

Thursday Morning - Abstracts WRM 1 - 73

WRM 1

An Introduction to the America Invents Act

Sandra Thompson, sthompson@buchalter.com. Buchalter Nemer, Irvine, CA 92612, United States

This session will provide both a broad and in-depth view of the new America Invents Act. This presentation will focus on a broad overview of the Act and the different sections that are now in force.

WRM 2

Practical Implications of the Leahy-Smith America Invents Act: Avoiding Prior Art Pitfalls and Other Traps for the Unwary

Rose M. Thiessen, Rose.Thiessen@Knobbe.com. Knobbe Martens LLP, Palo Alto, CA 94303, United States

The America Invents Act (AIA) introduced several changes to U.S. patent law. On March 16, 2013, the AIA moved the U.S. from a First-to-Invent system to a First-to-File system. This and other provisions of the AIA that became effective on March 16, 2013 may result in a patent application filed on or after this date being more vulnerable to attack than if it were filed before this date. Among the changes, the new law expands the universe of references or disclosures that can potentially be asserted as "prior art" against a patent application, since the date of conception of the claimed invention is longer be a factor in excluding a reference from being asserted as "prior art." Thus, there may be additional publications or disclosures that qualify as "prior art" under the new law that would not qualify under the old law. Other changes under the AIA include changes to grace periods, institution of derivation proceedings, and changes to prior user rights.

WRM 3

The AIA 1 Year on: the New Landscape for Challenging Patents

Richard G. A. Bone, RBone@VLPLawGroup.com. VLP Law Group LLP, Palo Alto, CA 94303, United States

The America Invents Act (AIA) has altered the landscape of options for challenging patents both before and after grant. Third parties may now submit prior art into the files of pending applications over a longer window of time than was previously possible. There are now three further ways to challenge patents after grant. I will describe how each of these procedures can be used to best effect, and comment on experience obtained so far.

WRM 4

How does the new patent law impact the research of biotech scientists and managers

Alex Y. Nie, anie@foley.com. Intellectual Property, Foley & Lardner LLP, Palo Alto, CA 94304, United States

The new patent law, formally known as "The Leahy-Smith America Invents Act (AIA)" came into full effect on March 16, 2013. Many of the changes brought about in AIA, as compared to the earlier patent law, are towards harmonization with other jurisdictions in the world. The best known example is the move from a first-to-invent to a first-to-file system. Also provided are more avenues for a third party to challenge a pending patent application or an issued patent at the patent office. How do these change impact decision-making in biotech companies, at least with respect to record keeping, patent filing and prosecution timeline, and cost allocation? Does the new law increase or decrease an inventor's burden to demonstrate possession of invention? How would such changes in the US impact global intellectual property (IP) protection? This presentation will first summarize the changes of law at a high level, and then provide some thoughts and practical recommendations regarding IP prosecution and protection for biotech companies.

WRM 5

Traditional medicine inspired drug discovery for some modern day diseases

A. A. Leslie Gunatilaka, leslieg@ag.arizona.edu. Southwest Center for Natural Products Research, School of Natural Resources and the Environment, College of Agriculture and Life Sciences, University of Arizona, Tucson, Arizona 85706-6800, United States

Traditional medicines in many parts of the world make use of plants to treat a variety of diseases including cancer and neurological disorders that increasingly burden modern day society. In our studies directed towards discovery of drugs to treat these diseases, we have screened extracts derived from plants of the US Southwest and herbal supplements available in the US in a panel of cell-based cytotoxicity and functional assays including the heat-shock induction assay that targets heat-shock response. Of those tested, extracts derived from two plants of the family Solanaceae, *Withania somnifera* (winter cherry; Indian ginseng; Ashwagandha) and *Physalis crassifolia* (yellow nightshade ground cherry) proved to be promising. Detailed chemical and biological investigations of these were undertaken because *Withania* and *Physalis* species are employed in traditional medicines in Asia and South America to treat cancer and neurological disorders. Bioactivity-guided fractionation of extracts derived from these two plants led to the isolation and identification of several steroidal lactones belonging to the withanolide class. Given their potential as lead molecules for drug discovery and development, we have developed an innovative soil-less aeroponic technique for cultivation of these plants and efficient production of active withanolides in large quantities for animal and structure-activity relationship (SAR) studies. Our studies suggest the potential of withanolides as anticancer and anti-neurodegenerative agents and the possibility of modulating their biological activities by structural modifications that may lead to natural product-based drugs to treat these modern day diseases.

This work was supported by the U.S. National Cancer Institute/National Institutes of Health, U.S. Department of Agriculture, and Arizona Biomedical Research Commission

WRM 6

Scientific and regulatory challenges in the US Botanical Marketplace

Joseph M Betz, betzj@od.nih.gov. Office of Dietary Supplements, National Institutes of Health, Bethesda, MD 20892, United States

Botanical products sold in the US can fall within one of several regulatory categories, including supplements, foods, and drugs. The FD&C Act assigns products to the appropriate category based on “intended use” as ascertained by labeling claims, advertising materials, or statements made by product manufacturers or distributors. Regulatory requirements surrounding each category are different, and there remains confusion about manufacturing requirements and permissible claims within each category.

According to FDA estimates, when the Dietary Supplement Health and Education Act (DSHEA) became law in 1994, there were about 600 U.S. supplement manufacturers producing approximately 4,000 products. By the year 2000, there were more than 29,000 dietary supplement products on the market with an average of 1,000 new products being added annually. Current estimates put the number of plants in the marketplace at 3000 and the number of products at 75,000. This can be contrasted with FDA's approval of only two botanical drugs since over the same approximate timeframe, Veregen in 2006 and Crofelemer in 2012. Differences in the regulatory paradigms and associated scientific rigor and expense imposed by those paradigms explain this discrepancy.

The DSHEA defines supplements as a special category of food that requires only limited premarket review of new ingredients and no premarket approval of products. As a result, there is no review of efficacy by FDA, no mandatory formulation standards, and no product registration required. Botanical products that fall into the drug category require the filing of Investigational New Drug Applications (IND) and New Drug Applications (NDA) that require extensive pre-market acquisition, submission and agency approval of manufacturing and composition information, pre-clinical and clinical safety data, and efficacy data.

This talk will provide a brief overview of supplement regulations; problems encountered by research agencies when reviewing grant applications, and will highlight policies for assisting investigators address these issues.

WRM 7

The Discovery of SP-303 (Crofelemer/Fulyzaq), a Novel Polyphenol Isolated from *Croton lechleri*

Michael S. Tempesta, natprod@aol.com. Phenolics, LLC, El Granada, CA 94019-2439, United States

One of the most famous folk remedies in Peru and surrounding regions consists of a deep red sticky liquid collected from *Croton lechleri* tree sap known as Sangre de Drago or dragon's blood. It is still used as a treatment for gastrointestinal disorders as well as topical anti-infective bandage, with the latex drying on the skin. Early work found taspine, an alkaloid with wound-healing and anti-ulcerative properties. A sample from the NCI collection (Tim Plowman) in the early 1980's was provided for initial antiviral bioassay (Lederle Laboratories) and fractionation to find other active components at the University of Missouri-Columbia. Very potent found bioactivity was found in the major polyphenol-containing fractions, and this was the basis for further purification and structure work, which will be described.

The early antiviral testing was carried out by the NIAID in the 1990's.

WRM 8

The development of the first oral botanical drug Fulyzaq™: connecting ethnobotany, conservation, biocultural diversity, global public health and indigenous knowledge

Steven R. King¹, sking@napopharma.com, Pravin Chaturvedi¹, Franklin C Ayala Flores², Cesar Gregorio Lozano Diaz³, Enrique Kayap Tsajamen⁴, Graciela Chimpa Mashian⁴, Mario F. Pariona⁵, Elsa N. Meza⁵, Edith Lazaro Soto⁶. (1) Napo Pharmaceuticals Inc., San Francisco, CA 94107, United States (2) Amazon Natural Products, Iquitos, Peru (3) LCH Negocios y Servicios, Yurimaguas, Alto Amazonas, Loreto, Peru (4) Comunidad Nativa Yamakay, Rio Morona, Loreto, Peru (5) Oak Park, Oak Park, Illinois, United States (6) Comunidad Nativa Yarina, Oxapampa, Peru

Crofelemer is a novel first in class compound extracted, isolated and purified from the stem bark latex of the widespread rapidly growing tree species *Croton lechleri*, (Sangre de Drago). The latex of this species is utilized orally by numerous indigenous and local peoples of the western Amazon basin for the treatment of diarrhea and many other therapeutic applications. Indigenous peoples discovered how to treat diseases with plant medicines several millennia before the development of the western scientific disciplines of chemistry, pharmacognosy and ethnobotany.

A new drug application (NDA) for Fulyzaq™ (Crofelemer), for the treatment of HIV/AIDS related chronic diarrhea, was approved by the US FDA on December 31, 2012. Clinical trials have also been conducted at the International Center for Diarrheal Disease Research (ICDDR) in Dhaka, Bangladesh, demonstrating significant reduction in fluid loss in patients with cholera-induced diarrhea. One goal of Napo is to make certain that crofelemer is made available to save lives in cholera outbreaks.

Crofelemer cannot be produced synthetically due to its complex chiral chemistry. The authors have created long-term sustainable production programs for *Croton lechleri* in collaboration with local business partners and communities. This includes reforestation research, large scale reforestation and management activities. Cultivation and wild harvest provides income to local communities. The development of crofelemer has also supported the conservation of biocultural diversity and will provide for long-term benefit sharing through the Healing Forest Conservancy (HFC).

Diarrhea continues to kill more than 2 million children per year and is one of the major causes of childhood illness and death. Napo and its partners are focusing on the development of a pediatric form of crofelemer that can be distributed to pediatric patients, to be used in combination with ORS and zinc, to prevent the severe dehydration and resulting death caused by infectious diarrhea in children.

WRM 9

Crofelemer: a Novel Antidiarrheal Medicine from the Amazon Rainforest-Mechanism of Action and Clinical Applications

Thomas J. Carlson, tcarlson@berkeley.edu. Department of Integrative Biology, University of California, Berkeley, Berkeley, CA 94720, United States

The red latex from the Amazon rainforest tree, *Croton lechleri*, is used as an oral treatment of watery diarrhea in South American rainforests. Crofelemer, a proanthocyanidin oligomer molecule, was extracted from *Croton lechleri* and found to be the primary active molecule. Studies have demonstrated that orally administered crofelemer treats watery diarrhea in humans through an anti-secretory mechanism. The mechanism of action is through the blockage of the CFTR and CaCC chloride ion channels. This medication works through a novel mechanism to treat watery diarrhea in humans.

WRM 10

65 years as a nuclear chemist - a retrospective view

Darleane C Hoffman, *darlhoffman@gmail.com*. Nuclear Science Division, Lawrence Berkeley National Laboratory, Berkeley, CA and Department of Chemistry, University of California, Berkeley, CA 94720, United States

I fondly remember my freshman year (1944) at Iowa State College where I began in Applied Art, but also had to take freshman chemistry, taught by Professor Nellie Naylor. Her lectures were so logical and clear, emphasizing chemistry as a fundamental science with many opportunities for both fundamental and applied research, that I changed my major to chemistry! Subsequent undergraduate research in nuclear chemistry exposed me to the thrill of discovering new isotopes, convincing me to study nuclear chemistry. I earned my B. S. in chemistry (nuclear) in 1948, some 65 years ago, and the Ph. D. in nuclear chemistry (1951). My subsequent career involved both fundamental and applied research. From the perspective of more than 65 years later, I will review changes in nuclear chemistry and radiochemistry and the dramatic changes in the status of women.

WRM 11

Darleane C. Hoffman: An element of success

Kimberly Thomas, *kwthomas@lanl.gov*. Los Alamos National Laboratory, Los Alamos, NM 87545, United States

Darleane C. Hoffman has had and continues to have a stellar career as one of the most preeminent nuclear scientists of our age. Her contributions to understanding symmetric nuclear fission and electron capture delayed fission processes were characterized by Glenn Seaborg as "probably the most important discovery in the understanding of the fission process in the last quarter century (20th)". Her work in isolating Pu-244 from natural bastnasite ore set a new standard for meticulous chemical separations of 10^{-15} g from kgs of starting material. Her "atom-at-a-time" heavy element investigations have elucidated chemical properties of rutherfordium through hassium along with confirming the 1974 discovery of element 106 paving the way for the official naming of the element "seaborgium" by IUPAC. For these and many other ground-breaking contributions to nuclear science, Darleane has been recognized with a myriad of awards, including the American Chemical Society's Priestly Medal ('00) and the US President's National Medal of Science ('97). These accomplishments are only part of her legacy, however. Perhaps even more important have been her contributions to future generations of nuclear scientists. She has stated that one of her own role models was Marie Curie and I'm sure Darleane's career would have received praise from Madam Curie. However, Darleane has built upon the successes of the likes of Madam Curie by expanding her role beyond the joys of science and discovery to include the joys of mentoring, mothering, friendships, and fun! She has been an outstanding role model for both women and men. She has been a superb and effective teacher. Her students are now teaching, leading, and nurturing future generations in the field in their own right. Today, she is still a role model and mentor to many of us and this talk will highlight some of her inspirational influences and legacies.

