicotinoids into mammalian toxic metabolites. Sacrificial batch experiments are underway to determine the rates and possible mechanisms behind these biotransformation reactions. Further experiments will also elucidate whether the mammalian toxic metabolite is a dead-end product or if the metabolite can be further transformed by the bioaugmented black carbons. If these insect and mammalian toxic compounds can be further degraded, bioaugmented black carbon may be a promising method to remove water in natural and engineered systems.

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OVERCOMING THE CELL MEMBRANE BARRIER IN NON-VIRAL GENE DELIVERY WITH MODULAR PORE-FORMING PEPTIDE CONJUGATES

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Although significant advancements in the field of non-viral gene therapy have been made towards the design of polymers that can effectively stabilize DNA in biological systems, bypassing the cell membrane remains a challenge for many vectors. Active targeting of DNA nanoparticles with ligands directed towards specific endocytic cell surface receptors can be an effective approach to this obstacle; however, receptor-mediated uptake faces its own set of problems. Receptor endocytosis is saturable, limiting the maximal rate of migration across the cell membrane, as well as generally dependent on nanoparticle size and surface charge, potentially requiring optimization of the nanoparticle for each receptor. As non-specific cell entry alternatives, cell-penetrating peptides have found use in non-viral gene delivery. Melittin is a peptide derived from bee venom that forms pores in lipid bilayers. Several melittin analogues have been designed with increased pore-forming potency and decreased overall charge, facilitating control over nanoparticle surface charge. To capitalize on the pore-forming characteristics of these analogues, we conjugated them to a polyacridine DNA binding peptide with a variety of bioconjugate linkers to form DNA nanoparticles with inherent cell-penetrating properties. These conjugates were tested in vitro for the ability to transfect HepG2 and primary mouse hepatocytes using luciferase expression as a readout. Direct conjugation of the melittin analogues to the polyacridine peptide resulted in luciferase expression almost equivalent to polyethylenimine, the gold standard for in vitro gene transfection. Thus, these pore-forming peptides can be used to facilitate cell entry and transfection, and further work is being conducted on translating the systems to in vivo models.

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Poster Abstracts

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CALCIUM CONCENTRATION EFFECTS IN NON-VIRAL TRANSFECTION OF BONE MARROW-DERIVED STEM CELLS

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Purpose
Bone tissue engineering is rapidly evolving as the technology to construct more complicated scaffolds develops. When designing a system for bone tissue engineering, the mineral concentration, cytokine presence, and pH level of the implantation site must be considered. Calcium (Ca^{2+}) is a key element to consider because it influences natural bone healing, and calcium is ubiquitously used in bone tissue engineer in scaffolds and cements. These materials can also incorporate gene delivery systems to further promote osteoblast differentiation. Thus, our goal was to identify how Ca^{2+} affects the transfection of bone marrow stromal cells, since these cells play a major role in bone healing and can infiltrate calcium-based scaffolds upon implantation.

Methods
Bone marrow-derived mesenchymal stem cells (BMSCs) and human embryonic kidney cells (HEK293T) were cultured, separately, in media containing Ca^{2+} concentrations ranging from 0 mM to 20 mM. To test gene transfection, plasmid DNA (pDNA) was complexed with polyethyleneimine (PEI) to form PEI-pDNA complexes and the complexes were incubated with the cells for four hours. Cell viability was determined 24 hours after transfection using MTS assays and transfection efficiency was quantified after 48 hours using flow cytometry. To examine the effects of Ca^{2+} concentrations on PEI-pDNA aggregation, the size PEI-pDNA complexes incubated in various Ca^{2+} concentrations was examined using a Zetasizer. Localization of the PEI-pDNA complexes with varying calcium concentrations was performed by labeling the PEI and pDNA with tetramethylrhodamine and YOYO-1, respectively; the labeled complexes were used to transfect BMSCs and at 1, 2 and 4 hours post incubation the complex localization was visualized with confocal microscopy. BMSC differentiation was determined by relative qPCR quantification of osteocalcin and CBFA1. Calcium deposition was qualitatively assessed after 3 and 14days using Alizarin Red staining.

Results
Our results indicate that Ca^{2+} levels between 8 - 12 mM positively impacted transfection of BMSCs with PEI-pDNA complexes in terms of cell viability and transfection efficiency. Cell viability of BMSCs when transfected increased to 87±8% form 11±1% when the cells were media containing 10 mM of Ca^{2+} compared to cells incubated in regular media. Transfection efficiency also increased to 7.5±3.6% from 1.8±0.3% when cells were transfected in the presence of 10 mM Ca^{2+}. A Ca^{2+} concentration of 10 mM also increased the expression of an osteogenic gene, osteocalcin, when the cells were transfected with pDNA encoding BMP-2.

Conclusion
Ca^{2+} at a 10 mM concentration can significantly reduce toxicity and enhance transfection efficiency when combined with PEI-pDNA complexes, and this combination can be specifically applied to further enhance the differentiation of BMSCs by using the combination of PEI-pBMP-2 and 10 mM Ca^{2+} as compared to PEI-pBMP-2 alone.

Poster 2

ISOLATION OF BIPHENYL-DEGRADING STENOTROPHOMONAS SP. FROM A PCB-CONTAMINATED WASTEWATER LAGOON USING iCHIP

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Polychlorinated biphenyls (PCBs) have been recorded in all realms of the Earth's biosphere including air, water, and even within living organisms. PCBs pose a direct threat to human and ecological health because of their toxic and recalcitrant nature. One approach to minimizing human exposure to PCBs is to remediate them in sediment using a process called bioremediation. Bioremediation utilizes the natural metabolism of microorganisms. PCBs can be dechlorinated and mineralized through bioremediation. It has been shown that a bioaugmentation strain (or consortia) often cannot survive the target environment into which it has been introduced due to both biotic and abiotic obstacles. To overcome these obstacles, a potential PCB-degrading bioaugmentation strain (*Stenotrophomonas sp.*) has been isolated from sediment gathered from a PCB-contaminated lagoon in Altavista, VA using isolation chip (iChip) technology, ensuring that the microorganism is genetically and metabolically adapted to thrive there. To isolate and culture PCB-degrading microorganisms that are native to the Altavista lagoon sediment, a "simulated lagoon" was established by filling a glass container with PCB-contaminated sediment and water gathered from the actual Altavista lagoon. A 96-well iChip was inserted into the simulated lagoon and left to incubate for 1 month. The contents of the iChip were transferred to liquid culture supplemented with biphenyl crystal as the sole carbon and energy source and let incubate until exponential bacterial growth was observed. The 16S rRNA gene of the most promising isolate iChip was sequenced using Sanger methods.

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

IDENTIFICATION OF RAD52 INHIBITORS USING A FRET BASED ANALYSIS

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Altered DNA repair mechanisms are responsible for the survival of neoplastic cells and the accumulation of double stranded breaks (DSBs), resulting in an increase in incidences of genomic instability like stalled replication forks and interstrand cross links (ICLs). DSBs are repaired by RAD51 and RAD52 mediated homologous recombination (HR), which relies on the BRCA pathway that includes BRCA1, BRCA2 and PALB2.
Studies have reported that RAD52 inhibitors have an anti- tumor potential as they induce cell death in BRCA deficient cells through the process of synthetic lethality.
Our project investigates the potential of using RAD52 effector compounds at inducing cell death in BRCA deficient cancer cell lines, using newly synthesized chemical compounds that share structural similarities with a known, naturally occurring RAD52 inhibitor, Epigallocatechin (EGC).

We will utilize FRET (Förster resonance energy transfer) based assays to evaluate the efficiency of these compounds at inhibiting RAD52 activity and compare them against EGC in order to obtain a novel RAD52 inhibitor that shows anti-tumorigenic potential.

Poster 5

REGULATION OF DNA REPAIR THROUGH RPA CONFORMATIONAL DYNAMICS

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Homologous recombination (HR) repairs deleterious forms of DNA damage such as interstrand DNA crosslinks, stalled replication forks and double strand breaks. An important player in the regulation of HR is the recombination mediator, Rad52 in yeast or BRCA2 in humans. Recombination mediators promote assembly of the active species in HR, the Rad51 nucleoprotein filament. They help to overcome the kinetic block presented by Replication Protein A (RPA) tightly bound to ssDNA. RPA acts as the first responder to exposed ssDNA. RPA not only acts to protect DNA, but it also acts as a regulator of DNA metabolic processes that proceed from RPA-coated ssDNA. Six flexible DNA-binding domains (DBDs) allow RPA to bind with high affinity, but also hand off ssDNA to lower affinity downstream repair proteins. Using single molecule total internal reflection fluorescence microscopy (smTIRFM) in combination with an environmentally sensitive fluorescent label, we were able to observe the microscopic associations and dissociations of individual DBDs of RPA. DBDs on the both termini of RPA exist in a range of conformational states with different degree of engagement to ssDNA. Addition of Rad52 restricts the dynamics of DBD-D, a DBD which interacts with the 3' end of the occluded ssDNA, resulting in a decreased contact with ssDNA. This suggests a mechanism by which the recombination mediator promotes displacement of individual RPA domains to promote filament formation by Rad51. The interaction of Rad52 with both RPA and ssDNA are critical for the effect on RPA DBD-D dynamics. In addition of regulation by protein partners, the RPA response is DNA repair may also be regulated by phosphorylation. Phosphorylation at S178 in RPA70 promotes the interaction between two adjacent RPA molecules. Bulk and single molecule studies of phosphomimetic RPA revealed that phosphorylation of DBD-A resulted in DBD-A having less contact with ssDNA, but cooperativity between RPA bound adjacently on ssDNA. The dynamic interaction between RPA and ssDNA is also present in the human DNA repair system.

