COLLEGE OF PHARMACY
MEDICINAL CHEMISTRY
UNIVERSITY OF MICHIGAN

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The Johnson & Johnson University of Michigan College of Pharmacy **Medicinal Chemistry Symposium**

Sponsored by:

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Thursday, April 18

2:00pm-5:00pm

Palmer Commons

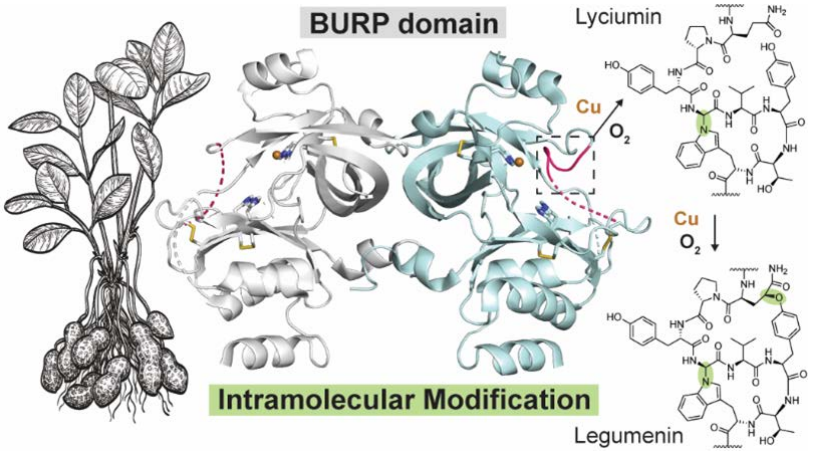
4th Floor Forum Hall

Dr. Lisa Mydy
Roland Kersten Lab Postdoc

"Let those BURP domains RiPP! The structure and function of a BURP domain protein in plant ribosomal biosynthesis"

Abstract:
Macrocyclic peptides are an attractive, emerging scaffold in drug discovery. Peptide cyclization can increase resistance to proteolysis compared to linear peptides, improve target specificity, and may enhance oral bioavailability or cell membrane permeability.[1] Cyclic peptides can be generated by all forms of life as Ribsomally synthesized and Post-translationally modified Peptides, or RiPPs. RiPPs with side-chain-to-side-chain macrocyclic bonds derived from C-H functionalization of unactivated carbons are difficult to achieve by synthetic means and can significantly expand the current peptide chemical space. To this end, we show that BURP-domain proteins are a new source of bioactive cyclic peptides. BURP domains are autocatalytic, copper-dependent macrocyclases, however their enzyme mechanism is largely unknown.[2]

BURP-domain proteins are named after their four founding members (BNM2, USP, RD22, and PG1β) and only found in plants. Many BURP-domain proteins form chemically diverse crosslinks between the aromatic side chains of tyrosine or tryptophan and unactivated amino acid carbons in the presence of copper. BURP-domain proteins represent RiPP precursor peptides, which comprise a catalytic BURP domain and substrate core peptide(s), often in the same polypeptide chain. We present the first experimentally determined protein structure of a BURP domain (USP-type) from the peanut plant, AhyBURP. X-ray crystallography studies show that AhyBURP has a previously unreported protein fold and novel copper sites for catalysis. Functional assays demonstrate the requirement for dioxygen with copper for core peptide cyclization, and we provide evidence for a radical-based, sequential mechanism from the 8 amino acid linear core peptide to the formation of monocyclic (lyciumin) and then bicyclic (legumenin) peptides. In addition, our data supports the macrocyclization of a core peptide by an intramolecular reaction, contrary to the dogma of intermolecular RiPP biosynthesis.[3] Our work is the starting point for the mechanistic investigation for new macrocyclic peptides derived from BURP domains and intramolecular reactions in RiPP natural product biosynthesis.



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Dr. Greg Bowden
Peter Scott Lab Postdoc

"Statistical Design of Experiments (DoE) and High-Throughput Experimentation as Tools for Radiosynthesis Optimization and Efficient Radiochemical Data Acquisition"

Abstract:
Advancements in radiochemistry, like the copper-mediated radiofluorination (CMRF) reaction, are transforming radiopharmaceutical development for nuclear medical applications. However, translating these complex multicomponent reactions into reliable, fully automated cGMP-regulated production protocols for physiologically relevant radiolabeled molecules remains a significant challenge. This task has proved notoriously difficult via the traditional "One Variable at a Time" (OVAT) optimization approach, which is experimentally inefficient and prone to finding local optima, adding significant cost and time to developing novel radiopharmaceuticals. There is, thus, an important and unmet need to bring data-driven solutions to the complex optimization problems of radiopharmaceutical research and development. We have thus worked to implement "Design of Experiments" (DoE) into our radiopharmaceutical development program. DoE is a statistical toolkit that aims to select an optimal set of experiments to maximize the amount of information obtained within a defined region of experimental space. This data is then used to map a given region of experimental space across multiple variables and responses simultaneously, identify and characterize significant process variables, or model a detailed response surface. This information facilitates the identification of optimal reaction conditions, can guide further optimization studies, or aid in general decision-making.