WRM 12

Tribute to Prof. Darleane Hoffman: Pioneering nuclear chemist and architect of the next generation

David E. Hobart, *dhobart15@gmail.com*. National Security Education Center, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, United States

In celebrating the significant contributions of Darleane Hoffman, it is fitting that we pay tribute to her lifetime achievements and scientific discoveries. Scientist, author, leader, mentor, educator, conference organizer, committee member, element discoverer, and stateswoman, she is an internationally recognized expert in the study of the actinide and transactinide elements. Darleane has broken many glass ceilings in her role as a female scientist in a formerly male-dominated discipline. She was the first female division leader at Los Alamos National Laboratory and the second female on the chemistry faculty of the University of California, Berkeley where she continues to educate the next generation of students in nuclear and radiochemistry. Darleane was co-founder of the Seaborg Institute at Lawrence Livermore National Laboratory and served as its first director. The discoveries and achievements of the Grand Dame of nuclear chemistry have touched the lives of many and her legacy will continue for generations to come.

WRM 13

The many elements of Darleane Hoffman: A grateful student comments on her accomplishments and influences

Mary P Neu, *mneu@lanl.gov*. Los Alamos National Laboratory, Los Alamos, NM 87544, United States

Darleane Hoffman inspires radiochemists, transuranic researchers, and generations of scientists. Her interests and impacts extend well beyond her seminal contributions to heavy element chemistry, and into the fields of radionuclide migration in the environment, chemical separations, trace element analysis, chemical automation, and women in science. Throughout her career, Darleane, has been an exemplary leader in serving the scientific community. She championed nuclear- and radiochemistry on IUPAC and ACS committees, served on countless advisory groups for the U.S. DOE and other federal agencies, and co-led the creation and expansion of the G.T. Seaborg Institutes at the U.C. managed national laboratories. Darleane is among the most accomplished and recognized women scientists, having received the National Medal of Science, the ACS Priestley and Garvan-Olin Medals, and many other major awards. Throughout her career she also mentored and championed other scientists, supporting them to lead and garnering recognition for their accomplishments. Darleane was “Leaning In” well before the concept was en vogue. In this talk I will briefly highlight just a few of her many technical contributions and, using my own career as an example, describe her impact as a mentor.

WRM 14

Success of the Glenn T. Seaborg Institute at Lawrence Livermore National Laboratory is due in large part to the pivotal vision and leadership of its first director, Dr. Darleane Hoffman.

Annie B. Kersting, *kersting1@llnl.gov*. Glenn T. Seaborg Institute, Lawrence Livermore National Laboratory, Livermore, CA 94550, United States

Dr. Darleane Hoffman was instrumental in the establishment of the LLNL branch of the Glenn T. Seaborg Institute. As its first director, Dr. Hoffman's vision and leadership helped establish the Institute as a national center for the education and training of undergraduate and graduate students, postdocs and faculty in actinide science. The scientific staff conducts collaborative research with the academic community in radiochemistry, nuclear forensics and super heavy element discovery.

- *Radiochemistry*: We are focusing on understanding the fate and transport of actinides in the environment. Current research is focused on determining the dominant biogeochemical processes that control actinide transport in soil and groundwater at low environmental concentrations and nanoscales.
- *Forensics*: A major focus of nuclear and biological forensics is identifying signatures, which are the physical, chemical, and isotopic characteristics that distinguish interdicted illicit nuclear, biological, or radioactive material from one another. Signatures enable researchers to identify the processes used to initially create materials.
- *Heavy Element Discovery*: Research in the discovery of super heavy elements currently focuses on investigating the chemical and physical properties of the heaviest man-made elements in efforts to understand fundamental nuclear research, with spectroscopic, chemical, and decay studies.

- *Education:* The Seaborg Institute hosts a yearly summer research program designed to give graduate students hands-on research opportunities at LLNL. Students conduct research under the supervision of a staff scientist, and present their work at the end of the summer. This program facilitates the training of the next generation of nuclear scientists and engineers to solve critical national security problems in the field of radiochemistry and nuclear forensics. This program has created a successful pipeline of top quality students. Since 2002, 12 have become postdoctoral fellows, and 10 have been hired as career scientists at LLNL, 3 have faculty appointments and 3 are staff scientists at other national laboratories.

WRM 15

Insights in enzyme modification for renewable solar hydrogen

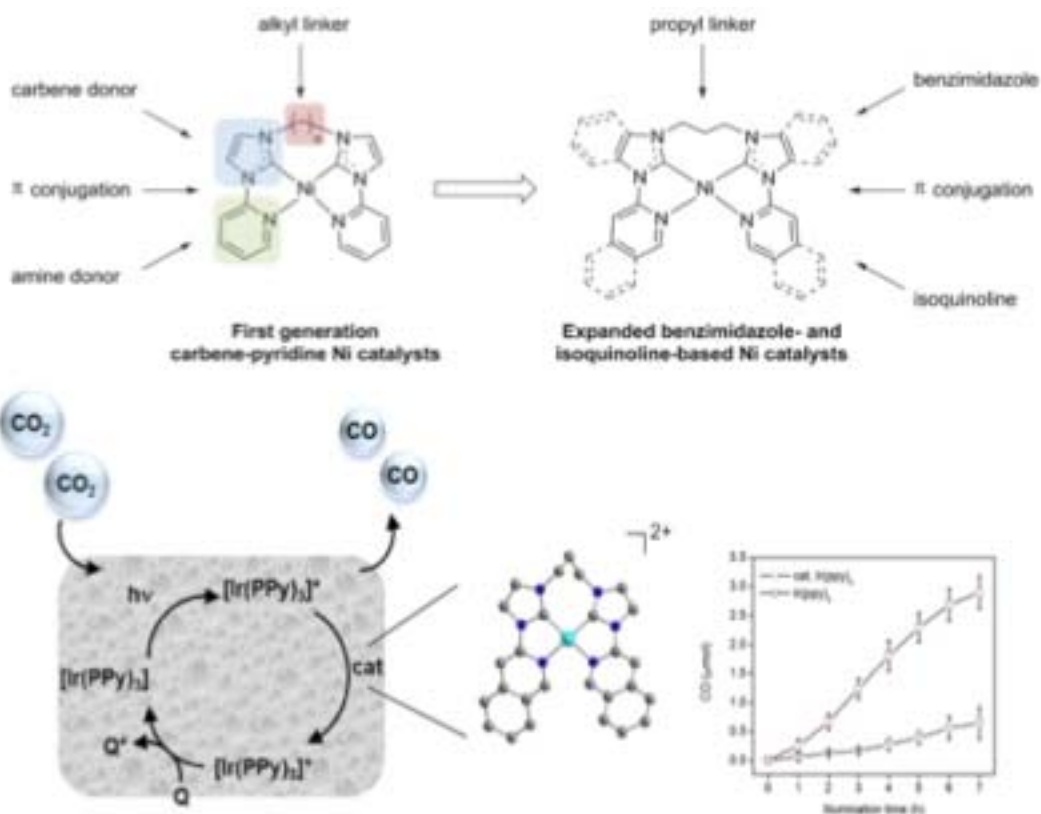
Isaac T Yonemoto, *iyonemot@jcvl.org*, Phillip D Weyman, Hamilton O Smith. Department of Synthetic Biology and Bioenergy, J Craig Venter Institute, San Diego, CA 92121, United States
I discuss our efforts at “synthetic biochemistry”: using a first principles understanding to modify enzymes at the residue level to improve activity. In the example of [NiFe] hydrogenase, our objective is to improve the activity of the hydrogen-oxidizing enzyme in the proton-reducing direction, with an eye towards coupling the enzyme to biological photosystem. Our strategies are guided by basic chemistry, while only somewhat constrained by observations gleaned from traditional bioinformatic analysis. For example, two amino acid substitutions affecting electron transport result in a >3x improvement in proton reduction activity. Although we observe favorable results, some of our data remain unexplained at a basic level, leaving some open mechanistic questions to be answered.

WRM 16

Visible light photoredox catalysis: Selective reduction of carbon dioxide to carbon monoxide by a nickel N-heterocyclic carbene-isoquinoline complex

Nikolay Kornienko, *nick_kornienko@yahoo.com*, Sara V Thoi, Charles Margarit, Peidong Yang, Christopher Chang. Chemistry, UC Berkeley, Berkeley, California 94709, United States

The solar-driven reduction of carbon dioxide to value-added chemical fuels is a longstanding challenge in the fields of catalysis, energy science, and green chemistry. In order to develop effective CO₂ fixation, there are key considerations that must be balanced, including: 1) catalyst selectivity for promoting CO₂ reduction over competing hydrogen generation, 2) visible-light harvesting that matches the solar spectrum, and 3) the use of cheap and earth-abundant catalytic components. We present a new family of earth-abundant nickel complexes supported by simple N-heterocyclic carbene-amine ligands that exhibit high selectivity for the electrocatalytic and photocatalytic conversion of CO₂ to CO. Systematic changes in the carbene and amine donors of the ligand have been surveyed for electrochemical reduction of CO₂ in terms of current density and catalytic onset potential. Using an earth-abundant [Ni(^{Pr}bimiq1)]²⁺ (where ^{Pr}bimiq1 = bis(3-(imidazolyl)isoquinolyl)propane catalyst with Ir(ppy)₃ (where ppy = 2-phenylpyridine) and an electron donor, we have developed a visible-light photoredox system for the catalytic conversion of CO₂ to CO that proceeds with high selectivity and activity and achieves turnover numbers and turnover frequencies reaching 98,000 and 3.9 s⁻¹, respectively. Further studies reveal that the overall efficiency of this solar-to-fuel cycle may be limited by the formation of the active Ni catalyst and/or the chemical reduction of CO₂ to CO at the reduced nickel center and provide a starting point for improved photoredox systems for sustainable carbon-neutral energy conversion.



WRM 17

Synthesis, crystal structure, and transport properties of a new Li-containing layered material, Li_xSn_{3-x}As₂

Kathleen Lee, ktlee@ucdavis.edu, Kirill Kovnir. Department of Chemistry, University of California, Davis, Davis, CA 95616, United States

Li-intercalation compounds are a class of materials that have generated much interest for uses as Li-ion battery electrode materials and as ionic conductors in solid-state electrolytes. Herein we report the synthesis and structural and electronic characterization of the novel Li-intercalation compound, Li_xSn_{3-x}As₂ (0.65 ≤ x ≤ 0.8). The crystal structure of Li_xSn_{3-x}As₂ can be described as an analog of a hypothetical binary compound Sn₃As₂, which is similar to the binary pnictide, Sn₄As₃. Sn₃As₂ consists of alternating layers of Sn and As atoms that are combined in 5-atom thick blocks that stack along the c-axis. Similarly, the crystal structure of Sn₄As₃ has 7-atom thick blocks stacked along the c-axis. The crystal structure of Li_xSn_{3-x}As₂ is similar to Sn₃As₂, but a portion of the Sn atoms in the central layer is randomly substituted with Li atoms. Mössbauer spectroscopy confirms the presence of two types of Sn atoms. ⁷Li solid-state NMR spectroscopy indicates possible local ordering of the Li and Sn atoms. Li_xSn_{3-x}As₂ exhibits a homogeneity range and variation in unit cell volume with varying Li content. Metallic properties and the anisotropic electrical resistivity are supported by the anisotropic crystal structure and quantum chemical calculations. Further electronic, magnetic and electrochemical properties of this compound will be discussed.

WRM 18

Selective light-driven aerobic hydroxylation of C-H bonds using hybrid P450 biocatalysts.

Lionel E Cheruzel. Chemistry, San Jose State University, San Jose, CA 95192-0101, United States

Selective functionalization of unactivated C-H bonds using molecular dioxygen as the sole oxidant remains one of the holy grail of catalysis. The Cytochrome P450 superfamily of heme-

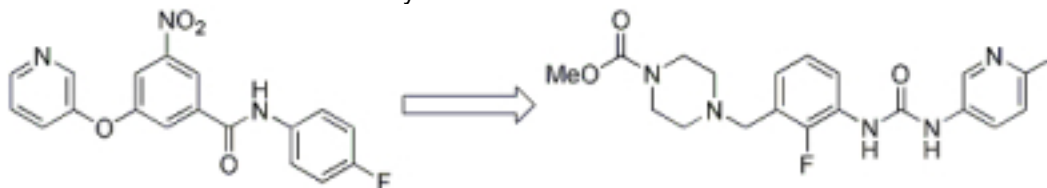
thiolate enzymes catalyzes a myriad of oxidation reactions often with high regio and stereo selectivity using molecular dioxygen as the source of oxygen atom and two reducing equivalents. Our laboratory has focused on utilizing the photochemical properties of Ru(II)-diimine complexes covalently attached to non-native single cysteine residue of P450 heme domain mutants in order to provide the necessary electrons to the heme domain and utilize their synthetic potential to perform light-driven hydroxylation reactions. The optimization of the hybrid enzymes has led to efficient biocatalysts capable of performing the selective hydroxylation of organic substrates with high total turnover numbers and catalytic rates.