Poster 6

A NEW SPIROBISNAPHTHALENE FROM A COPROPHILOUS *PREUSSIA* ISOLATE AND CLARIFICATION OF THE STRUCTURE OF A KNOWN SPIROBISNAPHTHALENE

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Fungi are versatile biocatalysts. One important capability that many fungi possess is the ability to produce unique secondary metabolites that display inhibitory bioactivities against other fungi, bacteria, and cancer cells, among other effects. Studies of such metabolites have led to many distinctive pharmaceuticals and drug leads, yet many fungi remain unexplored as potential producers of useful natural products. .

While studying coprophilous (dung-colonizing) fungi as sources of antifungal agents, strain TTI-0686 was obtained from rabbit dung collected in Colorado. Fermentation of this fungus led to production of a crude extract that showed activity against *Cryptococcus neoformans*, *Candida albicans*, and *Staphylococcus aureus*. Silica gel column chromatography, followed by reversed phase HPLC, afforded a known spirobisnaphthalene, along with a new analogue. Analysis of ^{1}H NMR and MS data led to literature reports describing two similar possible structures for the known metabolite, which were reported separately in the literature as spiro-mamakone A and spiropreussione A. Upon closer examination of the reports, it was noted that the two papers had used different NMR solvents. ^{1}H NMR data were obtained in both solvents for the isolated compound, and the results matched the data from both papers, indicating that the two literature reports had characterized the same compound. Further analysis by 2D NMR determined that the correct structure for this compound matches that originally reported for spiro-mamakone A. The structure of the new analogue was established by analysis of MS and 2D NMR data and by comparison with the data for spiro-mamakone A. Spiro-mamakone A showed activity against *C. neoformans* and *S. aureus*.

Poster 7

A NEW DECARESTRICTINE-DERIVED METABOLITE FROM A COPROPHILOUS ISOLATE OF *PENICILLIUM SACCULUM*

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Secondary metabolites are organic compounds that are produced by a wide variety of organisms from the building blocks of primary metabolism. They are not essential for growth, but may foster organism survival in various ways via involvement in antagonism, competition, communication, regulation, etc. Such compounds can have useful properties. Fungi are prominent producers of secondary metabolites that have value as herbicides, insecticides, antifungal agents, antibiotics, and other types of pharmaceuticals. The research presented here is focused on investigation of coprophilous fungi—a chemically underexplored group. These fungi colonize animal dung and often produce antimicrobial metabolites with effects on competing microorganisms. Given the need for new antimicrobial agents with novel modes of action, together with the track record of fungi as metabolite producers, we have targeted this group of organisms as potential sources of new antibacterial and antifungal agents.

Studies of an isolate of *Penicillium sacculum* (TTI-0705) obtained from mule deer dung from Colorado led to identification of a new decarestrictine-derived metabolite, along with the known compound decarestrictine B. Decarestrictines are 10-membered lactones that are produced by various fungi including other species of *Penicillium*. Some of them are known to have inhibitory effects on cholesterol biosynthesis. The new analog consisted of a decarestrictine subunit linked to an unusual tricyclic tetrahydrofuroindole moiety. The structure of the new metabolite was assigned mainly by analysis of 2D NMR and HRESIMS data. Details of relative configuration of the new compound were elucidated on the basis of NOESY data, ^{1}H NMR comparison with related decarestrictines, and molecular modeling. Although the original extract showed antifungal activity against the human pathogenic fungi *Candida albicans* and *Cryptococcus neoformans*, as well as the bacterium *Staphylococcus aureus*, the new compound described here did not show significant activity in these assays.

Poster 8

RESISTIVE PULSE SENSING FOR MONITORING DEGRADATION PROCESSES OF PLGA IN AQUEOUS MEDIA

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Many novel delivery systems are under development as a means to improve the effectiveness of therapeutic agents by targeted action, thereby maximizing drug efficacy while minimizing adverse side-effects. Poly(lactic-co-glycolic acid) (PLGA) is a copolymer that has been used extensively as a drug delivery agent PLGA particles are FDA approved for the delivery of selected drugs such as Paclitaxel for the treatment of human diseases. This presentation will center on our investigation of the degradation chemistry of PLGA particles in pH 7.4 phosphate buffered saline (PBS). In this work, particles were synthesized with a composition of 50:50 poly(D,L-lactide-co-glycolide) polymer. The size of the PLGA particles was monitored by analysis of samples collected during the degradation experiment. Resistive pulse sensing was used to measure particle sizes with the nCS1 Particle Sizer (Spectradyne, Inc.). Particle size obtained with the nCS1 was compared to those obtained in parallel by more conventional sizing methods of scanning electron microscopy and dynamic light scattering. In a preliminary experiment, the synthesized PLGA particles were suspended in pH 7.4 PBS at 4 °C. After 37 days, the particles experienced a 21% reduction in diameter going from 374 to 294 nm. This presentation will include a discussion of the resistive pulse detection method as well as a description of the degradation process for PLGA copolymer.

Poster 9

DEHALOCOCCOIDES SP. REDUCTIVE DEHALOGENASE FUNCTIONAL GENES AS POTENTIAL BIOMARKERS IN ANAEROBIC PCB-CONTAMINATED SEDIMENT MICROCOSMS

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Polychlorinated biphenyls (PCBs) contaminate 19% of US superfund sites and represent a serious risk to human and environmental health. One promising strategy to remediate PCB contaminated sediments utilizes organohalide respiring bacteria (OHRB) that dechlorinate PCBs. However, functional genes that act as biomarkers for PCB dechlorination processes (i.e. reductive dehalogenase genes) are poorly understood. We developed anaerobic sediment microcosms that harbor an OHRB community dominated by the genus *Dehalococcoides*. During the 430-day microcosm incubation, *Dehalococcoides* 16S rRNA sequences increased two orders of magnitude to 10^7 copies/gram of sediment, and at the same time PCB118 decreased by as much as 70%. In addition, the OHRB community dechlorinated a range of penta- and tetra-chlorinated PCB congeners including PCBs 66, 70+74+76, 95, 90+101, and PCB110 without exogenous electron donor. We quantified candidate reductive dehalogenase (RDase) genes over a 430-day incubation period and found rd14, a reductive dehalogenase that belongs to *Dehalococcoides mccartyi* strain CG5, was enriched to 10^7 copies/gram of sediment. At the same time, pcbA5 was enriched to only 10^5 copies/gram of sediment. A survey for additional RDase genes revealed sequences similar to strain CG5's rd4, and rd8. Ongoing work aims to quantify these rd14 transcripts in sediment free microcosms that have demonstrated PCB dechlorination after multiple transfers. In addition to demonstrating the PCB dechlorination potential of native microbial communities in contaminated freshwater sediments, our results suggest candidate functional genes with previously unexplored potential could serve as biomarkers of PCB dechlorination processes.

Poster 10

ELUCIDATING MECHANISMS OF CATALYSIS AND ALLOSTERIC INHIBITION OF CASPASE-7

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Caspase-7 (C7), a cysteine protease involved in executing an apoptotic cascade, is a highly sought-after target for drug discovery. C7 inhibitors are thought to have significant therapeutic potential for treating neurodegenerative diseases, autoimmune diseases, and ischemic reperfusion injuries. C7 is initially translated as an inactive proenzyme (a.k.a. zymogen) known as procaspase-7 (P7). P7 was canonically thought to be completely catalytically inactive until cleavage of the L2/L2' loops by an upstream caspase during the apoptotic cascade. However, P7 was recently shown to have low levels of catalytic activity in vitro. Previously published crystal structures of P7 and small molecule-inhibited C7 (PDB IDs: 5V6Z, 5V6U) show similar changes in the orientation of the catalytic dyad, as well as enhanced B-factors, compared to active C7. Thus, P7 presents a natural paradigm for allosteric inhibition. Our research elucidates the catalytic mechanism of mature C7 and determines the functional rationale for P7 inhibition. Rates of acylation and deacylation for C7 and P7 were determined by fluorometric, pre-steady state kinetics assays performed using a stopped flow. Kinetics data show C7 catalyzes cleavage of the peptide backbone through a fast acylation phase and rate-limiting deacylation phase. Surprisingly, data show acylation and preacylation are largely unencumbered for P7. The diminished steady state catalytic rate for P7 can be attributed almost exclusively to disruption of deacylation. These mechanistic insights into zymogenic allostery will allow targeting of our in silico investigation to the chemical and physical steps of deacylation. Later, we hope to expand our investigation to include a model of small molecule-mediated allosteric control.