Using DoE, we have improved the synthesis performance of several established radiotracers of clinical importance, making cGMP syntheses both higher yielding and more reliable through an increased margin for error. The increased margin also enables longer and more complicated automated protocols, expanding radiopharmaceutical space through synthetic flexibility. More importantly, DoE has allowed us to identify substrate-specific radiolabeling conditions capable of radiolabeling compounds that would not be considered possible with standard radiolabeling protocols. In combination with emerging high-throughput radiochemical methods, DoE's experimental efficiency and ability to broadly survey radiochemical space position it as an unexplored tool for acquiring the large, reliable chemical datasets needed to bring predictive AI and ML models to bear for radiopharmaceutical development. This presentation will explore the future role of the DoE in data-driven radiopharmacy.

Dalia Soueid
Amanda Garner Lab PhD

"Adaptation of RiPCA for the Live-Cell Detection of mRNA-Protein Interactions"

Abstract:
RNA-binding proteins (RBPs) make up a class of ~2,000 proteins that bind to and regulate the diverse functions of various types of RNAs, and accordingly, are involved in controlling many cellular processes. Disruption of RNA-Protein Interactions (RPIs), consequently, has been implicated in human diseases ranging from neurodegenerative and autoimmune diseases to several cancers. Hence, targeting RBPs and RPIs has surfaced as a new frontier in RNA-targeted drug discovery which takes advantage of the endogenous regulation of messenger RNA (mRNA). The aim of this work is to characterize the high-affinity interactions of RBPs with mRNA motifs through live-cell detection using an assay previously developed for the detection of pre-miRNAs and their RBP partners, RNA-interaction with Protein- mediated Complementation Assay (RiPCA). Our goal is to be able to expand RiPCA to allow us to study other more complex RPIs in cells composed of RNAs that are larger and more structurally diverse than pre-miRNAs and that bind to proteins which perform a variety of cellular functions. My efforts towards developing these assays will be discussed, as well as future directions aimed at further improvement of this assay technology. Through RiPCA optimization, we hope to generate a platform for detecting and validating various RPIs in live cells to enable screening and drug discovery efforts.

Andrew Outlaw
Tim Cernak Lab PhD

"Late-Stage Saturation of Drug Molecules"

Abstract:
The available methods of chemical synthesis have arguably contributed to the prevalence of aromatic rings, such as benzene, toluene, xylene, or pyridine, in modern pharmaceuticals. Many such sp2 -carbon-rich fragments are now easy to synthesize using high-quality cross-coupling reactions that click together an ever-expanding menu of commercially available building blocks, but the products are flat and lipophilic, decreasing their odds of becoming marketed drugs. Converting flat aromatic molecules into saturated analogues with a higher fraction of sp3 carbons could improve their medicinal properties and facilitate the invention of safe, efficacious, metabolically stable, and soluble medicines. Herein, we demonstrate that aromatic and heteroaromatic drugs can be readily saturated under exceptionally mild rhodium-catalyzed hydrogenation, acid-mediated reduction, or photocatalyzed-hydrogenation conditions, converting sp2 carbon atoms into sp3 carbon atoms and leading to saturated molecules with improved medicinal properties. These methods are productive in diverse pockets of chemical space, producing complex saturated pharmaceuticals bearing a variety of functional groups and three-dimensional architectures. The rhodium-catalyzed method tolerates traces of dimethyl sulfoxide or water, meaning that pharmaceutical compound collections, which are typically stored in wet DMSO, can be reformatted for use as substrates for chemical synthesis. This latter application is demonstrated through the late-stage saturation (LSS) of 768 complex and densely functionalized small-molecule drugs.

Christine Gelin, PhD
Principle Scientist,
The Janssen Pharmaceutical Companies of Johnson & Johnson

Biosketch: Christine obtained her Ph.D. in organic chemistry at The Scripps Research Institute in the laboratory of Professor K.C. Nicolaou where she worked on the synthesis of complex natural products. Christine started her career as a medicinal chemist at Novartis in Cambridge, Massachusetts in the Ophthalmology group where she worked on programs to treat age-related macular degeneration. In 2012, she joined Johnson & Johnson as a medicinal chemist for the Neuroscience therapeutic area where she supported numerous programs supporting mood disorders. Currently, she leads the La Jolla Parallel Medicinal Chemistry team within Johnson & Johnson Global Discovery Chemistry. Her team focuses on the application of high throughput chemistry capabilities to accelerate drug discovery programs.