WRM 19

Discovery of the First Small Molecule Activators of Cardiac Myosin for the Treatment of Heart Failure

Alexander R. Muci, amuci@cytokinetics.com, Department of Medicinal Chemistry, Cytokinetics, Inc., South San Francisco, CA 94080, United States

The design, synthesis, and optimization of the first, selective activators of cardiac myosin are described. Starting with a poorly soluble, nitro-aromatic hit compound, potent, selective, and soluble myosin activators with improved pharmacokinetics were designed and prepared, culminating in the discovery of *omecantiv mecarbil*. *Omechantiv mecarbil* is currently in Phase IIb clinical trials for the treatment of systolic heart failure.



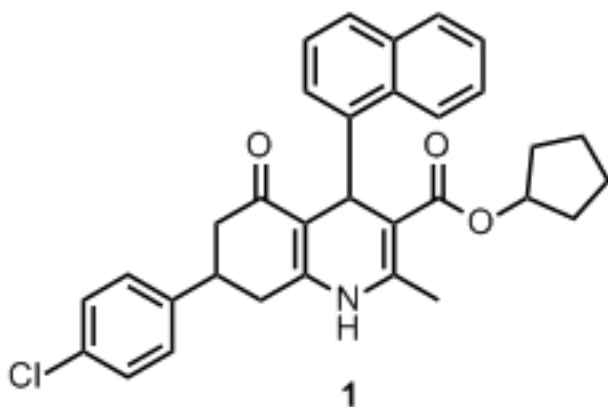
WRM 20

Hit-to-Lead Optimization of a Pan-Genotypic Tetrahydroquinoline Scaffold for the Treatment of HCV

Eda Canales¹, Eda.Canales@Gilead.com, **Kerim Babaoglu**³, **Rudolf Beran**², **Caroline Bush**², **Michael Clarke**¹, **Sara Eng**⁴, **Robin Higgins**¹, **Tetsuya Kobayashi**¹, **Ruben Martinez**¹, **Philip Morganelli**¹, **Bernard Murray**¹, **Roland Saito**¹, **Hung Trinh**⁴, **Matthew Paulson**², **Scott Lazerwith**¹.
(1) Department of Medicinal Chemistry, Gilead Sciences, Foster City, CA 94404, United States
(2) Department of Biology, Gilead Sciences, United States (3) Department of Structural Chemistry, Gilead Sciences, United States (4) Department of Drug Metabolism, Gilead Sciences, United States

There are 6 major genotypes of hepatitis C virus (HCV), and several more subtypes. The chronic infections caused by this family of viruses are a leading cause of cirrhosis, liver cancer, and liver transplantation worldwide. In the past decade, intensive efforts have focused on the discovery of novel antiviral agents to improve both the tolerability and efficacy of HCV therapy, as compared with the current standard treatment of peginterferon, ribavirin and telaprevir or boceprevir. Although there have been numerous studies of small molecules designed to treat HCV with varying modes of action, the majority of these therapeutics are limited to activity against genotype 1 infection. Thus, there is an urgent need for new agents with broader or even pan-genotypic efficacy.

The title presentation will describe the SAR exploration and optimization of a hit molecule identified from an in-house screening library. These efforts led to the identification of a lead compound with potent pan-genotypic activity (HCVcc EC₅₀2a = 23 nM, 1b/2a = 24 nM), improved physicochemical properties (Log D 3.1) and improved microsomal stability (T_{1/2} = 48 min).



WRM 21

Small Molecule BTK Inhibitors: an Update from Pharmacyclics

Zhaozhong J Jia, zjia@pcyc.com. Medicinal Chemistry, Pharmacyclics, Inc., Sunnyvale, CA 94085, United States

Pharmacyclics' ibrutinib (PCI-32765) is a first-in-class small molecule inhibitor for Bruton's tyrosine kinase (BTK) under Phase III clinical development for B cell malignancies. It binds covalently to Cys481 of BTK and suppresses B cell receptor (BCR) activation of primary B lymphocytes. Ibrutinib's discovery and some of our recent work for identifying a backup covalent inhibitor for BTK will be discussed.

WRM 22

Identification of Potent, Selective and Orally Bioavailable TYK2 Inhibitors for Psoriasis and Inflammatory Bowel Diseases (IBD)

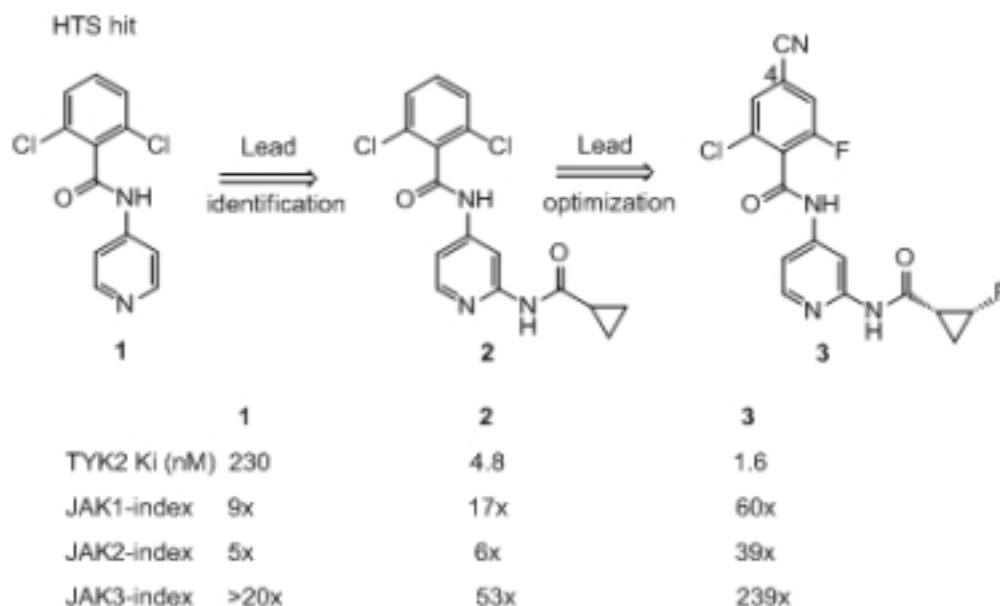
Jun Liang, liang.jun@gene.com. Discovery Chemistry, Genentech, South San Francisco, California 94080, United States

The Janus kinases (JAKs) are a family of four protein tyrosine kinases (JAK1-3 and TYK2) that regulate a wide range of cytokine and growth factor receptors that mediate inflammation and hematopoiesis. To block interleukin-12 (IL-12) pathways, we sought potent and selective TYK2 inhibitors, as potential therapy for psoriasis and IBD.

Compound **1** was identified as an ATP-competitive hit through HTS. Docking suggested the pyridine N hydrogen-bond to backbone NH of TYK2 hinge. To improve potency, a second hinge binder, in the form of cyclopropylamide (**2**), was introduced. Co-crystal structures of **2** with TYK2 and JAK2 were obtained to guide optimization. P-loop conformation was significantly different between the two enzymes, so C4-nitrile was designed to exploit this difference while blocking metabolism. There was a residue difference in the area where cyclopropyl group was bound: Arg901 in TYK2 vs. Gln853 in JAK2. (1*R*,2*R*)-2-fluorocyclopropyl showed improved TYK2 potency and JAK2-selectivity. Combining the two moieties, and replacing a Cl with F to lower cLogD, led to compound **3**. It was potent and selective in cell assays and blocked IL-12 pathway in vitro, as measured by interferon-gamma (IFN γ) production in human whole blood.

3 exhibited excellent oral exposure in mouse, and was further evaluated in IL-12 mouse PK/PD model. Statistically significant, dose-dependent response was observed, demonstrating for the first time that selective inhibition of TYK2 is an effective way to block IL-12 pathway in vivo.

Figure 1: Lead identification and optimization of TYK2 inhibitors

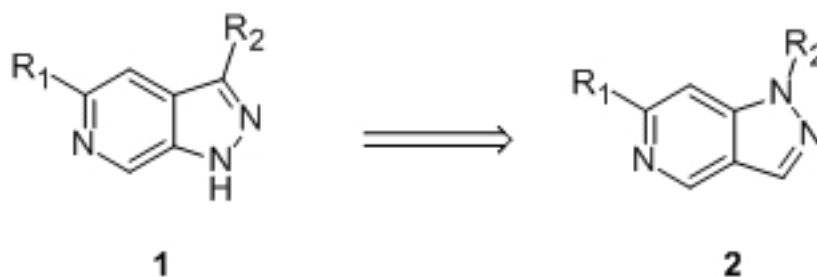


WRM 23

Discovery of potent and bioavailable Pim inhibitors for multiple myeloma

Xiaoqing Wang, wang.xiaoqing@gene.com. Department of Discovery Chemistry, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, United States

Pim kinases are emerging as promising targets for the development of cancer therapeutics. Two experimental Pim inhibitors, AZD-1208 and LGH447, are currently in phase-1 clinical trials for hematological and solid tumors. This talk will describe our efforts in discovering potent and bioavailable Pim inhibitors targeting multiple myeloma (MM). 6-Azaindazole analogs **1** were identified through a fragment-based approach based on an internal library hit. Analogs of **1** have excellent Pim potency both in biochemical and cellular assays. However, they have close to zero bioavailability in rat despite exhibiting low to moderate clearance as well as moderate in vitro permeability and solubility. In vitro metabolite identification (Met-ID) revealed the major metabolite and potential hot spots of metabolism. Further studies identified intestine as the major site of metabolism. Based on these information, we designed new analogs **2** which drastically improved the bioavailability while maintaining good Pim potency.



WRM 24

Using the Tools of Green Chemistry and Biomimicry to Identify new Functional BioBased Chemicals for Industrial Applications.

Martin J Mulvihill, marty_m@berkeley.edu. Center for Green Chemistry, UC Berkeley, Berkeley, Ca 94720, United States

To effectively advance Biobased feedstock development, new approaches are needed to integrate synthetic biology, green chemistry, and chemical/biological/toxicological informatics. The successful development—and adoption by society—of new safer biobased chemicals hinges on the integration of knowledge in chemistry and engineering with an understanding of the health and ecosystem impacts of chemicals. This presentation will explore how computational tools and biomimicry can be used to identify, design, and sustainably produce inherently safer chemicals.

WRM 25

Biobased chemicals and fuels in historical and economic perspective

Abraham Ringer, aringer@berkeley.edu. Department of Environmental, Science, Policy and Management, University of California, Berkeley, Berkeley, CA 94720, United States

In recent years, cracks have begun to appear in what for decades has been the long-term stable dominance of petroleum-based technological regimes in both the chemicals and fuels production industries. In particular, biotechnology, already an important force in pharmaceuticals and industrial agriculture, has developed to the point where it now may make sense as a major production platform even in these more capital-intensive, lower-margin businesses and there has been considerable investment into biobased chemicals and fuels from incumbent producers and upstart capital alike. This talk will chart the current landscape in biobased chemicals production, looking at both structural and systems aspects and comparing it to historical cases of technological change in chemicals, fuels, and other industries.

WRM 26

Cost effective production of cellulosic two and three carbon molecules using the ZeaChem process

Bryan Yeh, byeh@zeachem.com. ZeaChem, Inc, Menlo Park, CA 94025, United States

The market for two carbon (C₂) and three carbon (C₃) molecules such as acetic acid and propionic acid are worth \$485 and \$595 billion respectively. The key to penetrating these markets is to offer a fungible product that can be produced at costs below those made with petroleum feedstock yet offer the attribute of being renewable. ZeaChem has developed a cellulosic biochemical process that has a 40-50% higher yield than other processes, yet leverages mature technology to enable commercialization with favorable economics. In February, 2013, ZeaChem produced cellulosic ethanol from its demonstration facility in Boardman, Oregon using hybrid poplar. The same process also produced cellulosic acetic acid as well as cellulosic ethyl acetate. This paper will highlight the integrated process from biomass hydrolysis to hydrogenation and describe the current economics and pathway to commercialization.

WRM 27

Small molecule modulators of lipid production in microalgae and NMR spectroscopic analysis of lipids for biofuel applications

Lisa A. Anderson, laanderson@ucdavis.edu, Diana M. Wong, Megan A. Danielewicz, Jordon R. Boothe, Annaliese K. Franz. Department of Chemistry, University of California, Davis, Davis, CA 95616, United States

This research aims to improve current microalgae biofuel technology by modulating lipid production with chemical triggers, catalyzing conversion to biodiesel, and determining lipid composition for fuel properties. We have developed a phenotypic assay for analysis of intracellular lipids using Nile Red fluorescence in order to screen a collection of diverse bioactive organic molecules with four strains of commercially-viable oleaginous microalgae (*N. salina*, *N. oculata*, *Nannochloris* sp., and *P. tricornutum*). Several small molecules identified in microplate screening increased lipid productivity >200% without decreasing growth and biomass production. Lead compounds were further investigated in the context of larger batch culture experiments (e.g., 500 mL) and demonstrated to increase lipid levels while maintaining or increasing the specific growth rate. Bioactive molecules such as forskolin and quinacrine were identified as

promising probes of microalgae lipid pathways and antioxidants such as epigallocatechin gallate (EGCG) and butylated hydroxyanisole (BHA) may represent new probes of oxidative signaling pathways. Several compounds are relevant and economically viable for industrial applications based on a cost analysis of quantities for large-scale microalgae biofuel production. Lipid extracts have been evaluated by NMR spectroscopy and GCMS. The conversion of TAGs to biodiesel has been investigated by real-time NMR spectroscopy.