Poster 11

CARDIAC-SPEICIFIC DELETION OF PROHIBITIN-1 IN MICE LEADS TO MITOCHONDRIAL DYSFUNCTION AND HEART FAILURE

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Prohibitin proteins (PHBs) are composed of PHB1 and PHB2 to form a ring-like structure located in nucleus, cytosol, and mitochondria, where they are associated with the progression of diseases through regulating mitochondrial metabolism and modulating signaling pathway. In the mitochondria, PHBs are thought to act as scaffold-like chaperone proteins responsible for stabilizing respiratory chain, activating oxidative phosphorylation system (OXPHOS), minimizing reactive oxygen species (ROS), and coordinating fission/fusion. It has been found that the loss of PHB1 in liver leads to the progression of liver damage due to the impaired mitochondrial function in liver cells. However, the extent to which PHB1 regulates mitochondria and electromechanical function of the heart, is not known. We established a cardiac specific PHB1 deficient mouse strain by crossing floxxed *phb1* mice with mice expressing Cre recombinase under control of myosin heavy chain (MHC) promoter. Surprisingly, the vast majority of cardiac-specific PHB1-deficient mice (cPHB1$^{-/-}$) die during development, *in utero*. Those that are born develop severe dilated cardiomyopathy by 8 weeks of age. Heart weight/body weight ratio is ~2-fold greater in the KO mice vs. WT. Echocardiography reveals severely enlarged right atria and ventricles in cPHB1$^{-/-}$ mice, corresponding to significantly decreased ejection faction (EF), increased end diastolic volume (EDV) and end systolic volume (ESV) compared to wild-type littermates ($P < 0.05$). Furthermore, cPHB1$^{-/-}$ mice have derangements in OXPHOS as evidenced by decreased glucose and fatty acid-supported oxygen consumption rate, mitochondrial ATP production. These preliminary findings implicate PHB1 as a critical regulator of myocardial development and function, due in part to its role in maintaining OXPHOS and controlling metabolism.

Poster 12

DEVELOPMENT OF A 3D-PRINTED, GENE-ACTIVATED CALCIUM PHOSPHATE CEMENT BONE REGENERATIVE SCAFFOLD

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Purpose:
The goal of this study is to investigate how modification of 3D printed calcium phosphate cement scaffolds can enhance their ability to regenerate bone upon implantation into defect sites. Specifically, the method of mineralization and treatment after mineralization can impact the surface morphology of the scaffolds, potentially impacting the ability of cells to adhere to the scaffolds and begin the regenerative processes of resorbing the scaffold and producing new bone. Additionally, a gene therapy capability can be granted to the scaffolds by incorporating reagents that can transfect local cells with genes of interest. The resulting gene-activated matrices can assist with the regeneration of bone by inducing production of regenerative growth factors over an extended period. This technique circumvents stability and dose issues that similar protein-based approaches must face, the release of transfection reagents can be controlled with release systems such as nanoparticles and diffusion from the scaffold itself.

Methods:
Cylindrical scaffolds 7.5mm in width and 1mm in height were printed from a calcium phosphate cement in an oil-based carrier fluid. The scaffolds were then mineralized via immersion in water or exposure to water vapor in a highly humid environment for 3 days. Some vapor-mineralized scaffolds were then immersed in water or simulated body fluid for an additional 3 days. The resulting scaffolds were pre-incubated in complete DMEM growth medium for 24 hours, then seeded with HEK 293T cells and allowed to incubate for 4 hours. The scaffolds were then fixed, dehydrated, and imaged with scanning electron microscopy.

Results:
The differently treated scaffolds showed differing surface morphology, with the “water only” scaffolds having the highest apparent surface roughness while the “vapor only” scaffolds have the lowest. Cells appeared to adhere to all scaffolds, though the number of cells adhered was so low that relative adherence could not be accurately quantified. The “water only” scaffolds showed large cracks throughout the strands of the scaffold, whereas the other scaffolds did not.

Poster 13

RESOLUTION OF OPTICALLY ACTIVE α-HYDROXY KETONES IN PSEUDO-SOLID-PHASE BY MECHANO-BIOCATALYSIS

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Optically active α-hydroxy ketones are very important molecules for many drugs, inhibitors, and natural products. Specifically, benzoins and furoins are used as urease inhibitors and building blocks of different heterocyclic drug products and other organic compounds. These compounds are generally synthesized as racemic mixtures via benzoin condensation by using a catalyst such as cyanide, thiamine, and chiral thiazolium & triazolium salts. These racemic compounds can be directly resolved into its pure *R*-enantiomer via a lipase catalyzed selective acetylation reaction of the *S*-enantiomer. Generally, the lipase catalyzed acetylation reaction is carried out in organic solvents such as tetrahydrofuran (THF) over 24-72 hours. We would like to offer a game changing approach where the use of toxic organic solvents is eliminated or reduced, and the total time of reaction is decreased significantly. To accomplish this, we propose to carry out the reaction in the pseudo-solid-phase while controlling mechanical forces by grinding with a ball mill. Preliminary findings demonstrate the feasibility of this solvent-reduction (90% v/v less solvent) approach. In this preliminary work, the lipase reaction was performed using a mortar and pestle, where THF solvent was completely eliminated by replacing with only 10% (v/v) DMSO. Currently, we are optimizing reaction conditions for both enantioselective acetylation of benzoin and furoin in a ball mill. In this presentation, pseudo-solid-phase reaction conditions will be detailed, and results of these reactions will be presented. Our final goal is to extend this mechano-biocatalytic approach in other areas of biocatalysis for the improvement of green chemistry.

Poster 14

DEMETHYLATION OF 4'-METHOXY-4-MONOCHLOROBIPHENYL IN WHOLE POPLAR PLANTS

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The troubling persistence of polychlorinated biphenyl (PCBs) has been reported, even though PCBs have been banned for more than 30 years. Thus, it is important to study the biotransformation of PCBs to reveal their environmental fate processes. As the well-known metabolites of PCBs, hydroxylated polychlorinated biphenyls (OH-PCBs) are generally more toxic than their parent PCBs. They can interrupt reproductive processes, the endocrine system, and brain function. In vitro, OH-PCBs were more toxic to neural and hepatic cell lines than their corresponding PCB congeners. In vivo, greater toxicity of OH-PCBs was reported than their parent compounds in plants.

OH-PCBs are widely distributed in most environmental matrices including water, sediment, air, birds, mammals, and human blood, plasma and serum. OH-PCBs can be further transformed to methoxylated polychlorinated biphenyls (MeO-PCBs). MeO-PCBs are likely more lipophilic and persistent than OH-PCBs according to their chemical structure and physical-chemical properties. Thus, MeO-PCBs pose a potential chronic health risk. The detection of MeO-PCBs in sewage sludge of China was reported. However, the information on transformation between OH-PCBs and MeO-PCBs is quite limited.

In this work, a model plant, poplar (*Populus deltoides* × *nigra*, DN34), was used to investigate the biotransformation of 4'-methoxy-4-monochlorobiphenyl (4'-MeO-PCB 3) in plants. Results show that poplar plants can take up and metabolize of 4'-MeO-PCB 3 after 10 days hydroponic exposure. 4'-MeO-PCB 3 was uptaken and translocated from roots to shoots in exposure groups. The highest concentration of 4'-MeO-PCB 3 was observed in the bottom bark of exposed poplar plants. A demethylation product, 4'-hydroxy-4-monochlorobiphenyl (4'-OH-PCB 3), was detected in all plant tissues and solution samples of the exposure groups. 4'-OH-PCB 3 was mainly accumulated in the middle bark and bottom bark. No parent chemical or demethylation products were detected in blank controls, while small amounts of 4'-OH-PCB 3 were detected in the solution of unplanted controls. However, the amounts of 4'-OH-PCB 3 in exposure groups was much higher than that in unplanted controls. Results indicate that demethylation of 4'-MeO-PCB 3 mediated by poplar trees occurred during 10 days exposure. The findings in this work provide new insight into potential biotransformation and fate pathways of toxic transformation products, OH-PCBs, in ecological systems.

Poster 15

TIME LAPSE CRYSTALLOGRAPHY OF POL ETA- CATALYZED NUCLEOTIDE INCORPORATION

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DNA damage is caused by environmental factors such as ultraviolet radiation and oxygen free radicals. Ultraviolet radiation causes thymine-thymine dimers and oxygen free radicals cause 8-oxoguanine. This damage will cause DNA replications forks to stall. Our cells have developed a pathway called Translesion Synthesis (TLS) to bypass the damaged DNA. Bypass occurs with the use of non-classical polymerases such as DNA polymerase eta (Pol Eta). Currently, we do not know the mechanism of how Pol Eta accommodates the damaged DNA during nucleotide incorporation. With a technique called time lapsed X-ray crystallography, we will capture these different conformations during nucleotide incorporation starting specifically with the 8-oxoguanine damage. This will give us a deeper understanding into how cells replicate DNA through damage, a process that is one of the major causes of cancer.