Title: Innovative Chemistry Capabilities to Accelerate Modality Agnostic Drug Discovery

Abstract:
The talk will highlight the impact of innovative chemistry capabilities to shorten the Design-Make-Test-Analyze cycle for discovery programs. In the last couple of years a Global Chemistry Capabilities, Analytical and Purification group has been built within the Global Discovery Chemistry organization at Johnson & Johnson. Taking a modality agnostic approach, high throughput chemistry technologies have enabled accelerated hit identification, rapid reaction optimization, and accelerated SAR exploration. Additionally, collaboration with high impact academic research groups, such as the Cernak Laboratory, has led to the discovery of new chemical transformations to expand the suite of chemical transformations for the synthesis of highly complex molecules, such as heterobifunctional degraders. Internal and external efforts to grow the conventional toolbox of synthetic transformations presents chemists with the advantage to access more structurally diverse compounds than in the past.

Lee Cronin, PhD
Regius Chair of Chemistry,
Advanced Research Centre,
University of Glasgow

Biosketch: Lee Cronin was born in the UK and was fascinated with science and technology from an early age getting his first computer and chemistry set when he was 8 years old. This is when he first started thinking about programming chemistry and looking for inorganic aliens. He went to the University of York where he completed both a degree and PhD in Chemistry and then on to do post docs in Edinburgh and Germany before becoming a lecturer at the Universities of Birmingham, and then Glasgow where he has been since 2002 working up the ranks to become the Regius Professor of Chemistry in 2013 aged 39. He has one of the largest multidisciplinary chemistry-based research teams in the world, having raised over $35 M in grants and current income of $15 M. He has given over 300 international talks and has authored over 350 peer reviewed papers with recent work published in Nature, Science, and PNAS. He and his team are trying to make artificial life forms, find alien life, explore the digitization of chemistry, understand how information can be encoded into chemicals and construct chemical computers.

Title: Will Chemputers Dream of Electric Drugs?

Abstract:

I will explain why 'Chemputation' is a universal approach to explore chemical reactivity, discovery of new reactions, and molecules, as well as program chemical synthesis that allows us to translate all procedures, manual or automatic, into an executable chemical programming language that can run the processes on a chemputer. This code is written in the world's first universal programming language for chemistry: χDL (pronounced Chi-DL). This new approach maps into a universal programming language for chemistry that is accessible to ALL synthetic chemists and will work on ALL robotic systems (subject to suitable specification). We demonstrate that the process is universal, and by analogy with computation, we call systems capable of universally turning code into reliable chemistry and materials processes Chemputation, see Figure.

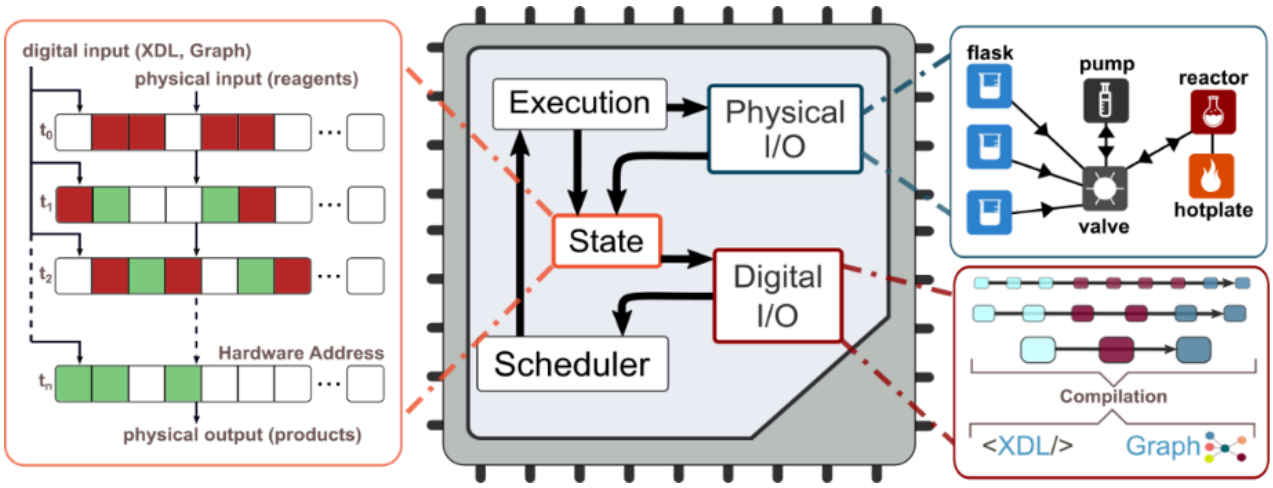

Figure: Depiction of a chemical state machine (CSM) for synthesis that is capable of Chemputation. The input is a combination of reagents, process information and hardware addresses. The CSM organizes the reagents and the processes by using a scheduler that then gets executed in the hardware as a function of the available state until the product is formed.

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