WRM 28

Use of Osmium (III) Complexes to determine influence of base mismatches on DNA-Protein Crosslinking

Kelsey R Miller, *kelsmill@mymsmc.la.edu*, **Zitadel A Perez**, *Eric D.A. Stemp*. Department of Physical Sciences and Mathematics, Mount St. Mary's College, Los Angeles, California 90049, United States

8-oxoguanine is a common oxidation product in DNA and can lead to missense mutations. The metallointercalator $\text{Ru}(\text{phen})_2\text{dppz}^{2+}$ is a useful luminescent probe for DNA that has also found use as a guanine-selective oxidizing agent via the flash-quench technique. Here, we introduce its osmium analogue as a way to selectively oxidize 8-oxoguanine in double-stranded DNA. As visualized by DNA-protein crosslinking and Maxam-Gilbert sequencing. With a $3+/2+$ couple of 1.15 V, $\text{Os}(\text{phen})_2\text{dppz}^{3+}$, this metallointercalator should be able to oxidize 8-oxo-G (~ 0.7 V) without oxidizing guanine (~ 1.3 V). MALDI mass spectrometry data confirms that oxidizing guanine using $\text{Ru}(\text{NH}_3)_6^{3+}$ and $\text{Ru}(\text{phen})_2\text{dppz}^{2+}$ produces 8-oxoguanine. In plasmid DNA where 8-oxo-G has been incorporated as above, further flash-quench treatment with $\text{Os}(\text{phen})_2\text{dppz}^{2+}$ and $\text{Co}(\text{NH}_3)_5\text{Cl}^{2+}$ leads to crosslinking with histone protein in gel shift experiments. Furthermore, in gel shift experiments with a duplex of the oligonucleotide 5'-ATATGATAT8GATATGATAT-3' (8 = 8-oxo-G), flash-quench treatment with $\text{Ru}(\text{phen})_2\text{dppz}^{2+}$ in the presence of histone produces a band of intermediate mobility (presumably 1:1 crosslink) and well-shifted material. In contrast, analogous treatment with $\text{Os}(\text{phen})_2\text{dppz}^{2+}$ produces only the band of intermediate mobility, consistent with the presence of only a single site that is oxidizable by the osmium complex. A Maxam-Gilbert sequencing gel shows damage only at the 8-oxo-G site upon flash quench treatment with the osmium complex, as expected. Lastly, control experiments indicate that with a duplex of the oligonucleotide 5'-ATATGATATGGATATGATAT-3' flash quench treatment with $\text{Ru}(\text{phen})_2\text{dppz}^{2+}$ in the presence of histone produces well-shifted material, whereas treatment with $\text{Os}(\text{phen})_2\text{dppz}^{2+}$ does not produce crosslinked material, as expected since the osmium (III) complex formed should not be capable of guanine oxidation. Taken together, these results show that $\text{Os}(\text{phen})_2\text{dppz}^{2+}$ is a promising selective oxidant of 8-oxoguanine in double stranded DNA.

WRM 29

Metal dependence of the Mre11 DNA repair nuclease

Oswaldo D. Rivera^{1,2}, *odrg95@gmail.com*, **Tasida Barfoot**¹, **Yang Gao**¹, **Scott W. Nelson**¹. (1) Biochemistry, Biophysics & Molecular Biology, Iowa State University, Ames, IA, United States (2) Ciencias y Tecnología, Universidad Metropolitana, San Juan, Puerto Rico

The Mre11 protein, along with Rad50, forms a four-subunit complex that is involved in the primary step of DNA double-stranded break (DSB) repair. DSBs are the most drastic form of DNA damage and if incorrectly repaired may lead to rearrangements of chromosomal DNA, cellular dysfunction, and cancer development. Mre11 is a nuclease (i.e., a DNA degrading enzyme) that requires the presence of divalent metal cations in its active site for proper enzymatic activity. The affinity of Mre11 for these metals and the type of metals that may be used for its nuclease activity are not known. The goal of this project is to determine the relative affinities for a variety of potential metal cations and to characterize the activity of Mre11 with these cations. Mre11 is known to have an active site with a special affinity for Mn^{2+} . Other metals, Mg^{2+} , Zn^{2+} , Ca^{2+} , and Ni^{2+} , were chosen not only because some of these biologically relevant divalent cations may support nuclease activity, but also because they may exhibit some interesting mechanistic differences. Through the use of 1-position 2-aminopurine nuclease assays, we can determine how enzyme activity varies from metal to metal, and if some of these metals can also act as

potential inhibitors. The assays revealed readily detectable nuclease activity using Mg^{2+} , in addition to the already supported Mn^{2+} . They also indicated that the Mre11 active site was highly specific for these two divalent cations, as none of the others exhibited any measurable nuclease activity. The most plausible kinetic mechanism model for the Mg^{2+} supported reaction showed that, unlike Mn^{2+} , Mg^{2+} and the DNA substrate show no binding synergism. This suggests that the Mg^{2+} bound in the active site of Mre11 is unable to form an interaction with the DNA substrate.

WRM 30

New wide pore C18 phase for fast and efficient purification of peptides by flash chromatography

Melissa Wilcox, *melissa.wilcox@grace.com*, **Joseph Bystron**, *joe.bystron@grace.com*, **Mark Jacyno**, *mark.jacyno@grace.com*, **Chitra Sundararajan**, *N.K. Bopanna*, **Reno Nguyen**, *reno.nguyen@grace.com*. *Grace Discovery Sciences, Deerfield, IL 60015, United States*

Peptides and proteins are becoming increasingly popular for their potential use as therapeutic drugs. To earn and maintain a share in the fast-growing peptide market, peptide researchers and manufacturers are constantly trying to improve and optimize the various steps in peptide synthesis.

One of the main bottlenecks in peptide synthesis is the purification step. Techniques such as FPLC and Preparative HPLC are limited by small loading amounts, long separation times, poor recoveries and high costs.

In this work, we demonstrate that flash chromatography can be a powerful tool in the fast and efficient purification of a diverse range of peptides. A new wide pore C18 phase expands flash purification capabilities to larger sized peptides, while providing better resolution. We present data to show the benefits of higher loading and faster purifications in peptide purification. This rapid purification technique ensures less degradation of peptides and provides better recovery, yields and purity.

WRM 31

Biosynthetic, stimulus-sensitive protein brushes inspired by neurofilament sidearm domain

Nithya Srinivasan, *nithya@berkeley.edu*, **Maniraj Bhagawati**, **Badriprasad Ananthanarayanan**, **Sanjay Kumar**. *Department of Bioengineering, University of California, Berkeley, Berkeley, CA 94720, United States*

The grafting of polymer chains onto surfaces at high density to yield “polymer brush” coatings is a widely employed strategy to reduce biofouling and interfacial friction. Here we report the design, development, and characterization of synthetic intrinsically disordered proteins (IDPs) based on the C-terminal sidearm domain of the human neurofilament heavy chain protein. Dynamic light scattering measurements indicate that the recombinant wild type protein adopts an extended conformation with a hydrodynamic radius of ~ 10 nm, much larger than the expected value for a folded protein. This macromolecule adopts an extended, disordered conformation in solution and can be grafted at high density in an oriented fashion to solid supports, as measured by quartz crystal microbalance with dissipation studies. The resulting IDP brushes are responsive to multiple stimuli such as solution pH and ionic strength. The swelling and collapsing behavior of the brush exhibits similar salt-dependence and comparable dynamic range to a synthetic, weak polyelectrolyte brush. This study provides evidence that stimuli-responsive polymer brushes can be fabricated from proteins and introduces these molecules as a new class of “smart” biomaterial building blocks.

WRM 32

Analysis of chemical changes in soil composition due to the effects of plant growth

Paul Johnson¹, **Ling Huang**², *Ling.Huang@scc.losrios.edu*. (1) *Software Development, Davis, CA, United States* (2) *Chemistry, Sacramento City College, Sacramento, CA, United States*

A garden experiment was carried out to determine and investigate any changes in soil composition due to the introduction of plants. Chemical, statistical and soil analyses were conducted. The environmental experiment conducted is for illustrative purpose only. Similar analyses could be conducted if you were to examine the effects of invasive species over native species on any change in soil composition. Mint, grass, lavender and wild flowers were planted in pots together with a control (a pot of loose soil). No fertilizer was added and the plants/controls were watered every other day with equal amounts of water. The soil was analyzed before potting and was analyzed after sufficient growth of the plants (approximately 4-6 months). A store bought soil test was used to analyze the pH, nitrogen, phosphorous and potassium levels. Lab spectrophotometer and atomic absorption spectroscopy were used to find levels of magnesium, calcium, phosphorous, nitrogen, zinc and iron. The soil test results using all three methods were compared and examined including 'before' and 'after' value comparisons.

Keywords: environmental chemical analysis, standard test, lab spectrophotometer, atomic absorption, spectroscopy.

WRM 33

Phytotoxicity and reduced translocation during root uptake of organic contaminants by wheat seedlings

Anfei He, *Oheanfei@tongji.edu.cn*, Yang Chen, Daniel Sheng. Department of Environmental Science, Tongji University, Shanghai, China

Elucidating the mechanism of plant uptake of organic pollutants is critical to the understanding of both crop contamination and phytoremediation in the contaminated environment. This study was conducted to evaluate the phytotoxicity and in turn reduction in the plant uptake of organic compounds. The root uptake of 4-chloro-3-methylphenol (CMP) by wheat seedlings from water at a constant CMP concentration and its subsequent translocation were determined. Meanwhile, the plant transpiration, lipid peroxidation and changes in fatty acid profiles were also quantified. At the CMP concentration of 45 mg/L, its uptake reached maxima of about 19.6 mg/kg in shoots and 61.7 mg/kg in roots. The transpiration substantially slowed down from 1.13 to 0.51 mg/mg/d within the initial 24 h of uptake. These observations indicated the phytotoxicity of CMP to wheat seedlings and, as a result, reduced transpiration leading to diminished CMP translocation from roots to shoots. Malondialdehyde (MDA), a lipid peroxidation metabolite, in shoots increased to an extremely high level following 12 h of CMP root uptake, but decreased markedly in roots in 48 h, which indicated that shoots initiated a self-protection mechanism adapting themselves to lipid peroxide damage, while roots suffered severely. This damage to plant cells changed the fatty acid profiles that in 48 h two of the major fatty acids (C16:0, C18:1) decreased while C18:3 increased in shoots. In roots C16:0 and C18:1 increased while C18:2 decreased. These changes manifested increased root cell permeability but decreased shoot cell permeability during CMP uptake. CMP was clearly toxic to wheat seedlings and reduced its root-to-shoot translocation.

WRM 34

Trace determinations of hexavalent chromium in soil using automated solvent extractions and ion chromatography

Terri T Christison, *terri.christison@thermofisher.com*, Richard Jack, Lipika Basumallick, Linda Lopez. Thermo Fisher Scientific, Sunnyvale, CA 94088, United States

Hexavalent chromium, Cr (VI), or chromate is an industrial contaminant from plating, steel production, chemical, and leather tanning industries. Although chromium III is an essential nutrient, hexavalent chromium, Cr (VI), compounds are classified as mutagenic carcinogens, associated with various cancers of internal organs. Therefore the U.S. EPA has defined hexavalent chromium as a regulated toxic contaminant, and the state of California established a Public Health Goal (PHG) of 0.2 µg/L and 2.5 µg/L total chromium in drinking water. More recently in 2009, the EPA has proposed further reducing the PHG (to 0.02 µg/L) which requires a method with 10-fold increased sensitivity.

Soil and sludges can also be contaminated by hexavalent chromium. However, extractions from soils and sludges could be very labor intensive following the EPA method 3060A. Automated Solvent Extraction (ASE) provides higher extraction efficiencies and has been approved by the EPA for extractions of pesticides, PCBs, and PAHs. With the introduction of corrosive-compatible

ASE system, the advantages of automation can be used to extract hexavalent chromium from the difficult matrix of soil. Here we demonstrate the whole solution, from automated sample preparation to analysis. Soil samples were extracted by ASE using a caustic base solution. The resulting samples were analyzed for hexavalent chromium according to EPA 218.6 conditions: ion chromatography separation, post-column addition, and detected by absorbance at 530 nm. The reproducibility was 0.4 to 2% RSD with 105% recovery and calculated LOQs of 1.6 µg/L. Water samples were directly analyzed with a modified EPA 218.6 to obtain lower LOQs (0.003 µg/L) with similar RSDs and recoveries.