Poster 16

NETWORKS OF COUPLED-RESIDUES PROMOTING CATALYSIS MAY BE A CHARACTERISTIC OF ALL ENZYMES

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Enzymes have dynamic, internal motions on the timescales of femtoseconds to seconds which recruit residues across the protein. Femtosecond-picosecond motions can occur at the active site and may be linked to a coinciding event on the same timescale: catalysis. Protein motions are known to be linked to orchestrated motions of residues, called networks of coupled-residues. We hypothesize protein motions are linked to catalysis through networks of coupled-residues and this structure-function relationship is a classifying feature of all enzymes. We are using formate dehydrogenase and dihydrofolate reductase as model enzymes for predicting networks of coupled residues with the elastic network model and molecular dynamics simulations, two-dimensional infrared spectroscopy, steady-state kinetics, and crystallography to assess the validity of predicted networks in our model enzymes.

Poster 17

STUDIES TO IMPROVE CELLULAR PENETRATION OF QUINAZOLINEDIONES

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Topoisomerases are enzymes responsible for managing DNA topology, supercoiling, and catenation. Catalytic inhibitors of topoisomerases and topoisomerase 'poisons' are of pharmacological interest because of their cytotoxic potential as antibiotics or anticancer agents. Fluoroquinolones are clinically used antibiotic topoisomerase poisons, meaning that they bind bacterial type II topoisomerases to form a complex with the topoisomerase and nicked DNA. The binding of topoisomerase poisons prevents the religation of nicked DNA, ultimately leading to DNA damage and cell death. Fluoroquinolones have also been developed to poison human type II topoisomerases, making anticancer fluoroquinolones. However, anticancer topoisomerase poisons like etoposide or anticancer fluoroquinolones can lead to treatment-related malignancies. As such, for anticancer purposes, catalytic inhibitors that do not poison topoisomerases are desirable. Our lab has discovered that N1-biphenyl fluoroquinolones catalytically inhibit both human type I and type II topoisomerases without poisoning and these are therefore of significant interest for anticancer drug development.

Fluoroquinolones face target-mediated antibiotic resistance in the clinic, where amino acid substitutions in bacterial topoisomerases prevent fluoroquinolone binding. Quinazoline-2,4-diones (diones) share a similar core structure with fluoroquinolones and are capable of binding and poisoning topoisomerases in the same manner as fluoroquinolones but are equipotent with wild-type and fluoroquinolone resistant topoisomerases. N1-biphenyl diones have also been found to inhibit human topoisomerases as well as or better than N1-biphenyl fluoroquinolones. However, diones have poor human or bacterial cellular penetration and are highly susceptible to bacterial efflux pumps. Four approaches to improving the cellular penetration characteristics of diones will be discussed, with a focus on the synthesis of antibiotic quinazolinedione dimers.

Poster 18

THE AXCTIVATION OF σP, AN EXTRACYTOPLASMIC FUNCTION σ FACTOR THAT CONTROLS β-LACTAM RESISTANCE IN BACILLUS THURINGIENSIS AND RELATED SPECIES

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Antibiotic resistance has drastically reduced the efficacy of antibiotics, resulting in increasingly dangerous and untreatable infections. Antibiotic resistance can be controlled by extracytoplasmic function (ECF) σ factors; which are understudied transcription factors found exclusively in bacteria that activate transcription in response to specific extracellular stresses. σP is an ECF σ factor that controls resistance to some commonly prescribed βlactam antibiotics in Bacillus cereus, B. thuringiensis, and some strains of B. anthracis. In the absence of these β-lactams, σP is sequestered by RsiP, the membrane-spanning anti-σ factor that inhibits σP activity. σP is categorized in the ECF01 group, of which many are activated when the anti-σ factor is proteolytically degraded in response to stress. This process is generally accomplished by sequential site-1 and site-2 proteases. There is considerable variability between the known site-1 proteases, but the site-2 protease, a transmembrane metalloprotease called RasP, is highly conserved. Thus, we hypothesized RsiP is degraded in response to β-lactams and RasP cleaves RsiP at site-2. Using B. thuringiensis as a model, we found RasP is required for σP activation and cleavage of RsiP at site-2 in the presence of β-lactams. We have also shown RasP cleavage at site-2 of RsiP is not the rate-limiting step in σP activation. These data suggest RsiP is cleaved by a currently unknown site-1 protease. We have identified a putative penicillin binding protein (PBP) that is required for σP activation. We hypothesize this PBP senses σP-inducing βlactams and responds by activating site-1 cleavage, by interacting with either the site-1 protease or RsiP. Future studies seek to define the role of this PBP in σP activation and identify the site-1 protease. The overall goal of this work is to contribute to what is known about the ECF01 group and to define a novel mechanism for the control of β-lactam resistance.

Poster 19

APPROACHES TO TARGETING ADENYLYL CYCLASE 1 FOR NOVEL PAIN THERAPEUTICS

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Chronic pain is a major concern in public health with financial costs projected to surmount $600 billon in the next year. Patients afflicted with chronic pain endure extreme emotional, physical, and social burdens, resulting in severely diminished quality of life. Unfortunately, drugs currently used for chronic pain management, such as NSAIDs, opioids, neuronal stabilizers, and antidepressants, do not typically provide sufficient relief to restore full quality of life, and in many instances these treatments themselves limit patients, such as opioid treatment preventing a patient from legally driving. Recent preclinical studies have identified neuronal adenylyl cyclase type 1 (AC1) as a novel target for treating chronic pain. AC1 is highly expressed in neuronal tissues associated with pain processing and neuronal plasticity, and studies using AC1 knockout mice provide direct evidence linking AC1 to chronic inflammatory pain conditions. Furthermore, AC1 inhibitors would lack the side effects associated with other agents (e.g. opioids) used to treat chronic inflammatory pain. The development of AC1 inhibitors represents a unique challenge, as demonstrated by a prior preclinical AC1 inhibitor, NB001. NB001 has significant shortcomings, including modest selectivity over other adenylyl cyclase isoforms, likely due to its adenine-like structure. Compounds of this type are called P-site inhibitors and act by binding to the active site of AC that is conserved among all isoforms. Additional concerns for adenine-containing molecules like NB001 include effects on other cellular processes such as DNA synthesis. We hypothesize that developing a small molecule inhibitor of AC1 will allow us to mimic the AC1 knockout phenotype and provide a new avenue for the treatment of chronic inflammatory pain. We designed our studies to target NOT the conserved P-site or forskolin-binding site, but rather a novel approach, targeting the unique protein-protein interaction of AC1 and calmodulin (CaM). AC1 and AC8 are both activated by CaM, however, the CaM binding domains are unique in structure and location providing an unprecedented opportunity to achieve AC1 selectivity. Thus, the goals of this proposal are to: 1) develop a novel AC1/CaM biochemical screening assay, 2) implement this novel assay in a high throughput screen to interrogate a library of 100,000 compounds for inhibitors of the AC1/CaM protein-protein interaction, and 3) validate and chemically optimize lead molecules using cellular assays focused on selectivity and potency to guide medicinal chemistry efforts. To date, we have completed initial studies to develop the novel screening assay, established a subset of the necessary assays, and cemented the collaboration between the University of Iowa and Purdue University for the successful completion of our aims. We anticipate the identification of selective AC1 inhibitors that ultimately be improved and applied in models of chronic inflammatory pain.

Poster 20

ISOLATION AND IDENTIFICATION OF LYSOZYME RESISTANT MUTANTS IN *C. DIFFICILE*

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Clostridioides (Clostridium) difficile is an opportunistic pathogen responsible for approximately 500,000 infections and 30,000 deaths in the US each year. For *C. difficile* to establish infection a perturbation of the host microbiome is required. This dysbiosis is most often achieved when patients receive an antibiotic regiment. *C. difficile* is resistant to a wide range of antibiotics and antimicrobials, allowing it establish infection. This is likely due in part to the unique nature of the *C. difficile* cell envelope, which includes features such as an S-layer, a high proportion of peptidoglycan (PG) deacetylation, and a high proportion of LD crosslinks make up the PG. However, we lack a complete understanding of the *C. difficile* cell envelope is constructed. To identify novel features involved in cell wall biogenesis and modification in *C. difficile* we performed a selection using lysozyme. This selection was done using a lysozyme sensitive strain that lacks *csfV*, which normally encodes an Extracytoplasmic function σ factor, σ^V, that is partially responsible for mediating lysozyme resistance in *C. difficile*. We isolated three mutants with between 8-16-fold increase in lysozyme resistance. Whole genome sequencing revealed that two of these mutations were in two separate histidine kinases of two-component regulators. The third mutation was in an ABC transporter ATP binding protein, which is directly downstream from another two-component system. Targeted knockdown of the mutant genes was performed using CRISPRi and resulted in decreased lysozyme resistance, similar to the parental strain. This indicates that the mutations identified are responsible for increased lysozyme resistance. Future work will involve identifying exactly how these two-component systems and ABC transporter are working to influence lysozyme resistance.

Poster 21

NUMERICAL ANALYSIS OF TEMPERATURE AND CEM_{43} PROFILES IN AN INFECTED TISSUE SUBJECTED TO THERMAL AND COOLING TREATMENT

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Current approaches to treat medical implant biofilm infections involve invasive surgical procedures to replace the implant, which not only endanger patients' lives, but also cost USA billions of dollars annually. Thermal treatment of biofilm infections *in-situ* is an alternative approach to mitigate the biofilm and is possible via remote heating of the implant's surface. However, as the thermal treatment can be effective at lethal temperatures for human cells (>43°C), it would cause damage to the tissue next to the implant. To address this issue, applying a cooling treatment, immediately after the thermal shock is pursued via using technology of thermoelectric devices which enables heating that can be immediately reversed.
To predict the extent of tissue damage caused by an effective thermal shock for *in-vitro* mitigation of bacterial biofilms (70°C for 5 min), and accordingly, to determine optimum time and temperature conditions for the cooling treatment, temperature profile of subcutaneous tissue as well as cumulative equivalent minutes at 43°C (CEM_{43}) profile, were determined via numerical solution of one dimensional bioheat transfer model (Pennes' equation). Numerical analysis showed that 7.5 mm deep into the tissue would be exposed to temperatures higher than 43°C. Moreover, the shocked tissue temperature would decrease to below 43°C in less than 70s if cooling treatment was applied at 12°C. A cooling treatment at 12°C should be applied for 4 min to maintain CEM_{43} below 20 min (tissue damage threshold).

Poster 22

INCORPORATION OF ZOLEDRONIC ACID INTO A DEGRADABLE DRUG-ELUTING IMPLANT COATING FOR IMPROVED OSSEOINTEGRATION

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The overall goal of any bone implant is to adhere strongly and quickly to the surrounding bone so there is minimal implant movement. However, in 10% of primary hip and knee replacement surgeries there is a need for revision surgeries. The most common cause being aseptic prosthetic loosening which ultimately leads to osteolysis. Poor osseointegration is one of several contributing factors that can lead to an implant failing. Osseointegration is the process by which the implant surface forms a direct bond with the surrounding bone tissue. The most commonly used method in surgical practice today is the use of bone cement to fill any gaps between the bone and implant surface. The major drawback to using bone cement is a tendency for the cement to fragment and cause a foreign body reaction which leads to a local inflammatory response and chronic complications for the patient. One approach to improve osseointegration of implants has been to coat the implant surface with osteoinductive and/or osteoconductive therapeutics such as growth factors and bisphosphonate compounds respectively. Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and are used to treat bone disorders because of their high affinity for bone tissue over other tissue types. Zoledronic acid (ZA) is a nitrogen containing bisphosphonate compound and was the chosen drug for these studies, because it is already used in clinical practice, delivered via infusion, and has shown promising results for improving osseointegration. To date, however, ZA has not been incorporated into a degradable polymer matrix coating. Poly(lactic-co-glycolic) acid (PLGA) is an FDA approved degradable polymer that has been used in several commercially available drug delivery systems. PLGA is uniquely qualified as a drug delivery vehicle because its release kinetics can be finely tuned to fit specific needs by varying the ratio of lactic acid to glycolic acid monomers. The purpose of this study was to develop a degradable polymeric coating for bone implants which incorporates ZA. We hypothesized that this sustained release and local delivery method will result in increased osseointegration compared with uncoated implants. To create the coating, it was necessary to formulate a coating solution that would be able to encompass the hydrophilic drug ZA with the hydrophobic polymer PLGA. To overcome this barrier, the drug was formed into a complex in order to decrease its hydrophilicity and make it soluble into a similar solvent as PLGA, namely dichloromethane. This was done using the reverse microemulsion (RM) technique where the drug was first complexed with calcium (Ca) then coated with the lipid 1, 2-dioleoyl-sn-glycero-3-phosphate monosodium salt (DOPA). In the end, ZA/Ca/DOPA complexes were successfully synthesized using the RM technique. The ZA content within the complexes was determined to be 418.075 µg using ion exchange high performance liquid chromatography and the encapsulation efficiency was 21.3%. The mean hydrodynamic diameter, PDI and zeta potential for the complexes was 93.727 nm, 0.543 and -0.004 mV respectively. TEM micrographs showed that the complexes were spherical in shape and polydispersed. The PLGA/ZA complex coating solution had a final drug concentration of 10.619 µg/mL and was used to coat titanium implants.

Poster 23

CHARACTERIZING POLOXAMER GELS FOR THE CLINICAL ADMINISTRATION OF ANALGESIC COMPOUNDS TO CHRONIC WOUND SITES

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As the population of the United States ages, chronic wounds present a significant and growing health problem. Chronic wounds are typically observed in elderly patients as diabetic, pressure, or vascular ulcers. Clinical treatment of these ulcers is a difficult process, primarily due to the pain involved in routine care activities that require prolonged caregiver contact at the wound site. Such pain is often treated systemically through the administration of drugs that cause adverse effects on prolonged use. Although topical treatments avoid systemic adverse effects, they are typically formulated as gels or creams which require painful manual spreading at the wound site. Poloxamer 407 is a polymer that, in solution, is a liquid at low temperatures and forms a gel upon heating to approximately physiological temperatures. Poloxamer 407 is a potential vehicle for delivery of analgesic drugs to chronic wound sites that can be administered as a liquid with minimal caregiver contact and form a gel for prolonged drug release, minimizing the need for reapplication. The goal of this study is to determine the gelation and drug delivery properties of poloxamer solutions in order to evaluate them as potential analgesic delivery vehicles for use in clinical chronic wound treatment.

Aqueous solutions of 15%, 17%, and 20%w/w poloxamer were prepared via dissolution of solid polymer under constant stirring. Diclofenac sodium was added to the 17% and 20% solutions at concentrations ranging from 0.5% to 2%w/v. The blank poloxamer solutions were evaluated for their viscosities and gelation temperatures ($T_{sol\text{-}gel}$) using a rheometer. Poloxamer solutions containing diclofenac sodium were also evaluated for their $T_{sol\text{-}gel}$. Additionally, poloxamer solutions containing 1% of either naltrexone hydrochloride, naproxen sodium, or sodium-4-aminosalicylate were evaluated rheologically to observe the effect of drugs with varying physicochemical properties on poloxamer $T_{sol\text{-}gel}$. Finally, drug release and permeation studies were conducted to compare 17% and 20% poloxamer solutions containing diclofenac sodium to a commercial gel and a solution of diclofenac sodium in water.

Poloxamer solution viscosity was found to vary directly with percentage of poloxamer in solution, while poloxamer $T_{sol\text{-}gel}$ was found to vary inversely with concentration with 20% gel showing a mean±SD $T_{sol\text{-}gel}$ of 23.00 ± 0.01°C and 17% gel showing a $T_{sol\text{-}gel}$ of 27.67 ± 0.58°C. The 15% poloxamer solution did not form a gel at physiological temperatures. Addition of drug compounds generally caused poloxamer solution gelation temperature to increase. The largest effects occurred with addition of the most lipophilic drug compound tested, diclofenac sodium. The largest change in $T_{sol\text{-}gel}$ was observed in the 17% poloxamer and 2% diclofenac sodium solution, which showed an increase in $T_{sol\text{-}gel}$ of approximately 8.33°C. Drug release and permeation from poloxamer solutions was observed to be slower than release from a solution of the same concentration in water without poloxamer but faster than release from a commercial solution of the same concentration. Future studies will evaluate the drug delivery properties of poloxamer vehicles in a model *in vivo* chronic wound site.

Poster 24

MANIPULATION OF AZINE ANHYDROBASES TO ACCESS A DIVERSE RANGE OF PHARMACOPHORES

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Heterocycles are common structural moieties amongst FDA approved pharmaceuticals, with piperidines and pyridines the most prevalent functional group. Novel synthetic manipulation of these heterocycles are high demand reactions in drug discovery programs, particularly methods capable of introducing enantioenriched carbon centers or $sp^{2/3}$-sp^3 coupled products. An underexplored route to achieve these transformations is envisioned to proceed through dearomatized pyridine rings, generating the so-called azine anhydrobases.
The dearomatization process converts the unreactive pyridine aromatic system into highly malleable olefins or unique carbon nucleophiles, with properties dependent upon activation strategy. Our team is exploring multiple synthetic strategies to obtain structurally complex pharmacophores and natural products, combining the envisioned dearomatization process with transition metal catalysis. Current results indicate the formation of 3,4-azafluorene antibiotics or allylated picolyl scaffolds, both of interest to natural product and medicinal chemistry communities.

Poster 25

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

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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 health-based cleanup guidelines for dioxane, including 1 μg L^{-1} in California, 0.35 μg L^{-1} in Colorado, and 0.25 μg L^{-1} 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 cleanup strategy. However, questions remain if this technology can alone remediate dioxane, especially from deep groundwater plumes. Bioaugmentation of deep 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 degradation rate of dioxane by hybrid poplar (*Populus deltoides x nigra*, DN34) via bioaugmentation. However, CB1190 has been shown to be ineffective at relatively low dioxane concentrations (<500 μg L^{-1}) commonly encountered in the field. 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 phytoremediation of dioxane by hybrid poplar to low target concentrations in bench-scale experiments. Also, we compare dioxane degradation rates of poplar bioaugmented with CB1190 to that of novel bioaugmentation candidates, including *Mycobacterium sp.* PH-06. Finally, we report the scale-up of CB1190 and PH-06 in 20-L fermentors in order to produce the large amounts of biomass needed for field applications.