WRM 35

Detection and Quantification of Inorganic Arsenic in Fruit Juices Using Capillary Ion Chromatography

Hua Yang, *hua.yang1@thermofisher.com*, IC/SP, ThermoFisher Scientific, Sunnyvale, CA 94085, United States

Growing Interest around the determination of arsenic (As) in fruit juices has been triggered by media reports claiming that some apple juice products may contain high amounts of arsenic. It is more important to detect and quantify inorganic (As(III) and As(V)) than organic arsenic, because inorganic forms of arsenic are highly toxic while the organic forms are not. The established analytical method for the various arsenic species is the separation of them by Ion chromatography (IC) followed by detection using ICP-MS. IC –ICP/MS can be an expensive technique, however, Ion chromatography (IC) with suppressed conductivity is a well established, lower cost method used by multiple industries for ion determination. The recently introduced high-pressure capable capillary IC systems combined with 4-mm particle ion-exchange columns have reduced eluent consumption and further improved separation efficiency. This study presents the detection and quantification of inorganic arsenic (Arsenate As (V) and Arsenite As (III)) using a high-pressure capillary IC system with 4 µm particle ion –exchange column.

WRM 36

Kinetics investigation of OH reaction with Styrene at 240 – 340 K and 1 – 3 Torr using the Relative Rate/Discharge Flow/ Mass Spectrometry Method

Joeson Cho, *joesoncho@csu.fullerton.edu*, Zhuangjie Li. Department of Chemistry and Biochemistry, California State University of Fullerton, Fullerton, CA 92831, United States

The kinetics of the reaction of hydroxyl radical with styrene at 240 – 340 K and 1 – 3 Torr were studied using the Relative Rate/Discharge Flow/Mass Spectrometry technique. The reaction was found to be pressure independent over the range of 1 – 3 Torr at both 298 K and 340 K. At 298 K, the rate constant was determined to be $k_{\text{styrene}} = (5.78 \pm 0.45) \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, which is in good agreement with Atkinson et al. and Bignozzi et al. The rate constant of this reaction was found to be negatively dependent on temperature at 240 - 340 K, and the Arrhenius expression for this reaction was determined to be $k_{\text{styrene}} = (9.50 \pm 0.03) \times 10^{-12} \exp[(551 \pm 41)/T] \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. Reaction mechanisms were also proposed based on the observed adducts products and their respective fragment ions in the mass spectrum. Based on the rate constant of styrene + OH at 277 K determined by the present work, the atmospheric lifetime of styrene was estimated to be 4.84 hours.

WRM 37

Kinetics investigation of OH reaction with naphthalene at 240-340 K and 1-3 Torr using the Relative Rate/Discharge Flow/Mass spectrometry technique

Masoud M Roueintan, *mroueintan@fullerton.edu*, Zhuangjie Li. Department of Chemistry and Biochemistry, CSU Fullerton, Fullerton, CA 92831, United States

The combination of the relative rate method with the discharge fast flow/mass spectrometer technique (RR/DF/MS) was employed to determine the rate constant for the gas phase reaction of hydroxyl radical (OH) with naphthalene at 240-340 K and a total pressure of 1-3 Torr. At 298 K, the rate constant was measured to be $k_1 = (2.57 \pm 0.21) \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, which is in an excellent agreement with literature values reported using different techniques. The reaction of OH with naphthalene was found to be essentially independent of pressure in a range from 1-3 Torr at both 298 K and 340 K. The rate constant of this reaction was found to be negatively dependent of

temperature, and an Arrhenius expression for the reaction of OH with naphthalene was determined to be $k_1 = (10.6 \pm 0.15) \times 10^{-11} \exp [(982 \pm 66)/T] \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ at 240-340 K. The atmospheric lifetime of naphthalene was estimated to be 9.4 h using the rate constant of naphthalene OH determined at 277 K in the present work.

WRM 38 - withdrawn

WRM 39

Unusual Zn Clusters Supported by Formamidinates

Yi-Ju Tsai, *ytsai@pacific.edu*, **Qinliang Zhao**, *Department of Chemistry, University of the Pacific, Stockton, CA 95219, United States*

Using anionic formamidinates with different substituents as the supporting ligands, Zn clusters of different geometries were successfully synthesized and fully characterized. Two of the Zn Complexes are dimeric, in which the metal cores are held together by parallel formamidinates, while the rest complexes are trimeric where the Zn ions and ligands are arranged in an unusual geometry. Detail structural comparison indicates the size and location of the substitutes on the ligands play important roles in governing the geometry of the products. All clusters are thermally robust but relatively reactive toward group transfer reagents. A tetrameric cluster with an interstitial oxo was consistently obtained when a small amount of oxygen was present.

WRM 40

Monometallic Complexes Supported by Ligands with Excessive Basic Centers

Yi-Ju Tsai, *ytsai@pacific.edu*, **Qinliang Zhao**, *Department of Chemistry, University of the Pacific, Stockton, CA 95211, United States*

A good catalyst often contains the right reactive center and the right supporting environment. Two ligands with six or seven binding atoms were used to stabilize a single metal ion. Monometallic nickel and cobalt complexes were successfully synthesized and structurally characterized. In each of the monometallic complexes, the metal core is stabilized by four binding atoms, which leaves free basic centers adjacent to the metal center. The pendant bases could potentially be utilized as proton relays in small molecule activation, mimicking the phenomenon discovered by DuBois and Borovik. Studies on the reactivities of the monometallic complexes are in process.

WRM 41

Characterization of Derivatized Cyclams and Their Applications in Metalation

Angelique Cao Minh, *a_cao@u.pacific.edu*, **Qinliang Zhao**, *Department of Chemistry, University of the Pacific, Stockton, CA 95219, United States*

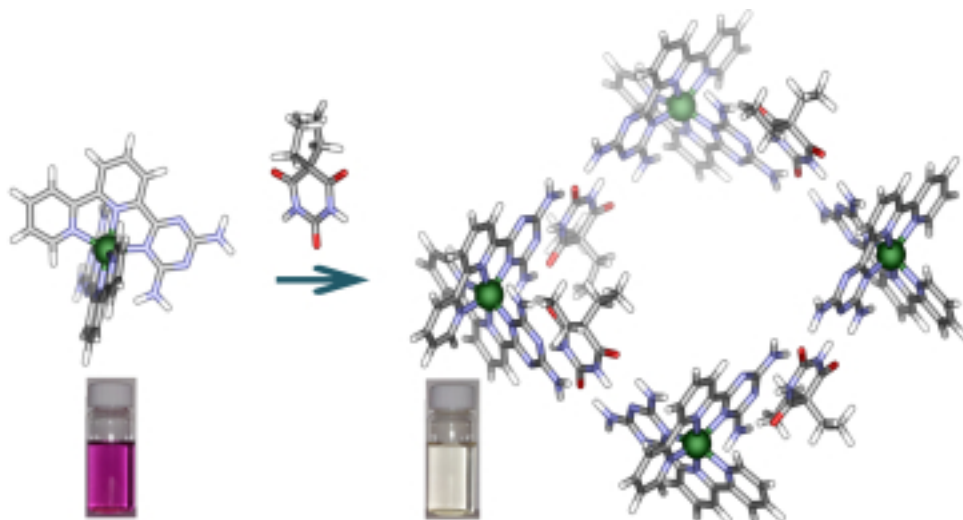
The roles of 1, 4, 8, 11-tetraazacyclotetradecane (Cyclam, a saturated macrocyclic polyamine) in stabilizing transition metal ions have been extensively studied. To obtain new complexes with unique physical properties, experiments to derivatize Cyclam with different substitutes at the nitrogen positions were conducted. Two new macrocyclic ligands were synthesized and fully characterized. Metalation of each new ligand indicated that the pocket in the center was actually too small to hold most transition metal ions. The Cyclam with four phosphoryl pendant arms was able to stabilize two lanthanide ions. Each lanthanide ion, however, was stabilized by the oxygen atoms from the phosphoryl side arms, thus giving a butterfly-shaped dimeric complex.

WRM 42

Effects of Hydrogen Bonding Self-Assembly on the Spin Crossover Behavior of Mononuclear Complexes of 6-(3,5-Diamino-2,4,6-triazinyl)2,2'-bipyridine

Michael C Young, *myoun010@ucr.edu*, **Erica Liew**, **Richard J Hooley**, *Department of Chemistry, University of California - Riverside, Riverside, CA 92521, United States*

Spin crossover is normally controlled by thermal perturbation or photoexcitation. In this work, the formation of a hydrogen bonded network is used to modify the spin state of mononuclear complexes from a mixture of low and high spin centers to solely high spin. Given the differences between the d to π^* transition in the low and high spin states, this change allows this system to function as a colorimetric sensor for suitable hydrogen bonders, specifically barbituric acids.



WRM 43

Synthesis, characterization and kinetics study of Mo₃ clusters with a μ_3 -O and μ_3 -CR trinuclear core

Andrew J Burton, ajb397@saclink.csus.edu, **Jacqueline R Houston**. Department of Chemistry, California State University, Sacramento, Sacramento, CA 95819, United States

When attempting to understand the complex chemistry at the molecular level of heterogeneous catalysis, the cluster-surface analogy has been a helpful bridge between coordination chemistry and surface chemistry. By using a discreet well-defined model structure, specific functional groups and their individual reactivity can be studied. To study the Mo₃- μ_3 -C bond from a proposed intermediate structure during heterogeneous molybdenum carbide catalysis, two trinuclear organometallic clusters were synthesized and their reactivity examined in situ using NMR.

[Mo₃(μ_3 -O)(μ_3 -CCH₃)(μ -O₂CCH₃)₆(H₂O)₃]BF₄ was synthesized by refluxing Mo(CO)₆, acetic acid, acetic anhydride and triethylamine, then collected by eluting with KBF₄ from a cation exchange column. A co-crystallized structure containing two different cations, [Mo₃(μ_3 -O)(μ_3 -CR)(μ -O₂CCH₂CH₃)₆(H₂O)₃]⁺ where R = CH₂CH₃ and CH₃, was synthesized by refluxing Mo(CO)₆, propionic acid and propionic anhydride, then collected by eluting with ZnI₂ from a cation exchange column. Kinetics data collected using ¹H NMR shows that the alkylidyne ligand (μ_3 -CR) on each compound is labile to substitution when dissolved in water. ¹H NMR data of the co-crystallized structure shows a faster reaction of the Mo₃- μ_3 -CCH₂CH₃ than the Mo₃- μ_3 -CCH₃. When those rates are compared to the Mo₃- μ_3 -C bond distances, Mo₃- μ_3 -CCH₂CH₃ being longer than the Mo₃- μ_3 -CCH₃, there appears to be a correlation between bond length and dissociation rate of the alkylidyne.

WRM 44

Seeking the single molecule magnet: Investigating magnetic characteristics of low coordinate transition metal compounds

Aimee M. Bryan, aimeebryan@gmail.com, **Philip P. Power**. Department of Chemistry, University of California Davis, Davis, CA 95616, United States

Monomeric, low (two or three) coordinate, paramagnetic transition metal complexes of sterically bulky ligands have been synthesized and characterized in order to study their magnetic behavior. The complexes are derivatives of readily available and inexpensive transition metals (Fe, Co and Ni). These complexes are of interest because they have unusually large anisotropic internal magnetic fields. High internal fields arise from orbital magnetism which is a major factor in determining axial zero field splitting (ZFS) parameters. The axial ZFS is directly related to the energy barrier (U_{eff}) governing spin reversal. The ultimate goal is to synthesize compounds that have single molecule magnet (SMM) behavior and reversal of magnetization barriers (U_{eff}) above

kT (where T = 300 K). SMMs are a topic of intense research interest because of their potential applications in magnetic memory, high-density information storage and quantum computing technologies. Currently, the various factors that determine ZFS are not well understood but both in-state and out-of-state orbital angular momentum can be primary contributors. We have found unexpectedly large axial ZFS values in the range of -20 to -80 cm⁻¹ for two and three coordinate cobalt (II) complexes and of -37 to -112 cm⁻¹ for a series of iron (II) complexes. The major object of my research is to study the relationship between ligand fields and their effects on ZFS parameters.

WRM 45

Mild route to novel Ga–N and In–N compounds

Robert J Wilson, *rjwilson90@yahoo.com*, *Miriam V Bennett*. *Department of Chemistry and Biochemistry, San Diego State University, San Diego, CA 92182-1030, United States*

Here we present a new family of gallium– and indium–nitrogen compounds produced via the dehalostannylation of (Me₃Sn)₃N and Cl₃M–N(SnMe₃)₃ (M = Ga, In) in the presence of anionic gallium and indium halides. Combining these precursors in polar aprotic solvents at room temperature affords the novel molecules: [(Cl₃Ga)₂N(SnMe₃)₂]¹⁻, [(Cl₃Ga)₂NSnMe₃]²⁻, [Ga₃NCI₉]³⁻, [Ga₃(NSnMe₃)₃(SnMe₂)MeBr₅]¹⁻, [(Cl₂GaNSnMe₃)₃(μ-SnMe₂Cl)]²⁻ and [(ClIn)₆(NSnMe₃)₅(μ-Cl₃)]¹⁻. These compounds have been fully characterized and their solid-state reactivities investigated. Our success demonstrates the utility of this synthetic strategy in accessing both unassociated and oligomeric M–N (M = Ga, In) compounds. These products are rare examples of molecules containing N solely ligated by main group metal atoms and may have the potential to act as precursors to higher nuclearity molecules, nanomaterials, and high-purity bulk materials.