Poster 26

THE ABCF GENE FAMILY FACILIATES DISAGGREGATION DURING ANIMAL DEVELOPMENT

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Based on the presence of multiple aggregate bodies that stain with the amyloid oligomer reactive antibody, A11, and the amyloid stain, Thioflavin T, in the early stages of animal development, we hypothesize that amyloid type aggregates are involved in normal development and that dedicated disaggregases must be encoded by animal genomes and expressed embryonically. In addition to the well-known and ubiquitous amyloid disaggregase, Hsp104, which is present in all taxa except animals, the yeast genome encodes a fungal-specific disaggregase encoded by the *NEW1* gene. The New1 protein exhibits Hsp104-independent disaggregase activity toward the well-characterized Sup35 [PSI+] amyloid (prion). Because of the close phylogenetic relationship between Arb1/ABCF2 and New1, we investigated the role of yeast and animal Arb1/ABCF2 proteins in the processing of aggregated proteins.

Although Arb1/ABCF2 has not previously been implicated in amyloid processing, our work shows that Arb1 and the related Gcn20/ABCF3 contribute to the disaggregation of (heat denatured) aggregates and the processing of ordered (amyloid) aggregates needed for their propagation and inheritance in yeast. We find that animal orthologs of Arb1/ABCF2 and Gcn20/ABCF3 complement aggregation and growth phenotypes of strains with reduced levels of the corresponding yeast proteins, suggesting that the chaperone activities of the ABCF proteins are conserved.

Finally, we find that ABCF2 is important in development. Oligonucleotide-mediated reduction of abcf-2 mRNA in *Xenopus* embryos led to defects in gastrulation, as well as moderate to severe embryonic phenotypes. In addition, abcf-2 knock-down in stage 4 *Xenopus* oocytes caused a decline in the number and increased disorganization of Thioflavin T positive nucleolar associated aggregates compared to controls.

Our work suggests that the Arb1/ABCF2 protein may contribute to the disaggregation of endogenous amyloids present during early development, and that the disaggregation of these amyloids is crucial for normal progression through development. We note that Arb1/ABCF2 may have multiple functions or that the ribosome biogenesis defects previously reported in strains lacking normal levels of Arb1 may be the indirect consequence of altered folding of ribosomal constituents. (Supported by the Center for Biocatalysis and Bioprocessing (CBB) Seed Grant Program (2018-2019).

Poster 27

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

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Cancer Immunotherapy represents an important alternative to current standard treatment methods for inoperable cancers such as late-stage melanoma. A primary goal of cancer immunotherapy is to break immune tolerance in the immunosuppressive tumor microenvironment and mount an efficient immune effector response against tumor cells. One method of achieving this is to stimulate the immune system against tumor-associated antigens (TAA) expressed by cancer cells through viral vaccines such as the adenovirus or co-delivering TAA with adjuvants such as CpG oligonucleotides (ODNs). Viral therapies such as an adenovirus have been shown to elicit a cytotoxic T cell (CTL) responses in murine melanoma models and combining this with intratumoral administration of soluble CpG ODN further to enhances this effect. Despite the promising progress achieved with combinational immunotherapies, there is still room for improvement. One possibility is to vary the type of CpG ODNs used from the predominantly used CpG B to CpG A (G10) which has been shown to elicit a greater CTL response but is far less stable than CpG B due to its phosphodiester backbone being susceptible to enzymatic degradation. Encapsulating CpG A into polymeric nanoparticles (NP) such as Poly Lactic-co-Glycolic Acid (PLGA) will protect it from premature degradation, however, this approach is limited by the loading of CpG ODNs (approximately 5 ug CpG / mg particles).

The goal of this project is to enhance the viral cancer immunotherapy for melanoma, Ad5-TRP2 by providing intratumural delivery of CpG (G10). To protect the G10 from premature degradation it will be complexed with a novel PLGA nanoparticle formulation (PM) that possesses superior loading when compared to traditional PLGA nanoparticles. To demonstrate the efficacy of combining recombinant adenovirus type 5 vectors encoding TRP-2 (Ad5-TRP2) with intratumoral administration of the novel polymeric nanoparticle loaded with G10) offers robust anti-tumor activity in a murine melanoma model greater than with adenovirus alone.

Poster 28

DEVELOPMENT AND CHARACTERIZATION OF SPRAYABLE, THERMOREVERSIBLE HYDROGELS

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The goal of this project is to develop a sprayable, antimicrobial hydrogel to use as a treatment for burn wound infections. Pluronic F127, a commercially available thermoreversible hydrogel, and hyaluronic acid, an active healing agent and hydrogel, were combined in various percentages to test which formulations have desirable spray patterns, gelation temperatures, drug diffusion, and gel dissolution. Methylene blue was also incorporated into the gel for visualization and to act as a model drug in diffusion studies. To determine spray characteristics of the formulations, cold hydrogels were loaded into Aptar Pharma sprayers and sprayed at four, five, and six inches away from a target. The targets were photographed and analyzed to determine the spray spread and the sprays characterized via high-speed imaging to examine the plume differences from different nozzles. The gelation temperature of each gel composition was determined by parallel plate geometry, with a desirable gelation temperature between 21 and 32°C to avoid gelation while spraying but allowing gelation on skin. Diffusion and dissolution experiments were conducted in vitro to determine how quickly the gel compositions release drug and dissolve in saline solution. Future studies will include adding antimicrobial agents to the gel, antimicrobial testing, and transport studies across skin.

Poster 29

MAPPING THE METABOLIC PHENOTYPE OF TYPE II DIABETES MELLITUS IN HUMAN AQUEOUS HUMOR

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Our goal is to characterize the aqueous humor metabolome and proteome of humans with type II diabetes mellitus compared to controls, and identify differentially expressed proteins in specific diabetic disease states that may influence corneal endothelial cell (CEC) health.

Aqueous humor was biopsied from the anterior chamber of human eye donors (6 with advanced diabetes, 5 with nonadvanced diabetes, 5 nondiabetic controls) ≤5 hours postmortem using a 23-gauge needle or aqueous humor samples were collected from patients undergoing cornea transplant surgery. Protein fractions were isolated from each sample and subjected to multidimensional liquid chromatography and tandem mass spectrometry. Peptide spectra were analyzed statistically for largest differences associated with disease state and further bioinformatically for related mechanisms. We identified 1,003 differentially expressed protein isoforms including known risk factors for retinal diseases related to oxidative stress, inflammation, and the complement cascade ($P<0.05$). Gene ontology analysis showed diabetes disease progression has many protein footprints involved in binding, catalytic activity, and metabolic processes. Some of the most represented pathways involved in diabetes progression include acute phase response signaling, retinoid X receptor activation, complement system, and metabolism signaling.

This proteomic dataset gives insight into the mechanisms involved in diabetes disease progression relevant to adjacent structures including the corneal endothelium. These findings help prioritize new pathways for therapeutic targeting, and provide insight into potential biomarkers for determining anterior chamber health. Since diabetes is a metabolic disease and metabolism signaling was one of the most differentially expressed pathways in donors with varying degrees of diabetes, we are looking further into the aqueous humor changes using specific metabolomic assays and proteomic validation screens with human surgical aqueous samples.

Poster 30

REGULATION OF THE *S. AUREUS* SURVIVAL AND PATHOGENICITY BY REDOX SENSING HISTIDINE KINASE SrrB

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Staphylococcus aureus infections can lead to diseases that range from skin abscess to life threatening toxic shock syndrome. The SrrAB two-component system (TCS) is a global regulator of *S. aureus* virulence and critical for survival under the environmental conditions (hypoxia, oxidative and nitrosative stress) found at sites of infection. Despite the critical role of SrrAB in *S. aureus* pathogenicity, the signal(s) that SrrB histidine kinase senses and responds to, and the mechanism by which it is regulated remain unknown. The SrrB histidine kinase contains several domains, including an extracellular Cache domain and a cytoplasmic HAMP-PAS-DHpCA catalytic region. Here, we show that the PAS domain regulates both kinase and phosphatase enzyme activity of SrrB. Moreover, we show that heme binding to the PAS domain influences autophosphorylation and oligomerization. Small angle X-ray scattering analysis of the HAMP-PAS-DHpCA region indicates that the PAS and CA domains are flexibly linked and capable of domain-domain interactions, suggesting a mechanism by which the PAS domain might regulate enzyme activity. We also present the structure of the DHpCA catalytic domain. Importantly, this structure shows a cysteine disulfide bond in the CA domain that significantly affects autophosphorylation kinetics. Our *in vivo* data shows that the redox state of these cysteine residues affect *S. aureus* biofilm formation and Toxic Shock Syndrome Toxin -1 production. Together, our data are consistent with a model whereby the SrrB histidine kinase senses and responds the cellular redox environment through heme and a disulfide bond to support *S. aureus* survival and pathogenesis.

Poster 31

MEASUREMENT OF GLUCOSE AND β-HYDROXYBUTRYATE IN AQUEOUS BUFFERS AS FEASIBILITY FOR IMPROVED DIABETES CARE WITH MULTI-ANALYTE NEAR-INFRARED SPECTROSCOPIC SENSING

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In 2017, the Centers for Disease Control and Prevention estimated that more than 30 million people in the United States had been diagnosed with diabetes and this number continues to grow. Glucose levels in these people can vary widely and thus must be closely monitored to avoid hyper- and hypo-glycemia. Diabetic ketoacidosis (DKA) is a life-threatening condition observed under hyperglycemic conditions and manifests as excessive ketone bodies accumulated in the blood. The American Diabetes Association advises that ketone levels be checked when experiencing symptoms of hyperglycemia. Urine test-strips are the most common device for home ketone testing, but this method is insensitive and primarily measures acetoacetic acid concentrations, making it prone to false diagnoses. β-hydroxybutyrate in blood is a more sensitive and specific clinical marker for DKA and commercial test-strips are available for this measurement. Although β-hydroxybutyrate test-strips can be read with a common glucose meter, the use of multiple types of test-strips can be confusing, inconvenient, and costly for users, especially while experiencing extreme hyperglycemia. The need to collect a separate sample of blood for the β-hydroxybutyrate test-strip measurement adds to the overall complexity.
An alternative analytical approach is to measure both glucose and β-hydroxybutyrate simultaneously in either plasma or interstitial fluid (ISF) by near infrared (NIR) spectroscopy. The idea is to collect a NIR spectrum from a sample and extract the concentration of each analyte from this single spectrum. In this work, 50 standard solutions containing randomized concentrations of glucose, β-hydroxybutyrate and urea within a phosphate buffer were prepared and then collected using NIR spectroscopy in the combination region (5000 cm^{-1}-4000 cm^{-1}). Calibration models were built for each analyte using partial least squares (PLS) regression with a grid search designed to find the optimal wavenumber range for each analyte. Standard error of prediction (SEP) values are 0.04 mM for glucose and 0.05 mM for β-hydroxybutyrate. Those excellent SEP values support the feasibility of simultaneous quantification of glucose and β-hydroxybutyrate for diabetes care.

Poster 32

PHARMACEUTICAL EXPOSURES IN A TEMPERATE REGION WASTEWATER EFFLUENT-DOMINATED STREAM: MUDDY CREEK, IOWA

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The increasing use of pharmaceuticals has translated to a corresponding increase in concern over their potential impacts on ecosystem and human health worldwide. An important environmental pathway for such pharmaceutical exposure is via wastewater treatment plant (WWTP) discharge as incomplete removal of pharmaceuticals during wastewater treatment can potentially affect aquatic and terrestrial organisms. Small effluent-dominated streams represent an ideal scenario for evaluating and predicting aquatic responses to pharmaceuticals as such chemicals are continually discharged into these less diluted systems. To this end, Muddy Creek, a small (22.5 km^2) effluent-dominated temperate region stream that flows through the town of North Liberty, Iowa, was selected as a field laboratory for this study. Although the population serving the North Liberty WWTP is small (18,500 people), it is the second fastest-growing city in Iowa. To determine spatial and temporal trends in pharmaceutical exposures, four sampling sites were selected for this study: (1) approximately 100 m above the WWTP outfall, (2) the WWTP outfall, (3) approximately 100 m below the WWTP outfall, and (4) approximately 5 km downstream of the WWTP outfall. From September 2017 to August 2018, water samples were collected on a biweekly basis and analyzed for 13 pharmaceuticals by the University of Iowa and collected monthly and analyzed for 110 pharmaceuticals by the U.S. Geological Survey. The top 13 pharmaceuticals in terms of concentration accounted for over 85% of the overall chemical mass measured in the collected environmental samples. The total concentration of the top 13 pharmaceuticals ranged from 2,550 to 37,800 ng/L in the WWTP outfall. The parent-to-product ratios for five pharmaceuticals were calculated spatially and temporally as a measure of differential attenuation. Bench experiments are being conducted in the laboratory to elucidate transformation kinetics including photolysis, sorption, and biodegradation of targeted pharmaceutical mixtures. Ongoing and future efforts will relate pharmaceutical results to fish exposure and bioluminescent yeast estrogen assays to better understand potential environmental impacts from pharmaceutical exposures.

Poster 33

PROPER AMYLOID PROCESSING IS REQUIRED FOR EARLY *C. ELEGANS* DEVELOPMENT

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Insoluble protein aggregates known as amyloids are often associated with pathology of neurodegenerative diseases such as Parkinson's and Alzheimer's. Why there is no disaggregase in animals akin to the otherwise widespread Hsp100 class of chaperones that might disentangle these aggregates in metazoans has been puzzling.

The answer to this paradox may lie with emerging beneficial roles for amyloids in the persistence of memory and packaging of presecretory hormones, which may provide selective pressure for amyloidogenesis. We tested the hypothesis that amyloid aggregates are required for normal developmental processes using the nematode, *C. elegans.* Using well-established markers of amyloid oligomers (ThioT and antibody A11) and amyloid fibrils (X-34 and antibody OC), we surprisingly find that amyloids are present and indeed widespread in the *C. elegans* germline and early embryo, marking specific structures such as centrosomes, nuclear membrane, and the RNA processing bodies known as P granules. Interestingly, though newly fertilized worm oocytes and early embryos exhibit ubiquitous aggregate bodies, the presence of amyloid is largely absent by mid-embryogenesis, with the exception of the germline lineage. This suggests cell type-specific solubilization of these aggregates has occurred during embryonic development. Aggregates observed in the germline and early embryo are also sensitive to disaggregase activity since misexpression of yeast Hsp104 is sufficient to abolish the presence of amyloid oligomers marked by A11. Hsp104 misexpression also resulted in embryos with defective cell cycle timing, spindle alignment and increased embryonic lethality, suggesting the regulated processing of amyloids is required for normal development.

Although the chaperone network consisting of Hsp110-Hsp70-Hsp40 is known to be important for stress-induced aggregate regulation, it has no known role in development. To identify endogenous disaggregase type chaperones that regulate the developmental amyloids we observe, we looked for animal proteins that resemble the fungal specific disaggregase, New1. We show that the "F" subfamily of the ATP binding cassette (ABC) superfamily is necessary for worm germline and embryonic development. We further find that loss of ABCF function in *C. elegans* expands the size and distribution of amyloid oligomers. Together these data support a model whereby amyloids, and their proper regulation by ABCF proteins, are essential for normal animal embryonic development. (Supported in part by NIDCD R01 DC012049)

Poster 34

BIOINSPIRED COATINGS ON 3D PRINTED POLYMERIC SCAFFOLDS FOR BONE REGENERATION

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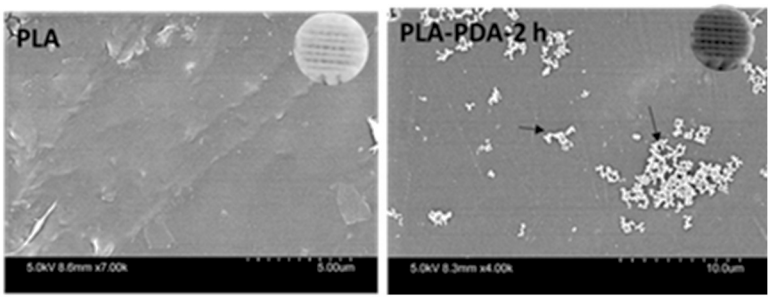
Three Dimensional (3D) printing offers enormous potential to tailor scaffolds with unique shapes and sizes for bone regeneration. The unique spatial and structural strength offered by 3D printing is also helpful in bone regeneration. Polylactic acid (PLA) is a biodegradable and biocompatible polymer which is widely used for tissue regeneration applications. Polydopamine (PDA) is a biocompatible, biomimetic protein found in mussels which can attach to any possible metal, non-metal and biological surfaces promote cell attachment, proliferation, and differentiation of stem cells. Polyethyleneimine (PEI) is an amine-rich polymer widely used in various biomedical applications and has been employed in bone tissue engineering because of its ability to facilitate cell proliferation and osteogenesis.

In the present study, we fabricated 3D printed PLA scaffolds using a fused deposition modeling based 3D printer. The scaffolds were surface coated with PDA and PEI by immersing the scaffolds in solutions (2 mg/mL) for 2 h. The amine-functionalized scaffolds were characterized for surface morphology using scanning electron microscopy (SEM), and surface wettability using contact angle measurements. Dental pulp stem cells (DPSC) were isolated from the third molars of patients with prior approval from the ethics committee, College of Dental Sciences. The stem cell markers CD34, CD45, CD73, Stro-1, and CD105, were evaluated using flow cytometry. Cell growth of DPSCs cultured with scaffolds was determined on days 3, 7 and 14 of culture. The degree of osteogenic differention was assessed using RT-PCR (for osteogenic genes) and alizarin red staining on day 7 and day 14, respectively.