WRM 46

Late transition metal complexes of a 1,3-dipyridylverdazyl: Studies of metal and ligand redox processes

Dorothy Chung, *david.brook@sjsu.edu*, *Servando Ponce*, *David Brook*. *Chemistry, San Jose State University, San Jose, CA 95182, United States*

Unlike most free radicals, verdazyl free radicals are relatively stable and can be isolated under ambient conditions. An interesting aspect of 1,3-dipyridyl substituted verdazyl is the additional pyridine ring results in lower steric hindrance that allows for better coordination of metal ions. Further experimentation has been done to create of similar complexes to the Nickel (II) complex reported by Richardson in 2010-. First row middle to late transition metals were successfully coordinated with the verdazyls as indicated by a red shift in the UV visible spectra. Electrochemical properties of the complexes were studied using cyclic voltammetry. The information suggests that both ligand and metal centered redox processes are present and reversible in these complexes.

WRM 47

Synthesis of rare earth pre-catalysts for the transformation of organic molecules

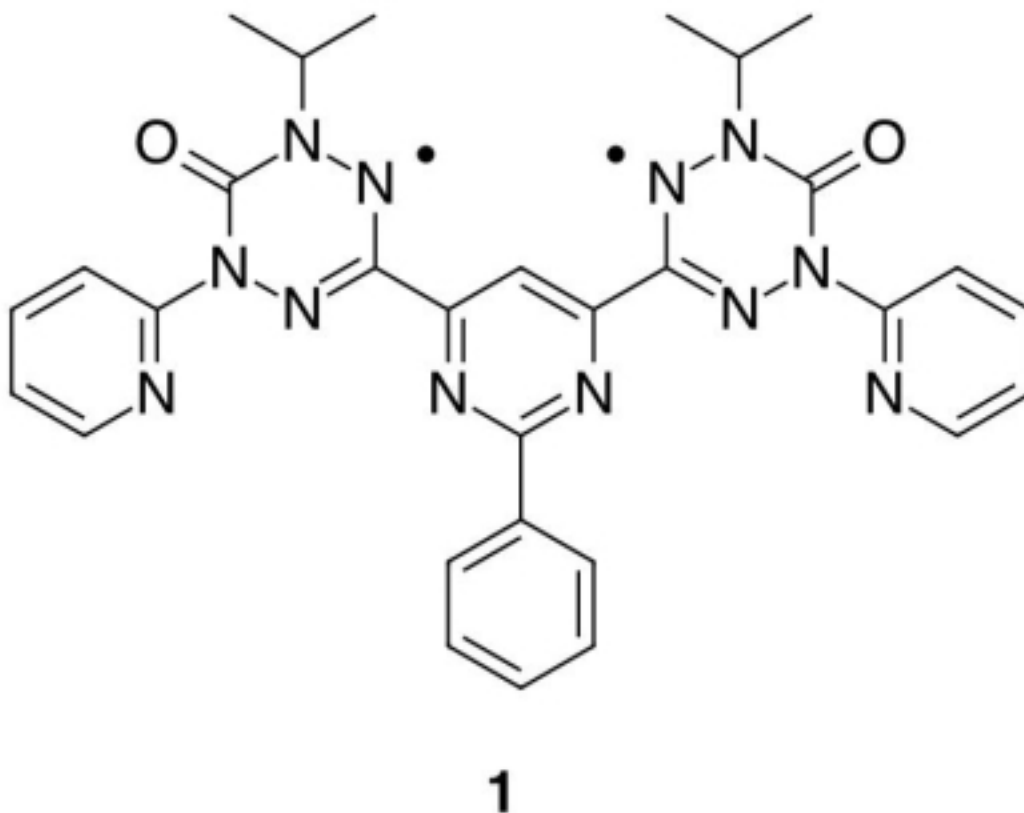
Scott D Bunge, *sbunge@kent.edu*. *Department of Chemistry and Biochemistry, Kent State University, Kent, OH 44242, United States*

The constraints of traditional organic synthetic methodologies have stimulated significant interest in new, more efficient and selective homogeneous catalytic approaches. Homoleptic rare earth (Ln) amido pre-catalysts have recently demonstrated the capability to catalyze numerous organic reactions. However, facile loss of the amido ligand set results in a catalytically active Ln complex that is often ill-defined and potentially oligomeric. This hinders both maximizing efficiency and selectivity. This work describes an approach for the synthesis and evaluation of alternative Ln guanidinate pre-catalysts. It is envisioned that the inherent basicity of a 1,1,3,3-tetraalkylguanidinate (TAG) ligand may be utilized to maintain coordination to a Ln center throughout a catalytic cycle; producing a novel well-defined monomeric Ln(TAG) catalyst. The intention is to impart increased turnover frequency and to develop control over the ligand architecture around the Ln center; which in turn generates selectivity. Our results have produced a series of 'proof of concept' Ln(TAG) complexes and demonstrate their increased turnover frequency when catalyzing several reactions. The results of this investigation will be presented.

WRM 48**Synthesis and characterization of polytopic verdazyl ligands capable of self assembly**

Erik Johnson, *David.Brook@sjsu.edu*, **David J. R. Brook**, *Department of Chemistry, San Jose State University, San Jose, California 95192, United States*

A verdazyl is a relatively stable type of free radical with the lone electron delocalized over four nitrogen atoms. We have synthesized the ditopic verdazyl ligand **1** and are investigating the coordination of metal ions to form grid complexes. Verdazyl ligand **1** was synthesized by reacting a bis-hydrazone with triphosgene and BOC protected isopropyl hydrazine, then deprotecting and oxidizing. Variable temperature ESR indicates that the ligand has a singlet ground state. Titration with Ni^{2+} suggests the formation of a 1:1 complex with the metal ion, which suggests the formation of a self assembled grid.

**WRM 49****Exploring Metal-Containing Monomers for Material Development**

Carolyn Tran-Math, *c_tranmath@u.pacific.edu*, **Qinliang Zhao**, *Department of Chemistry, University of the Pacific, Stockton, CA 95211, United States*

Ruthenium-containing polymers have been investigated with great interest as optically active materials. The optical properties were visualized following activation by UV-Vis irradiation, allowing the Ruthenium-containing material to reach a long-lived excited state that promotes reactivity and fluorescent properties. Herein, a new mixed-ligand complex, $[(\text{bipy})_2(\text{vmbipy})\text{-Ru(II)}]\text{Cl}_2$, – where bipy = 2,2'-bipyridine and vmbipy = 4-vinyl-4'-methyl-(2,2')-bipyridine)– was synthesized and structurally characterized. UV-Vis and spectrofluorometric analysis indicated its intrinsic optical property, which was further analyzed by electrochemistry and DFT calculations. At the same time, Nickel-containing analogues were synthesized for comparison. The study successfully verified the importance of the metal center and individual ligands in building a viable monomer for material development.

WRM 50**Computational and experimental study of the thermal cyclization of enediynes and dieneynones**

Cui Q. Li, *ghermanb@csus.edu*, Benjamin F. Gherman, John D. Spence. Department of Chemistry, California State University, Sacramento, Sacramento, CA 95819-6057, United States

Enediyne compounds, which can undergo Bergman cyclization and generate diradical intermediates, are potential antitumor drugs due to their ability to abstract hydrogen atoms from and cleave DNA. Modification of the enediyne core by insertion of a carbonyl group produces an enediynone, which can be further modified by changing one of the two alkynes into an alkene to give a dieneynone. These compounds can undergo cyclization along four different pathways, generating new diradical intermediates with simultaneous formation of a 5-, 6-, or 7-membered ring. Density functional theory (DFT) calculations are used to study the four reaction pathways of the enediynone and dieneynone to determine which are kinetically and thermodynamically preferred. Potential factors affecting these energetics, such as the aromaticity of the cyclized products and the electron-withdrawing ability of the carbonyl group, are analyzed. Concurrently, a model enediynone and dieneynone are being synthesized in a four-step process to experimentally study thermal cyclization of the two compounds to compare with the computational results.

WRM 51**Photoexcitation of enediyne compounds and implications for their bergman cyclization reactivity**

Phillip J. Marzouk, *ghermanb@csus.edu*, Benjamin F. Gherman, John D. Spence. Department of Chemistry, California State University, Sacramento, Sacramento, CA 95819-6057, United States

Enediyne-containing compounds have shown potential in chemotherapy drug design. Upon photoactivation, enediynes undergo Bergman cyclization to produce a diradical capable of abstracting hydrogen atoms from DNA and disrupting DNA strand integrity. Enediyne anticancer treatment efficacy could be increased by the selective photoactivation of enediynes in cancerous cells through the application of visible, rather than UV, light. Enediyne absorption wavelengths may be increased into the visible region based on the extent of conjugation in the enediyne supporting group and/or at the alkyne termini, and by including heterocyclic supporting groups. In the current work, time-dependent density functional theory (TD-DFT) calculations have been used to predict the absorption wavelengths of a range of enediynes. Further investigation into the electronic excited states obtained through TD-DFT geometry optimizations can be used to determine whether the corresponding excitations are likely to promote Bergman cyclization. Among the factors examined are the energy gap between the in-plane π and π^* orbitals of the alkynes in the electronic ground state and changes in the alkyne bond lengths, C¹-C⁶ distances, and Mulliken charge and spin populations of the alkyne carbon atoms in the electronic excited states.

WRM 52 - withdrawn**WRM 53****Pseudorotaxane formation targeting on nucleic acids**

Kazumitsu Onizuka, *Kazumitsu.onizuka@riken.jp*, Yoshihiro Ito, Hiroshi Abe. Nano medical engineering laboratory, RIKEN, Wako-shi, Saitama 351-0198, Japan

Rotaxane is a molecular architecture consisting of a dumbbell shaped molecule which is threaded through a molecular ring. In the nucleic acid chemistry, unique topological molecular architectures such as catenane and rotaxane have been constructed by taking advantage of base pairing. A variety of methods to construct topological molecular architectures have been developed for DNA topological labeling and DNA nanotechnology. However, these methods either require a toxic chemical reagent or an enzyme to form topological structures; thus, it is difficult to construct them inside the cell.

Currently, we are investigating novel methods to form topological molecular architectures that neither require a toxic chemical reagent nor an enzyme. To achieve this goal, we designed and synthesized two functional oligodeoxyribonucleotides (ODNs) and performed the pseudorotaxane formation reaction with both unmodified DNA and RNA oligonucleotides. The reaction proceeded rapidly at 37°C at pH 7.2, leading to the formation of a stable complex. We aim to create the pseudorotaxane architecture using functionalized ODNs and native RNA inside the cell. Furthermore, we expect that the molecular ring of pseudorotaxane will bind with mRNA tightly and strongly inhibit translation.



WRM 54

Adjuvant-free MUC1 glycopeptide antitumor vaccines containing Neu5Gc

Teri J Lanoue, tjlanoue@ucdavis.edu, Hamed Malekan, Hai Yu, Yanhong Li, Xi Chen.

Department of Chemistry, University of California-Davis, Davis, CA 95616, United States

MUC1 is a heavily O-glycosylated protein. It is overexpressed in many types of epithelial cancers with aberrant glycosylation forms. It has become a key target in the development of epithelial tumor vaccines. Tumor associated MUC1 often bears tumor associated carbohydrate antigens (TACAs) that are rare for healthy cells. These TACAs are often sialylated prematurely, and the expression of a non-human form of sialic acid *N*-glycolylneuraminic acid (Neu5Gc) is common in lung, breast, ovarian and prostate cancers. The introduction of Neu5Gc to sialylglycopeptide-based cancer vaccines could potentially improve selectivity and immunogenicity. The synthesis of such a promising new class of fully synthetic glycopeptide cancer vaccine candidates will be discussed.

WRM 55

Continuous flow synthesis of valuable triols in a tube-in-tube microreactor

Chan Yi Park, Chan Pil Park. Graduate School of Analytical Science and Technology, Chungnam National University, Daejeon, Republic of Korea

Triols involving three hydroxy group (-OH) are very important building block in the synthesis of various materials, each hydroxy group can be further transformed into other functional groups including ketone, aldehyde, halide, amine, and so on. Photooxygenation conducted with only light and O₂ gas is one of the most useful green chemical processes, which can be used in production of valuable fragrances, pharmaceuticals, and fine chemicals. However, the photooxygenation integrated with another chemical process was rarely studied.

In previous reports, microfluidic systems for the photooxygenation easily solved the problem related with short lifetime of singlet oxygen in organic solvents. Herein we report a continuous flow synthesis consisted of photooxygenation and TfOH catalyzed reaction. Singlet oxygen produced by O₂ gas and photosensitizer (Methylene Blue) yields allyl hydroperoxide regioselectively in a mono-channel microreactor with segmented flow of O₂ gas bubbles and liquid slugs, the intermediate was efficiently converted to the triols in the following TfOH catalyzed reaction with batch or continuous flow manner.

We newly designed and tested another microreactor with inner membrane tube (AF-2400) and outer transparent tube, the O₂ gas injected in inner tube was continuously diffused into reaction solution occupied in outer tube through gas permeable AF-2400 tube. The microreactor of tube-

in-tube type enhanced the contact efficiency between light (LED lamp), oxygen gas, and liquid including reagent and photosensitizer. More importantly, the microreactor was excellent in terms of productivity that is one of the most important issues in microchemical society. We carried out the syntheses of rose oxide and ascaridole from α -terpinene and (-)-beta-citronellol. The photooxygenation of hexamethylbenzene was tested, the product ratio of mono- and dual-reaction was perfectly controlled under exact reaction time and temperature as another example.