The scaffolds of 6.22 x 2 mm (diameter x height) were fabricated. The SEM image showed the scaffolds had a pore size of 0.18 ± 0.019 mm and a rho width of 0.40 ± 0.015 mm. The SEM images also showed the deposition of PDA particles on the PLA scaffolds (PLA-PDA). The PLA scaffolds had a contact angle of 87±1.6 while the contact angle for PLA-PDA was 6 ± 0.4. The isolated stem cells expressed stem cell markers CD34-, CD45-, CD73+, Stro-1+, and CD105+ specific for DPSCs. The cell growth study showed an increase in cell numbers across all groups. However, by day 14, the PLA-PEI group showed least cell proliferation compared to the control. The RT-PCR analysis showed upregulation of osteocalcin (6-fold), Runx2 (8-fold), and alkaline phosphatase (4-fold) genes in PLA-PDA compared to PLA-PEI and PLA scaffolds. The alizarin red staining showed a significant increase in mineralization with PLA-PDA scaffolds compared to PLA-PEI and PLA scaffolds.

Overall, the results suggest that the 3D printed scaffolds with PDA coatings might be the most suitable candidates for bone tissue regeneration.



The Scanning electron microscopy images of 3D printed PLA scaffolds with PDA coating for 2h. The insets show the optical images of the 3D printed PLA scaffolds before and after PDA coatings

Poster 35

GAMMA CYCLODEXTRIN COMPLEXATION IMPROVES THE ANTIOXIDANT ACTIVITY OF UBIQUINOL ON HUMAN CORNEAL CELLS AND PROVIDES HIGH CORNEAL PENETRANCE

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Background: Cyclodextrins (CDs) are cyclic oligosaccharides, formed of 6, 7, or 8 dextrose units (α-, β-, or γ-CDs, respectively). Due to their hydrophobic inner cavities, they can host many lipophilic molecules inside, while they improve their aqueous solubility and dissolution rate as the hydrophilic surfaces of CDs render them highly water-soluble. Cyclodextrins are widely used in literature and industry to improve oral bioavailability, palatability, stability, and antioxidant activity, and reduce toxicity of many drugs. Ubiquinol is the reduced and active form of coenzyme Q10 (CoQ10). Coenzyme Q10 is essential for the electron transport chain in the mitochondria as it plays a major role in oxidative phosphorylation and ATP production. Ubiquinol is practically insoluble in water, a character that limits its potential as a supplement to cell and tissue storage aqueous media. We hypothesize that the complexation of ubiquinol using γ-CD will improve its aqueous solubility/dispersibility, stability, and antioxidant activity.

Methods: The complex was prepared by trituration of a 1:10 molar ratio of ubiquinol and γ-CD using a mortar and a pestle in the presence of small volume of water/alcohol mixture (1:1) for one hour under light- and oxygen-protected conditions. The complex was characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD), and scanning electron microscopy (SEM). The antioxidant activity and cell uptake of the complex were evaluated and compared to that of ubiquinol alone in human lung epithelium cancer cells (A549) and human corneal cells (HCC) using dihydroethidium (DHE)-based reactive oxygen species (ROS) assay and high-performance liquid chromatography (HPLC), respectively. In addition, the penetrance of a coumarin-6/γ-CD through freshly collected porcine cornea was evaluated using confocal microscopy.

Results: In contrast to free ubiquinol, the complexed ubiquinol had good dispersibility in water. DSC and XRD profiles showed that some interaction between ubiquinol and γ-CD can be seen. ROS assay showed a significant concentration-dependent decrease of ROS levels in A549 cells when the complex was used, while there was no noticeable inhibition with free ubiquinol. HPLC assay showed that ubiquinol uptake in A549 was higher when the complex was used, compared to free ubiquinol. ROS levels in human corneal cells were dramatically reduced when even smaller equivalent concentrations of ubiquinol were used, while free ubiquinol had no effect on ROS levels. Stability of complexed ubiquinol in Optisol, a corneal storage medium, was higher than that of uncomplexed ubiquinol. Finally, a complex made between coumarin-6 and γ-CD (1:10) showed much higher penetrance through porcine corneas and was able to reach the endothelial layer while free coumarin-6 had poor penetrance and could not reach the endothelial layer.

Conclusion: Complexation of ubiquinol using γ-CD improves the antioxidant activity, stability, and potentially corneal penetrance of ubiquinol, which highlights its potential application as a corneal storage medium supplement and in eye drops.

Poster 36

BIOMOLECULAR CAPABILITIES OF THE CCOM NUCLEAR MAGNETIC RESONANCE FACILITY

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Nuclear Magnetic Resonance (NMR) Core Facility, Carver College of Medicine, University of Iowa, Iowa City, IA

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 37

HARNESSING GUT MICROBIOME-MEDIATED METABOLISM OF THE NATURAL ISOFLAVONE DAIDZEIN TO TREAT BREAST CANCER

Milad Rouhimoghadam[1], Jackson Dunning[1], Nicole Cady[2], Ashutosh K. Mangalam[2], and Edward J. Filardo[1]*
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The soy-derived isoflavone, daidzein (DZN) is a dietary estrogen whose postprandial serum concentration can exceed preovulatory estrogen concentrations by ten-fold, and whose metabolism is solely mediated by gut microbiota. Daidzein metabolism is measured by its bacterial conversion to S-equol via an operon that contains four primary genes: ***dzr*** (daidzein reductase), ***ifca*** (dihydrodaidzein racemase), ***ddr*** (dihydrodaidzein reductase) and ***tdr*** (tetrahydrodaidzein reductase}. Yet only a fraction of daidzein is metabolized via this pathway.

The influence of DZN on breast cancer biology remains inconclusive. Consumption of soy has been linked with a lower incidence of breast cancer in Asian countries and health-promoting capabilities. Results from preclinical studies evaluating the influence of soy isoflavones on breast cancer biology and estrogen-targeted therapy are equally confusing, with reports of phytoestrogens promoting pro- or anti-oncogenic responses. These disparities are suggested to be the result of diversity among individual human metabolomes. Another contributory factor is the lack of a pharmacological receptor-based mechanism for the action of DZN and its metabolites. A majority of studies in man and mice have focused on nuclear estrogen receptor (ER) as the sole arbiter of estrogen responsiveness, even though phytoestrogens show moderate or weak potency for ER. In contrast, DZN exhibits high potency for G-protein-coupled estrogen receptor (GPER), whose expression in primary breast tumors has been linked with clinicopathological parameters that define advanced disease.

Our ***central hypothesis*** is that bacterial conversion of DZN eliminates a potent and abundant GPER agonist thereby preventing chronic GPER stimulation and disease progression. We have begun to test this hypothesis by measuring the pharmacological properties of DZN and its metabolites (DHD, THD, ODMA and S-equol) *in vitro*, and by measuring DZN metabolites, bacterial metabolomes and GPER-positivity in breast cancer patients. Work is underway to compare the carcinogenicity of daidzein in mice fed a Western diet and lacking DZN-metabolizing bacteria relative to mice fed standard rodent chow (Eastern diet promote DZN-metabolizing bacteria). To complement these results, we have also amplified and expressed the four central DZN-metabolizing enzymes in *E.coli.* Genetically modified *E. coli* will utilized for microbiome reconstitution experiments in mice depleted of gut bacteria due to treatment with broad spectrum antibiotics.

We expect the outcome of this study will have a positive impact on development of gut microbial-flora/diet-based therapies for breast cancer as well as other cancers.

CBB/NIH Fellowships

YEAR	CBB Fellowship	*NIH Trainee Fellowship
1990-91	10	4
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	6	3
2018-19	6	6
2019-20	5	6
TOTAL	285	193 *Partially Sponsored by CBB

The Center for Biocatalysis and Bioprocessing
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Pufall, Miles	4-430 BSB	4-1820
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Schnieders, Michael	4-516 BSB	5-7891
Shea, Madeline	4-450 BSB	5-7885
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Updated 8/14/19

Winter Term Course

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.

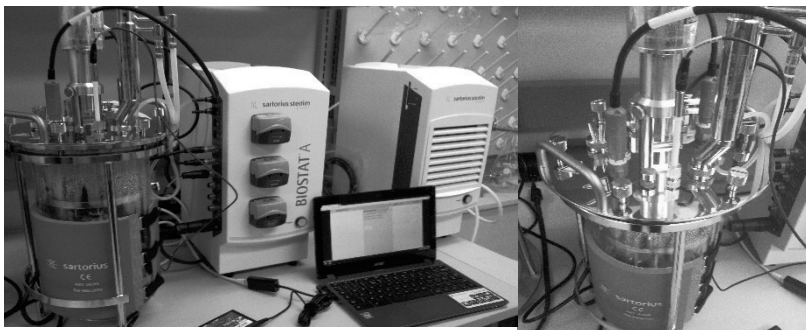

Figure: Sartorius Biostat A MO UniVessel 5-L Fermenters. These fermenters are dedicated for Upstream Biotechnology Processes Course.

Course Details

Scholarship: Dean Keller of the Graduate College has offered to provide full tuition scholarships for up to six students taking this course during the upcoming winter session.
Course Title: Upstream Biotechnology Processes
Course number: CHEM:4850:0001
Semester hours: 2
Instructors: Shuvendu Das, Sridhar Gopishetty, and Mark Arnold
Dates: 12/31/2019 – 01/16/2020
Meeting: T,W,Th, 9:00AM-12:10PM
Location: A 164A, MTF (Lecture) and B145, MTF (Lab), University Research Park (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

Notes

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