WRM 56

A Microchemical Synthesis of Chiral Epoxy Alcohols

Hyojin Lim, *Chan Pil Park*. Graduate School of Analytical Science and Technology, Chungnam National University, Daejeon, Republic of Korea

The enormous potential of epoxy alcohols as key building blocks in production of valuable materials has led to intensive research for their preparation, metal-catalyzed epoxidation of allylic alcohols with hydroperoxides was the most practical route. As alternative method, generation of allyl hydroperoxide by the photooxygenation of alkene and following epoxidation was noticeable. However, the photooxygenation in batch system resulted in tedious reaction time and low selectivity, which was bottleneck in efficient mass production of epoxy alcohol.

Herein we report a facile and efficient continuous flow process consisted of microchemical photooxygenation and microchemical epoxidation which is much safer than traditional batch epoxidation with increased selectivity. Microchemical systems for photooxygenation provide new strategies and new challenges; it can be connected into the mass production of epoxy alcohols without delayed synthesis of peroxide intermediate. Microreactor with discontinuous contact between alternating gas bubbles and liquid slugs has a larger gas-liquid contact area and light receiving area than a conventional batch system, controlling of the gas-liquid flow and absorbed light is very simple and efficient in the microreactor.

Methylene blue as photosensitizer and $\text{Ti}(\text{O}-i\text{-Pr})_4$ as epoxidation catalyst is perfect combination for mass production of epoxy alcohol, alkene is directly converted into epoxy alcohol with high yield and selectivity. Singlet oxygen produced by O_2 gas and photosensitizer yields allylic hydroperoxide, the hydroperoxide group plays the role as oxygen donor in the second epoxidation step. Finally, asymmetrical synthesis to produce a chiral epoxy alcohol is studied by adding a diethyl tartrate (L-(+)-DET) as a chiral auxiliary, the chiral product is conveniently synthesized. As such, the microchemical synthesis would be invaluable not only for the mass production of epoxy alcohol but also for asymmetric synthesis in continuous flow manner.

WRM 57

Novel Chemoenzymatic Approach towards Synthesizing Chondroitin Sulfate Analogs

Nova Tasnima, *ntasnima@ucdavis.edu*, Hai Yu, Mengyang Xue, Jingyao Qu, Yanhong Li, Xi Chen. Department of Chemistry, University of California, Davis, CA, Davis, California 95616, United States

Chondroitin Sulfate (CS) has been the subject of many clinical trials as it can be used for treating degenerative joint diseases such as osteoarthritis. CS is a type of glycosaminoglycan defined by the repeating disaccharide unit $(\text{GalNAc}\beta 1\text{--}4\text{GlcA}\beta 1\text{--}3)_n$ containing *N*-acetylgalactosamine (GalNAc) and glucuronic acid (GlcA). The disaccharide unit can be modified with *O*-sulfation at specific positions such as at the hydroxyl groups at C-4 and/or C-6 of GalNAc residues and/or C-2 of the GlcA units. Varying sulfation pattern of the CS gives rise to specific biological functions. Developing a novel chemoenzymatic method towards synthesizing structurally defined *N*-sulfated CS oligosaccharides has been proposed. It is hypothesized that these analogs will be less degradable comparing to native CS oligosaccharides. In this presentation, a list of azido-modified GalNAc derivatives are synthesized chemically and used as substrates for UDP-GalNAc biosynthetic enzymes and chondroitin synthases for producing azido-containing oligosaccharides. The azido-group can be reduced to an amine which can be selectively *N*-sulfated to produce CS oligosaccharide analogs for further function studies.

WRM 58

Water soluble verdazyls with polyhydroxy groups in the 1 and 5 positions

Diego A Matteo, david.brook@sjsu.edu, Tiffany Truong, Vanessa Gaoiran, David J. R. Brook. Chemistry, San Jose State University, San Jose, California 95192, United States

Verdazyls are stable heterocyclic free radicals with potential as spin probes, in part as a result of their structural diversity. The paramagnetic verdazyl core can be substituted at three different positions allowing for fine tuning of properties to suit the application at hand. In particular we are investigating methods to increase the water solubility of verdazyls through the introduction of hydroxy groups. Here we present our approach to verdazyls with 1,3-propanediol substituents at the 1 and 5 positions.

WRM 59

Heterocycle to Heterocycle Strategies: Isoxazoles and Oxadiazoles as Branch Points towards Skeletally Diverse Fluorescent Small Molecules

Teresa A Palazzo, tapalazzo@ucdavis.edu, Keith C Coffman, Joung S Yang, Dean J Tantillo, Mark J Kurth. Department of Chemistry, University of California Davis, Davis, CA 95616, United States

A series of heterocycle-to-heterocycle conversions are explored and explained via synthetic and computational methodology. Various 3-, 4-, and 5-substituted (2-nitrophenyl)-isoxazoles, when subjected to reduction conditions, are readily transformed into 4-aminoquinolines, 3-acyl-1*H*-indoles, and 4-quinolinones, respectively. It has also been demonstrated that bis(2-nitrophenyl)-isoxazoles follow chemoselective reduction pathways. Reduction of bis(2-nitrophenyl)-isoxazoles led to the discovery and elucidation of a novel domino reaction, providing access to a dibenzonaphthyridinone core. This work has recently been extended to oxadiazole systems in an analogous fashion. These highly fluorescent dibenzonaphthyridinones are being studied further to understand their environment dependent optical properties. Work is currently being done to explore the scope and utility of these processes.

WRM 60

A general and high yield method for the synthesis of 6-vinylfulvenes

Ihsan Erden, **Jingxiang Ma**, ma@sfsu.edu. Chemistry and Biochemistry, San Francisco State University, San Francisco, California 94132, United States

The synthesis of 6-vinylfulvene has been problematic since the discovery of the Thiele method for fulvene preparations. Though preparative improvements have been made for 6-alkyl or aryl fulvenes, 6-vinylfulvenes have remained relatively inaccessible. Neuenschwander's efforts have met with considerable difficulties in terms of yields, and for a few low molecular weight derivatives alternative syntheses had to be developed. In this work we have successfully developed general, and in most cases high yield methods for the preparation of 6-vinylfulvenes and will also report on some of their reactions with a variety of reagents.

WRM 61

Probing the scope of the chemical synthesis of S-ribosyl-L-homocysteine (SRH) from various homocysteine and ribose moieties

Emily I Showell-Rouse, eishowellrouse@usfca.edu, Brendan J Corcoran, Emily S Murzinski, Diana L Cudia, Megan E Bolitho. Department of Chemistry, University of San Francisco, San Francisco, CA 94117, United States

Quorum sensing (QS) is bacterial cell-cell communication used to monitor population density and regulate gene expression. Autoinducer-2 (AI-2) is the small molecule used for quorum sensing between species and has been shown to regulate pathogenic behavior in many bacteria. The controlled inhibition of AI-2 production could lead to alternative treatments for bacterial infections that should contribute less to the problem of antibiotic resistance than conventional antibiotics. S-Ribosyl-L-homocysteine (SRH) is converted into AI-2 by the enzyme LuxS; therefore, SRH analogs are targeted as potential competitive inhibitors of LuxS. Using a systematic approach, the scope of the chemical synthesis of SRH is being probed. To do this, protected homocysteine and ribose moieties will be coupled using an S_N2 -type reaction. L-Homocysteine has been fitted with varying protecting groups on both the carboxyl and the amine functional groups. These protected amino acid derivatives have been characterized and evaluated on their preparation ease and will be coupled to protected ribose derivatives bearing varying leaving groups to determine the

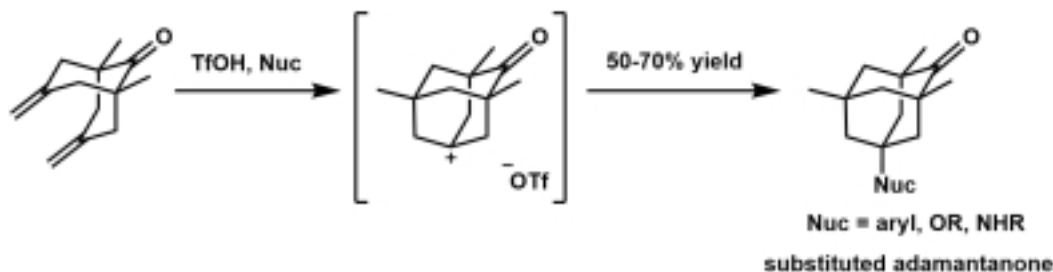
viability of each in the synthesis of SRH. Constructing a more facile and reliable synthesis of SRH will not only make this compound more accessible to scientists pursuing the study of quorum sensing, but also allow for the creation of SRH analogs utilizing the same synthetic foundation.

WRM 62

Concise Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonan-9-ones

Gloria S. Lee, *gs1001@chem.ucla.edu*, **Michael E. Jung**, *Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90095, United States*

Adamantane-based small molecules are useful in the treatment of a variety of conditions, ranging from neurodegenerative disorders such as Parkinson's and Alzheimer's disease, to viral infections such as HIV. In addition, the high level of symmetry and the peculiar non-planar geometry of the bridgehead adamantyl cation have fascinated chemists since the discovery of the adamantane core in 1933. We thus desired to efficiently construct substituted adamantanones, potential precursors to the corresponding adamantanes. Trifluoromethanesulfonic acid facilitates formation of the adamantanone core from 3,7-dimethylenebicyclo[3.3.1]nonan-2-one, which can be easily obtained in one step from commercially available starting materials. The resulting adamantyl cation may be trapped with a variety of nucleophiles to form tetrasubstituted adamantanones. Aromatic and heteroaromatic nucleophiles have proven to be successful, and oxygen and nitrogen nucleophiles can provide access to a wide variety of functionality at the newly formed tertiary position.



WRM 63

Organocatalytic enantioselective synthesis of polysubstituted spirooxindole derivatives via a Michael-Michael tandem sequence

Naresh Ramireddy, *naresh.ramireddy@utsa.edu*, **Santhi Abbaraju**, **Nirmal K Rana**, **John Cong-Gui Zhao**, *Chemistry, University of Texas at San Antonio, San Antonio, Texas 78249, United States*

In the field of asymmetric catalysis, methods to synthesize structurally complex natural products and bioactive compounds with multiple functionalities and chiral centers are very crucial. Spirooxindoles with multiple stereogenic centers are privileged heterocyclic systems that are featured in a large number of bioactive alkaloids and medicinally relevant compounds. Herein, we wish to report an efficient organocatalytic enantioselective method to construct highly functionalized spirooxindole derivatives with multiple chiral centers through a Michael-Michael tandem sequence. By employing a suitable organocatalyst, the desired products can be obtained in high yields (up to 90%) and with excellent stereoselectivity (dr > 95:5, ee up to 96%).

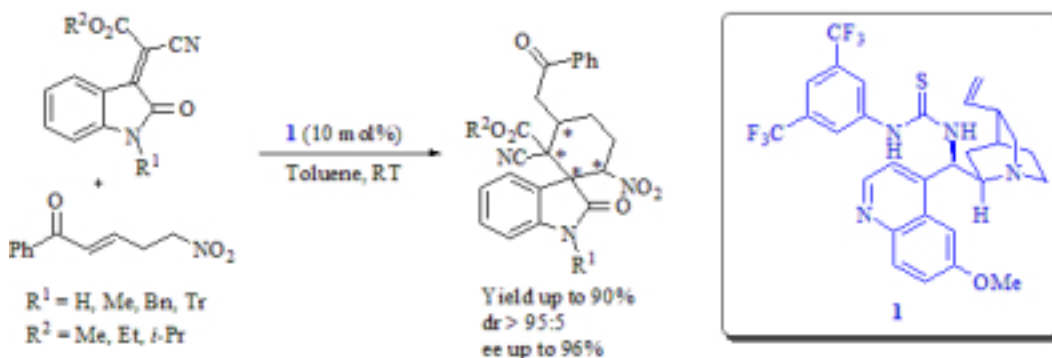


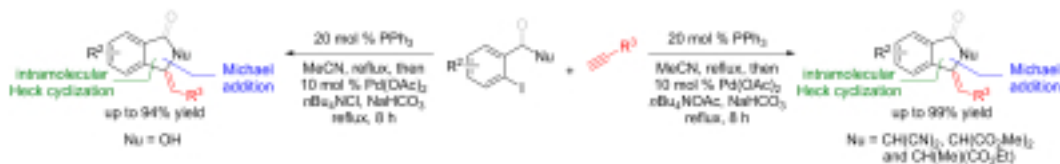
Figure 1

WRM 64

Phosphine/Palladium Sequential Catalysis Syntheses of Alkylidene Phthalans, Indanes, and Indanones

Yi Chiao Fan, ycfan@ucla.edu, Ohyun Kwon, *Chemistry & Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States*

A tandem nucleophilic phosphine/palladium-catalyzed reaction sequence for the construction of complex heterocycles from readily obtainable starting materials has been developed. The Michael–Heck reaction grants access to synthesize complex alkylidene phthalans rapidly in high yields accompanied by good stereoselectivities (*E/Z* ratios of up to 1:22). This novel technology has enabled the facile total syntheses of three different rare fungal metabolites—3-deoxyisoochracinic acid, isoochracinic acid, and isoochracinol—from the genus *Cladosporium*. One of these compounds, 3-deoxyisoochracinic acid, exhibits the growth of *B. subtilis*, one of the causes of food poisoning. To further expand the area of Michael–Heck catalysis, preparation of functionalized indanes and indanones is currently been developed. From easily accessible starting materials, indanes and indanones are isolated in good yields and good stereoselectivities, providing a gateway to valuable synthetic intermediates.

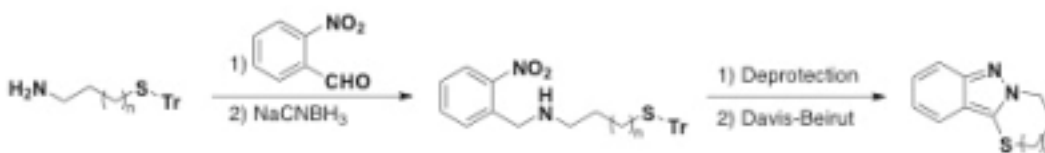


WRM 65

Synthesis and bioactivity of thiazolo-, thiazino- and thiazepino-2*H*-indazoles synthesized via the Davis-Beirut reaction

Kelli M. Gottlieb¹, Makhluf J Haddadin², Mark J Kurth¹. (1) *Department of Chemistry, University of California - Davis, Davis, CA 95618, United States* (2) *Department of Chemistry, American University of Beirut, Beirut, Lebanon*

The Davis-Beirut reaction is a simple yet effective method developed in our laboratory for synthesis of diverse 2*H*-indazoles containing oxo-ethers. Current research focuses on extending the scope of this reaction by incorporation of a sulfur atom in place of the oxygen. Thiazolo- (*n* = 0), thiazino- (*n* = 1), and thiazepino- (*n* = 2) 2*H*-indazoles are prepared from various *o*-nitrobenzaldehydes and S-trityl protected amino thiols.



Reductive amination of the *o*-nitrobenzaldehyde-derived imine followed by trityl deprotection and immediate treatment with aqueous base under Davis-Beirut conditions provides the desired heterocycles in good yield. These new thia-2*H*-indazoles (in analogy to previously synthesized oxa analogs) were screened as potential inhibitors of myeloperoxidase (MPO), an enzyme that causes oxidative damage to lung tissue in cystic fibrosis patients. Current data shows excellent inhibition of MPO by the thia-2*H*-indazoles.

WRM 66

Synthesis and Biological Activity of Fluorinated N-Methanocarbathymidine Analogs

Timothy A Dwight, tdwight@gmail.com, **Michael E Jung**, **Frederic Vigant**. Department of Chemistry and Biochemistry, University of California - Los Angeles, Los Angeles, CA 90095-1569, United States

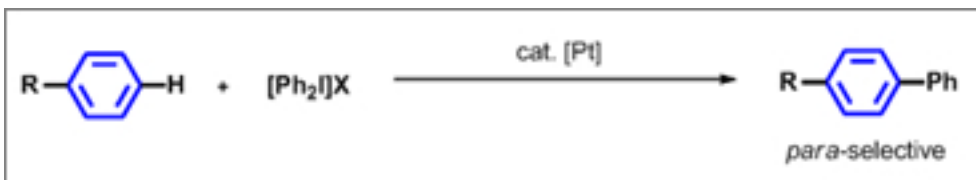
N-methanocarbathymidine (N-MCT) is an antiviral thymidine mimetic with potent activity against herpes simplex virus infections. Its bicyclo[3.1.0]hexane carbon framework locks it into a preferred conformation, closely mimicking the active conformation of natural sugars. This presentation will detail the synthesis of the 3' α -fluoro and the 3' β -fluoro analogs of N-MCT and evaluate their antiviral activity against herpes simplex virus.

WRM 67

Platinum-Catalyzed C–H Arylation of Simple Arenes

Anna M Wagner, awags@umich.edu, **Amanda J Hickman**, **Melanie S Sanford**. Chemistry, University of Michigan, Ann Arbor, MI 48104, United States

The biaryl linkage is a motif that is present in many of today's leading pharmaceuticals, materials, and agrochemicals. An attractive method to form these types of bonds is transition metal catalyzed C–H bond functionalization – which uses transition metal catalysts such as nickel, copper, or palladium to convert ubiquitous C–H bonds into desirable biaryl C–C bonds. This work presents the first highly site-selective platinum-catalyzed direct C–H arylation of simple arenes using diaryliodonium salts. Both the substrate scope and preliminary mechanistic insights of this reaction will be discussed.



WRM 68

An efficient and stereoselective method for constructing seven-membered carbo- and heterocycles

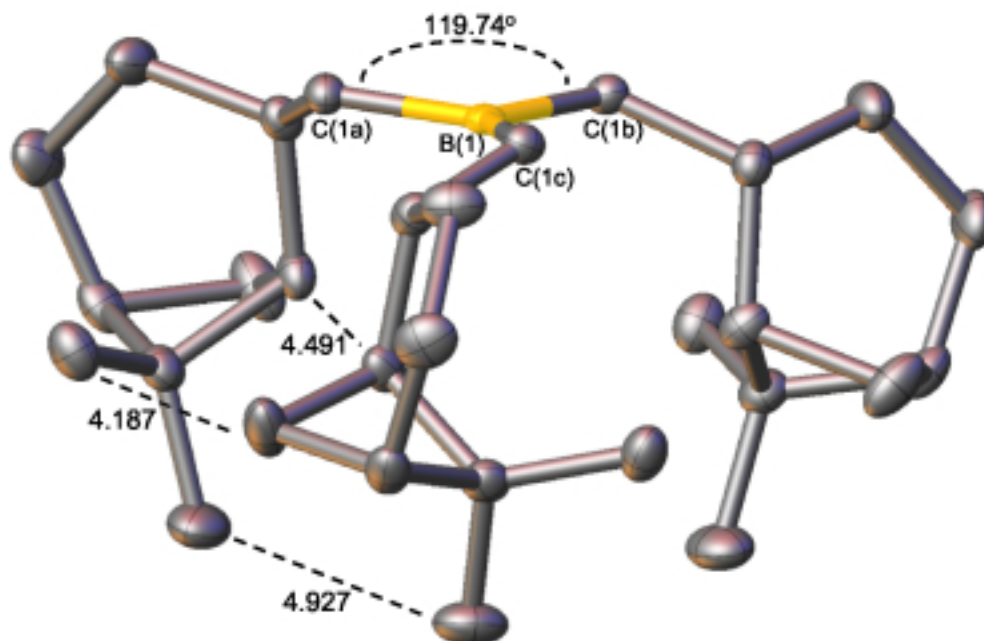
Gagik G. Melikyan, **Kellyanne Duncan**, kellyanneduncan@gmail.com. Department of Chemistry and Biochemistry, California State University Northridge, Northridge, CA 91330, United States

A novel versatile method for the synthesis of seven-membered carbo- and heterocycles was developed. The methodology allows for varying the topology of carbon tethers between transient radical centers as well as the stereoelectronic nature of the substituents attached to the acetylenic termini. A dicobalthexacarbonyl core is shown to stabilize the intermediate propargyl cations and also to stereodirect the radical C–C bond formation mediated by zinc or cobaltocene.

WRM 69

Evidence of unusual geometries stabilized by dispersion effects

The synthesis, spectroscopy, and structural characterization of a series of new trialkylboranes are described. The nature of the alkyl ligands, which possess bicyclic structures, confer unusual features on the structure of the trialkylborane. Their structures are exemplified by the illustration, which shows that all three ligands are located on one side of the central BC_3 plane contrary to steric expectations.



WRM 70

How to get the most out of your analytical laboratory: Cutting costs and maintaining quality in a high throughput lab

Andrew Morgenthaler, *morgenthaler@amyris.com*, Tom Treynor, Howard Fuller, Brian Van Deren, Dan McAdam, Michael Leavell. Amyris Inc., Emeryville, CA 94608, United States

Amyris is a renewable products company that provides sustainable alternatives to a broad range of petroleum-sourced products through the use of engineered microbes in fermentation. Amyris has developed an industrial synthetic biology platform that operates in a high throughput R&D environment, generating 400,000 samples a year to be quantitatively analyzed by a variety of analytical chemistry techniques including GC, HPLC, spectroscopy, and titrations. These analytical methods are expected to generate data with high efficiency and throughput while maintaining appropriate quality metrics driven by our customers. The continuous monitoring of assay performance over long periods of time provides the information necessary to support rapid scientific development within R&D and appropriate process control in manufacturing. This data can also be used to improve assay efficiency, which enables higher throughput and lower cost at equivalent or better quality. Various statistical models and tools have been developed and applied to several of the operational analytical assays at Amyris. Example methods, including our internal standard titer and purity methods, are presented to illustrate the power of this approach. In these studies, the number of sample replicates and injection replicates was reduced by 30-50%, resulting in substantial time and cost savings. Overall, this work has provided clear routes to reduce variability, improve accuracy, and reduce costs – over \$150,000 annually for just two assays.

WRM 71

Finding 80 needles in a hydrocarbon haystack: Measuring oxygenate impurities in farnesene by GC

Loren Perelman, *perelman@amyris.com*, **Don Diola**, Seham Afaghani, Lauren McDougald, Brian Van Deren, Sara Gaucher, Michael Leavell. Amyris Inc., Emeryville, CA 94608, United States

Farnesene, an acyclic sesquiterpene containing 4 double bonds, is manufactured by Amyris using engineered microbes in fermentation. It is used as a chemical building block in numerous downstream applications such as fuels, lubricants, polymers & plastic additives, and cosmetics. The sites of unsaturation make farnesene susceptible to ambient oxidative stress that results in the formation of a low amount of a wide variety of degradation products, including epoxides, aldehydes, ketones, and their subsequent degradation products, components that can negatively affect the downstream applications. While spectrophotometric methods exist to measure relative changes in the concentration of these oxygenates, these approaches, when applied to complex mixtures, are known to suffer from a variety of technical issues, such as competitive oxidation of functionalization reagents in ambient atmospheres and a lack of truly quantitative calibration standards to support the wide variety of chemistries present. To address these shortcomings and provide improved measurement capability of oxygenate species, a combination GC-FID/GC-MS method has been developed to support quantification of over 80 unique species using a generalized identification algorithm based on MS data and a quantification protocol by GC-FID. This approach enables general classification of molecule family (e.g., alcohol vs. aldehyde) and molecular weight, as well as greatly improved accuracy of oxygenate species measurement down to single-digit parts-per-million levels with precision at better than 5% without the use of derivitization or specialized analyte-specific detectors.

WRM 72

Engineering yeast for the expression and secretion of cellulase cocktails

Sarah Batt Throne¹, *sarah.batt@ars.usda.gov*, **Dominic Wong**¹, **David Wan**¹, **Silvia Xie**¹, **Eric Truong**¹, **Roy Doi**². (1) Bioproduct Chemistry and Engineering Research Unit, USDA, Agricultural Research Service, WRRRC, Albany, CA 94710, United States (2) Molecular & Cellular Biology, UC Davis, Davis, CA 95616, United States

Enzyme systems that digest the cellulose in plant cell walls have potential value in the biorefining of renewable feedstocks such as crop residues, straws, and grasses to biofuels and other bioproducts. The bacterium *Clostridium cellulovorans* is a useful source of biomass-degrading enzymes because it produces cellulase systems that degrade crystalline cellulose. The genes of three *C. cellulovorans* cellulases were individually cloned into the model eukaryotic organism

Saccharomyces cerevisiae. Active endoglucanase, exoglucanase, and β -glucosidase enzymes were constitutively expressed and secreted. The three cellulases were also co-cloned into *S. cerevisiae*, and PCR was used to confirm the presence of all three genes in engineered yeast clones. Enzyme activity was detected by analyzing the degradation of CMC in yeast cultures. This cellulase cocktail is being studied as a prospective component of enzyme systems for the conversion of cellulosic biomass to fermentable sugars.

WRM 73

Enzyme nanoassemblies for biomass conversion

Charles C Lee¹, charles.lee@ars.usda.gov, **Rena E Kibblewhite**¹, **Kurt Wagschal**¹, **Chad D Paavola**². (1) Bioproduct Chemistry and Engineering Research Unit, USDA-ARS, Albany, CA 94710, United States (2) NASA Ames Research Center, Moffett Field, CA 94035, United States

The vast majority of our fuel and chemical feedstocks are currently derived from fossil fuel sources. Much research is directed at deriving more of these products from renewable biomass substrates. One strategy is the utilization of enzymes to hydrolyze and convert biomass into value-added chemicals. Because of the complex nature of lignocellulosic biomass, many different enzymatic activities are required. We are tethering enzymes to an artificial protein scaffold to create nanoassemblies called rosettazymes. We demonstrate that enzyme blends complexed onto the rosettazymes have greater enzymatic activity than free enzymes. Multienzyme bioconversion of biomass into precursor chemicals using rosettazymes will be described.